ePresentation Sessions

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Ageing and dementia 1

EPR1001

The role of MAPT single nucleotide polymorphisms in the clinical phenotype of Alzheimer's disease

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Background and aims: One cardinal feature of Alzheimer's disease (AD) is neurofibrillary tangle pathology, which is composed of hyperphosphorylated microtubule-associated protein tau (MAPT). Genetic mutations MAPT are linked to an increased risk of AD and other neurodegenerative disorders. We investigated the role of genetic variation in MAPT in clinical and neuroimaging outcomes in AD.
Methods: Subjects were from the Alzheimer's Disease Neuroimaging Initiative database. Subjects had a diagnosis of mild cognitive impairment (MCI) (n=469) or AD (n=232) and underwent [18F]flortaucipir PET imaging for tau, clinical assessment, and whole genome sequencing. Genetic variation in MAPT was operationalized as minor allele carrier status on MAPT single nucleotide polymorphisms (SNPs). The predictive ability of minor allele carrier status for MCI to AD conversion and in annual rates of clinical decline in AD was assessed. Correlations with SNPs and in vivo tau uptake were also examined.
Results: No MAPT SNPs were associated with disease stage conversion. Three SNPs (rs1467967, rs1981997, rs7210728) were associated with an increased rate of decline on executive functioning (ß=0.075, p=0.049) or visuospatial abilities (ß=-0.049, p=0.029), or a decreased rate of decline on semantic fluency (ß= 0.032, p=0.015). Carrier status on 2 of these SNPs (rs7210728, rs1981997) were correlated with decreased tau uptake on [18F] Flortaucipir PET in Braak stage regions of interest (rs=-0.748 – -0.608, p≤0.001 - 0.006)
Conclusion: Genetic variation in MAPT may lead to differential clinical phenotypes in AD and may exert functional effects through cerebral tau levels. These findings support the use of MAPT genetic variation as a potential biomarker for AD prognosis.
Disclosure: Data collection and sharing for this project 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). Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report.

EPR1002

Early shunt surgery improves survival in idiopathic normal pressure hydrocephalus

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Background and aims: Shunt surgery improves symptoms in most patients with idiopathic Normal Pressure Hydrocephalus, iNPH. However, randomized trials have been scarce and the effect of shunt surgery has been questioned. Furthermore, the effect of shunt surgery on mortality has previously not been studied. Our aim was to examine the effect of delayed vs early shunt surgery on mortality in iNPH.
Methods: As earlier described (Andrén et al, JNNP, 2013) a random group of iNPH patients (n=33; iNPHDelayed) were unintentionally exposed to a delay of treatment due to administrative and economic shortcomings in 2010-2011 (waiting time 6 - 24 months). These were compared to patients treated within three months (n=69; iNPHEarly). We performed a long-term follow-up study (median follow-up time 6.2 years) of these two groups, with mortality as primary outcome. Kaplan-Meier survival curves and adjusted Cox proportional hazard models were analyzed. Causes of death were obtained from the national Cause of Death registry.
Results: Crude five-year mortality was 44.1% in iNPHDelayed and 14.5% in iNPHEarly (p=0.001). The age-adjusted hazard ratio (HR), in iNPHDelayed, was 2.57 (95% CI; 1.13-5.83), p=0.024. These findings remained significant after adjusting for baseline symptom severity, surgical complications, duration of follow-up, hypertension and cardiovascular disease. Causes of death were equally distributed between the groups except for death due to malignancy which was not seen in iNPHDelayed but in 4 cases in the iNPHEarly group (p=0.044).
Conclusion: The present data indicates that early treatment with shunt surgery increases survival in patients with iNPH.
Disclosure: Dr Wikkelso receives honorarium for lecturing by Codman, Johnson & Johnson and Likvor AB. The other authors declare no conflicts of interest.

EPR1003

Post intervention outcomes of physical exercise training in elderly with mild to moderate dementia

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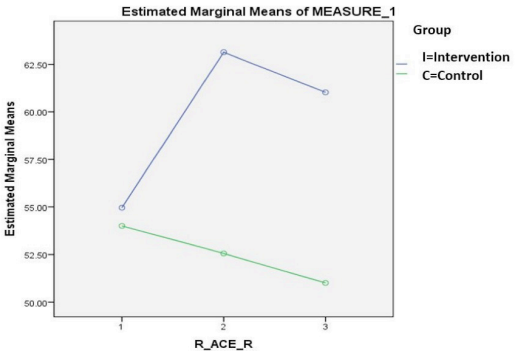
Background and aims: To study outcomes at 3 months post intervention by physical exercise training in addition to pharmaceutical therapy, in elderly diagnosed with mild to moderate dementia.

Methods: Longitudinal randomized study; 40 participants with mild to moderate dementia (AD, mixed or vascular), no major motor function impairment; randomized in 2 groups: with physical exercise training intervention(I): 5/7, 12 weeks (20 participants) and control group (C) (20 participants). We assessed cognitive and global evaluation scores (MMSE, Clock Drawing Test, R-ACE-R:Addenbrooke's Cognitive Examination/Romanian-version, Reisberg), functional tests (ADL, IADL), neuropsihiatric inventory (NPI-Q), GDS (Geriatric Depression Scale short version), QOL-AD (quality of life in AD) and SPPB (Short Physical Performance Battery). Follow-up after inclusion (T1) at week 12 from intervention (T2) and at 3 months post intervention (T3).

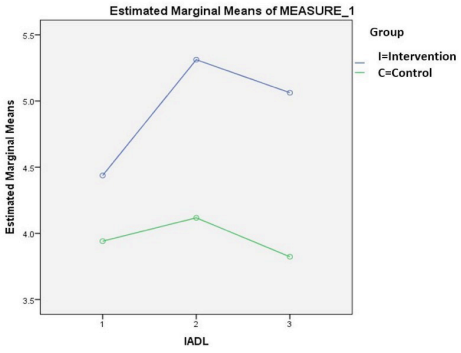
Results: Groups were homogenous at inclusion (T1), mean age: 79.35, 80% women, 90% from urban area. Statistically significant differences between groups at T3 were obtained (SPSS21.0) first by ANOVA (see table 1), than by MANOVA Repeated Measures for Clock Drawing Test [$F(5.14)=13.51$, $p<0.0001$], Total R-ACE-R [$F(2.30)=105.89$, $p<0.0001$, IADL [$F(2.30)=7.51$, $p<0.0001$], GDS [$F(5.14)=6.97$, $p<0.0001$] and QOL_AD [$F(2,30)=21.28$, $p<0.0001$]. No statisticaly significant differces for SPPB at T3.

Test	Group I Group C	N	Mean scores at T3	Standard Deviation	Std. Error Media	differences between groups at T3 (by ANOVA)
Clock Drawing Test	I	17	7.65	1.935	.469	[t(32) = 3,26, p < .005]
	C	17	5.29	2.257	.547	
F (verbal-fluency) (R-ACE-R subscore)	I	17	7.481	2.0789	.5042	[t(32) = 2,38, p < .001]
	C	17	5.979	1.5535	.3768	
VS (visuo-spatial) (R-ACE-R subscore)	I	17	11.47	2.902	.704	[t(32) = 3,23, p < .005]
	C	17	8.06	3.235	.785	
IADL (Instrumental ADL)	I	17	5.12	1.833	.445	[t(32) = 3,23, p < .005]
	C	17	3.82	1.811	.439	

Table1. Mean scores of tests at T3 (after 3 months post intervention) with statistically significant differences by ANOVA between I (intervention with Physical Exercise Training) and C (control) groups.



Evolution of R-ACE-R scores from T1 (inclusion) to T2 (12 weeks) and T3 (3 months post intervention) for I (intervention with Physical Exercise Training) and C (control) groups.



Evolution of IADL scores from T1 (inclusion) to T2 (12 weeks) and T3 (3 months post intervention) for I (intervention with Physical Exercise Training) and C (control)

Conclusion: Physical exercise training is beneficial for elderly with mild to moderate dementia, with positive results even 3 months post intervention, improving cognition, functionality, depression and quality of life scores. These outcomes decrease in time suggesting that a proper intervention should be supported for as long as possible in day care or specialized rehabilitation centers.

Disclosure: Nothing to disclose

EPR1004

Application of the 2018 NIA-AA research framework to an Italian large cohort of patients with cognitive impairment

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Background and aims: According to the 2018 NIA-AA research framework (2018-NIA-AA-RF), Alzheimer's disease (AD) is not defined by the clinical consequences of the disease, but by its underlying pathology, measured during lifetime by biological biomarkers. Our aims were to examine the 2018-NIA-AA-RF in the clinical scenario of a large cohort of patients with CI and to evaluate correspondence between cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers of ß-amyloid (Aß) deposition.
Methods: We retrospectively analysed 628 patients who underwent CSF analysis in our Centre and received a diagnosis according to their clinical follow-up and neuroimaging. Patients were divided as defined by the 2018-NIA-AA-RF, considering only CSF biomarkers. Prevalence of Normal, AD-continuum and Non-AD profiles in each clinical syndrome was calculated. When available, Aß pathology was evaluated also with 18F-Florbetapir PET and correlation between PET and CSF data was performed.
Results: Among patients diagnosed as AD, 87.3% were AD-continuum, whereas 11.3% Non-AD. The AD-continuum profile was found also in 12% of frontotemporal dementia, 40% of Lewy bodies dementia, 16% of atypical parkinsonism, and 32% of vascular dementia. Biomarkers profiles did not differ in amnestic e non-amnestic mild cognitive impairment. Half of the participants with negative amyloid-PET resulted AD-continuum according to CSF analysis, and no correlation between PET and CSF data was found.
Conclusion: The examination of the 2018-NIA-AA-RF in our clinical setting revealed an incomplete correspondence between the clinical syndromes and their underlying pathologic process. The partial agreement between CSF and PET data suggests that they are not perfectly interchangeable to quantify Aß burden.
Disclosure: Nothing to disclose

EPR1005

Aquaporin-4 genetic variation is associated with disease stage progression and pathology in patients with Alzheimer's disease

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Background and aims: It is hypothesised that the clearance of amyloid-ß (Aß), a pathological hallmark of Alzheimer's disease (AD), is facilitated by the glymphatic system via the aquaporin-4 (AQP4) water channels. The current study examined associations between genetic variations in AQP4 and risk of progression from mild cognitive impairment (MCI) to AD, annual rates of clinical decline, and amyloid uptake on PET imaging in AD.
Methods: Data was used from subjects in the Alzheimer's Disease Neuroimaging Initiative database who underwent [18F]florbetapir PET imaging, whole genome sequencing, and clinical assessment. Subjects had a diagnosis of MCI (n=469) or AD (n=232). Genetic variation in AQP4 was defined as minor allele carrier status on AQP4 single nucleotide polymorphisms (SNPs). Statistical analyses included cox hazard regressions, Mann-Whitney U tests and follow-up multiple regressions, and correlations.
Results: Minor allele carrier status on rs151244 was predictive of an increased risk of conversion from MCI to AD (p=0.042). Carrier status on rs2075575 was associated with a decreased annual rate of decline on a measure of global cognition (p=0.023), whilst carrier status on rs151244 was associated with an increased rate of annual decline on a measure of confrontation naming (p=0.038) and was correlated with increased [18F]florbetapir uptake in the isthmus cingulate cortex and subcortical brain regions (r=0.187 – 0.208, p=0.028 – 0.048).
Conclusion: These findings highlight the role of genetic variation at AQP4 in cognitive decline and risk of phenoconversion in AD. Deleterious genetic effects may be due to a failure to adequately clear amyloid from the brain by the glymphatic system.
Disclosure: Data collection and sharing for this project 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). Data used in preparation of this abstract was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report.

EPR1006

Magnetization transfer imaging in Alzheimer's disease

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Background and aims: Magnetization transfer ratio (MTR), an MRI derived measure which evaluates the magnetization exchange between tissue water and protons bound to macromolecules, has been associated with brain microstructural damage.We compared MTR in grey (GM) and white matter (WM) in patients with Alzheimer's disease (AD) and in normal elderly. Additionally, we analyzed the relationship between MTR and global cognition, assessed by Mini Mental State Examination (MMSE).

Methods: 91 patients with mild to moderate AD underwent clinical and MRI examination. Cognitive assessment was performed by MMSE. MRI protocol included a high resolution T1 weighted scan, a MT sequence and a FLAIR sequence for the assessment of white matter hyperintensities (WMH). Brain volumetry and regional segmentation were performed with FreeSurfer. MTR measures were generated for the whole cortex, lobes, hippocampus, deep gray matter structures, subcortical white matter, WMH and normal appearing WM (NAWM). An age-matched group of ninety-one normal elderly served as controls.

Results: No significant group differences were found in the distribution of sex, age and cardiovascular risk factors except for smoking. MTR was significantly reduced in NAWM (ß=-0.189;p=0.011), global subcortical WM (ß=-0.282; p<0.001), WMH (ß=-0.470; p<0.001),frontal WM (ß=-0.226;p=0.002), parietal WM (ß=0.265;p<0.001), temporal WM (ß=-0.221;p=0.003), occipital GM (ß=-0.224;p=0.001) of AD-patients (corrected for smoking and regional normalized volume). Diminished MTRs were significantly associated with poorer performance on MMSE in AD-patients in global cortex (ß=0.306;p=0.009), frontal GM (ß=0.327;p=0.006), occipital GM (ß=0.362;p=0.001), parietal GM (ß=0.267;p=0.024), temporal GM (ß=0.344;p=0.004), hippocampus (ß=0.351;p=0.003), global subcortical WM (ß=0.254;p=0.028), parietal WM (ß=0.228;p=0.044) and temporal WM (ß=0.291;p=0.006) after correction for sex, age, education and normalized regional volume.

Tab 3: Multivariate linear regression analysis[a] : MTR in AD-patients in comparison with healthy controls

	beta	SE	p value
NAWM	-0.189	0.001	**0.011***
Global subcortical WM	-0.282	0.001	**<0.001***
WMH	-0.470	0.004	**<0.001***
Frontal subcortical WM	-0.226	0.002	**0.002***
Occipital subcortical WM	-0.004	0.002	0.062
Parietal subcortical WM	-0.265	0.002	**<0.001***
Temporal subcortical WM	-0.221	0.002	**0.003***
Global cortical GM	0.005	0.002	0.95
Frontal cortical GM	-0.048	0.003	0.5
Occipital cortical GM	-0.224	0.003	**0.001***
Parietal cortical GM	-0.050	0.003	0.514
Temporal cortical GM	0.060	0.003	0.477
Hippocampus	-0.018	0.003	0.823
Thalamus	-0.225	0.004	0.168
Basal ganglia	-0.070	0.002	0.377
Caudate nucleus	0.300	0.005	0.031
Pallidus	0.037	0.004	0.788
Putamen	0.054	0.003	0.666

*after FDR (False Discovery Rate)
Beta = std. regression coefficient, SE= standard error, NAWM= normal appearing white matter, WM=white matter, WMH= white matter hyperintensities, GM=grey matter
[a] Adjusted for normalized regional volume and smoking

Multivariate linear regression analysis : MTR in AD-patients in comparison with healthy controls

Tab. 5 Multivariate linear regression analysis[a] : MTR and cognition, assessed by Minimental State Examination, in patients with AD

	beta	SE	p-value
NAWM	0.137	44.599	0.200
Global subcortical WM	0.254	40.771	**0.028**
WMH	0.026	13.879	0.807
Frontal subcortical WM	0.179	38.078	0.097
Occipital subcortical WM	29.625	0.192	0.068
Parietal subcortical WM	0.228	36.171	0.044
Temporal subcortical WM	0.291	25.112	**0.006***
Global cortical GM	0.306	33.058	**0.009***
Frontal cortical GM	0.327	18.734	**0.006***
Occipital cortical GM	0.362	13.577	**0.001***
Parietal cortical GM	0.267	15.514	**0.024**
Temporal cortical GM	0.344	18.362	**0.004***
Hippocampus	0.351	19.502	**0.003***
Thalamus	0.002	28.906	0.986
Basal ganglia	0.142	33.879	0.181
Caudate nucleus	0.193	17.683	0.060
Pallidus	0.101	27.247	0.356
Putamen	0.090	30.055	0.413

*after FDR
Beta = std. regression coefficient, SE= standard error, NAWM= normal appearing white matter, WM=white matter,WMH= white matter hyperintensities, GM=grey matter
[a]Adjusted for normalized regional volume, age, sex and years of education

Multivariate linear regression analysis : MTR and cognition in patients with AD

Conclusion: MTR reductions in WM and GM can probe AD-related microstructural changes and are associated with cognitive impairment in AD.

Disclosure: Nothing to disclose

EPR1007

Neuroanatomical changes in hypertensive patients may underlie increased risk of cognitive impairment.

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Background and aims: Hypertension is a known risk factor for cognitive decline in the older population. However, there is uncertainty regarding the pathophysiological basis of this association. We investigated the neuroanatomical differences between cognitively intact older adults with hypertension and normotensive individuals.

Methods: We identified 229 cognitively intact participants from the Alzheimer's disease (AD) Neuroimaging Initiative database. Grey matter volumes across a priori regions of interest, known to have a role in cognitive function, were compared between normotensive (n=93) and hypertensive (n=136) participants using voxel based morphometry analysis. The groups were matched for age, gender, parental history of AD and apolipoprotein E status. White matter lesion load and cognitive assessment scores were also compared between the groups.

Results: Hypertensive individuals were found to have volumetric reduction in the entorhinal cortices (P=0.01), left temporal pole (P=0.037), lateral occipital cortex (P=0.023), nucleus basalis of Meynert (P=0.022) and amygdala-striatal transition area (P=0.011) and the centromedial amygdala (P=0.019). Total ADAS-cog 14 scores revealed no difference between groups; however, hypertensive subjects had worse scores on spoken language (P=0.025) and word finding (P=0.004) subsections. There was no difference in white matter load volume between the groups (P=0.061).

Conclusion: Hypertensive older adults with no cognitive impairment have volumetric loss in the entorhinal cortex and nucleus basalis of Meynert, which are areas known to be associated with cognitive decline. Hypertensive related damage to these regions could underlie the increased rates of cognitive impairment in this population. These results further support the management of hypertension as a modifiable risk factor for cognitive decline.

Disclosure: Data collection and sharing for this project 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). Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report.

Ageing and dementia 2

EPR1008

Apolipoprotein E - risk or protective factor for Alzheimer's disease according to the new NIA-AA Research Framework guidelines? Analysis from patients of the Alzheimer Assessment Unit, Tor Vergata Hospital

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Background and aims: In the NIA-AA "research framework" Aβ determines whether an individual is in the "Alzheimer's continuum". Pathologic tau determines if someone who is in the AD continuum has AD. ApoE4 is the major risk factor for developing AD, while ApoE2 and ApoE3 are considered protective, however APOE genotype is not considered in staging AD.

Methods: Amnestic mild cognitive impairment patients were recruited and evaluated with MMSE, APOE genotype and CSF biomarkers.

Results: Based on NIA-AA classification patients were separated in A+/T- (n= 398) and A+/T+ (n=263). Cognitively unimpaired A-/T- were used as controls.

Among A+/T- patients, E2/E3 were 8.5%, E3/E3 63.8%, the E4 allele 27.7%. In the A+/T+, the E3/E3 genotype was present in 49.4% of patients, while patients expressing E4 allele represented 50.6% of the total. The differences in the distribution of APOE polymorphism in the three groups was statistically significant.

A subgroup of patients (n=183) was then clinically followed over 24 months. A+/T-E4+ patients showed slower cognitive decline respect to A+/T+ E3+, A+/T+E4+ and A+/T-E3+ patients.

Conclusion: APOE4 genotype was significantly more expressed in A+/T+ (AD) patients than in A+/T- (Alzheimer's pathologic change) group, and in the latter respect to controls. The A+/T- group represents, in terms of APOE genotype distribution, a different population. This data are in contrast with the NIA-AA2018 classification, which defines the A+/T- condition as part of Alzheimer's continuum. A+/T- group when associated to APOE4 genotype showed less cognitive decline, suggesting a positive relationship between ApoE4 and isolated Aβ-pathology on cognitive functions.

Disclosure: Nothing to disclose

EPR1009

Sex differences in Alzheimer's disease: current challenges and implications for clinical research

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Background and aims: Alzheimer's disease (AD) exhibits genotypic and phenotypic variability regarding risk factors, clinical manifestation, and disease progression. Sex differences appear to have a major influence but are insufficiently understood, thereby representing a potential hurdle for successful clinical trials. Thus, this work aims to provide an overview of sex differences in AD clinical trials with potential implications for clinical research and practice.

Methods: AlzForum Therapeutics Database was searched and recent published phase III clinical trials for mild cognitive impairment or AD [median publication year: 2013] were included (Fig. 1): results pertinent to 16 out of 210 drugs were analysed for sex demographics and sex stratification (Tab. 1). Additionally, a demographic analysis of sex differences in previous phase III clinical trials of approved AD drugs [median approval year: 2004] was performed (Tab. 2).

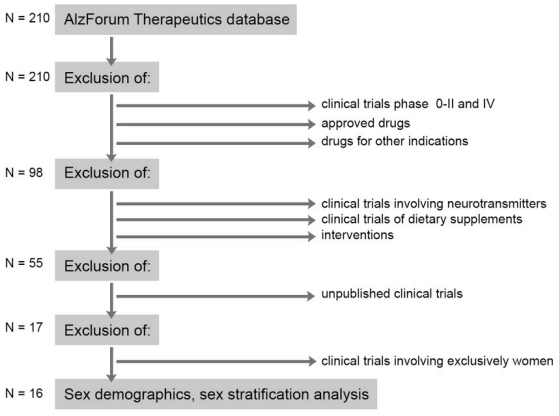

Figure 1. Phase III trials pertinent to unapproved AD drugs: selection process.

Drug	Male	Female	Female [%]	Sex stratified?	Reference
Solanezumab	897	1155	56.3	no	Doody et al. 2014
Solanezumab	898	1231	57.8	no	Honig et al. 2018
Semagacestat	714	820	53.5	no	Doody et al. 2013
Rosiglitazone	205	348	63.0	no	Gold et al. 2010
Rosiglitazone	1195	1627	57.7	no	Harrington et al. 2011
Rofecoxib, Naproxen	165	186	53.0	no	Aisen et al. 2003
Rofecoxib	325	367	53.0	no	Reines et al. 2004
Celecoxib, Naproxen	1368	1160	45.9	no	Lyketsos et al. 2007
Propentofylline	516	757	59.5	no	Rother et al. 1998
Prednisone	69	69	50.0	no	Aisen et al. 2000
Nilvadipine	190	308	61.8	no	Lawlor et al. 2018
LMTM	340	545	61.6	no	Gauthier et al. 2016
Linopirdine	167	215	56.3	no	Rockwood et al. 1997
Gantenerumab	No information on sex demographics.				Ostrowitzki et al. 2017
Gammagard (IVIg)	177	213	54.6	no	Relkin et al. 2017
Flurizan (tarenflurbil)	809	840	50.9	no	Green et al. 2009
Bapineuzumab	762	1155	60.3	no	Vandenberghe et al. 2016
Bapineuzumab	852	1305	60.5	no	Salloway et al. 2014
Verubecestat	874	1083	55.3	no	Egan et al. 2018
Total:	**10522**	**13385**	**56.0**		

Table 1. Unapproved AD drugs: analysed phase III trials.

Drug	Trial reference	Male	Female	Female [%]
Galantamine	GAL-INT-1	244	409	62.6
	GAL-INT-2	171	215	55.7
	GAL-USA-1	242	394	61.9
	GAL-USA-10	353	625	63.9
	GAL-95-05	212	342	61.8
	GAL-USA-11	261	462	63.9
	GAL-INT-10	347	618	64.0
Memantine	Study 9605	35	91	72.2
	MEM-MD-02	67	134	66.7
	Study 9403	37	47	56.0
	MEM-MD-50	189	487	72.0
Rivastigmine	Study 2320	398	792	66.6
	Trial 352	273	426	60.9
	Trial 303	297	428	59.0
	Trial 351	308	394	56.1
Donepezil	Study 326	533	901	62.8
	Total:	**3967**	**6765**	**63.0**

Table 2. Approved AD drugs: analysed phase III trials.

Results: The recent trials included 10,522 men and 13,385 women, thus 56.0% women. None of the studies were sex-stratified. The older approved drug trials included 3,967 men and 6,765 women, thus 63.0% women.

Conclusion: Although two-thirds of AD patients are female and sex implicates diagnostic and clinical differences, more recent clinical trials do not take this into account, while completed clinical trials of approved AD drugs were representative for the higher proportion of female AD patients. The reason could be lack of female enrollment or difficulty to retain women in long trials. The current lack of sex stratification potentially obscures the variability between men and women in AD, which might hinder the trials' ability to reflect a drug's clinical efficacy.

Disclosure: Antonella Santuccione Chadha is an employee at Roche Diagnostic.

EPR1010

Concordance between CSF biomarkers and amyloid PET imaging in clinical setting

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Background and aims: Decreased concentrations of amyloid β (Aβ) in the cerebrospinal fluid (CSF) and increased uptake of Aβ tracers in the brain on positron emission tomography (PET) are considered the most specific biomarkers of Alzheimer's disease (AD). Despite a high rate of concordance, results show discrepancies. Our aim was to investigate concordance between CSF amyloid measurements and amyloid PET scans.

Methods: We included N=76 subjects from a mixed cohort of demented and non-demented patients, who had undergone a lumbar puncture for CSF analysis and an amyloid PET with either Florbetapir (N=49) or Florbetaben (N=27) compounds. CSF specimens were assayed for Aβ, total Tau and phosphorylated Tau, using cut-offs for positivity of <600 pg/mL, >450 pg/mL and >61 pg/mL, respectively. Amyloid-PET scans were subdivided into positive and negative on the basis of quantitative measurement of global amyloid uptake in the brain.

Results: 45 out of 76 (59%) subjects showed concordant results between amyloid PET scans and CSF Aβ levels. Of these, 38 (84%) were positive and 7 (16%) negative exams. Among discordant cases, the majority (23/31 or 74%) had a positive PET scan in spite of normal CSF-Aβ levels (F+/A-). Interestingly, mean CSF concentration of Aβ in the F+/A- group was significantly different from F-/A- cases (683.3 vs 963.7 pg/mL).

Conclusion: In our cohort, overall concordance was 59% (Florbetapir 61%, Florbetaben 56%). According to our results, PET and CSF-Aβ measurements cannot be used interchangeably and PET imaging is particularly helpful for settling uncertain cases near the CSF-Aβ threshold.

Disclosure: Nothing to disclose

EPR1011

CSF BACE 1 levels correlate with other synaptic biomarkers in MCI due to Alzheimer's disease

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Background and aims: Neuropathological lesions in Alzheimer's disease (AD) are marked by amyloid plaques, neurofibrillary tangles and synaptic and neuronal loss. BACE1 protease starts the process of APP cleavage conducting to Aβ production. BACE1 is augmented in AD patients and is presynaptic. In MCI-AD patients, the concentrations of synaptic CSF biomarkers are enhanced and correlate with clinical outcome. The aim of this research was to correlate the levels of CSF BACE1 and synaptic biomarkers in MCI-AD, AD, non-AD patients and controls.
Methods: 246 individuals were included in the study. CSF samples were obtained after signed consents as part of the routine procedure in Paris and assessed in Gothenburg, in AD, MCI-AD, MCI non AD, other dementias and neurological controls. ELISA and mass spectroscopy were used to obtain, CSF levels of Aβ1-42, tau, ptau, GAP43, SNAP25, SNAP25aa40, synaptotagmin, neurogranin and BACE1
Results: In AD and MCI-AD, BACE1 levels were statistically enhanced compared to levels in MCI non AD, other dementias and controls. In AD and MCI-AD, BACE1 levels were comparable. This finding suggests that the BACE1 release in CSF is an early phenomenon over the evolution. Similar data were detected for the other synaptic biomarkers. A significant correlation was observed between BACE1 concentrations and the levels of all other synaptic biomarkers and tau, ptau, Aβ
Conclusion: CSF BACE1 concentrations are already increased in MCI-AD patients and could reflect brain enhanced levels leading to Aβ production as well as the slow process of synaptic demise responsible for the cognitive decline observed in MCI-AD patients.
Disclosure: Nothing to disclose

EPR1012

Association between volume of posterior nucleus basalis of Meynert and allocentric spatial navigation is mediated by thickness of entorhinal cortex

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Background and aims: Cholinergic deficit and atrophy of medial temporal structures are hallmarks of Alzheimer disease, causing early spatial navigation (SN) impairment. Aim of this study was to examine whether an association between allocentric SN and volume of the posterior nucleus basalis of Meynert (Ch4p) is mediated by thickness of the entorhinal cortex (EC) in individuals with subjective cognitive decline(SCD) and mild cognitive impairment (MCI).
Methods: 195 participants from the Czech Brain Ageing Study involving two groups (SCD=107, MCI=88) underwent structural MRI and SN assessment of allocentric, egocentric and mixed navigation using the human analogue of the Morris water maze.Ch4p volumes were computed using a mask based on a cytoarchitectonic map derived from a postmortem brain. Cortical thickness of the entorhinal cortex was obtained using FreeSurfer 5.3. Volumes were normalized to total intracranial volume. Associations were assessed using multivariate analysis of variance adjusted for sex, age and education. Covariate-adjusted causal mediation analysis was used to assess the mediation effect of EC thickness on association between the Ch4p and allocentric SN performance.
Results: Ch4p volume was associated with allocentric SN performance (β=-0.217, p=0.0015). EC thickness was associated with allocentric SN performance (β=-0.213, p=0.0019) and Ch4p volume (β=0.314, p<0.0001). We found partial mediation effect and total effect of EC thickness (proportion mediated=0.246; pmediation=0.026, ptotal=0.002).
Conclusion: The association between volume of the Ch4p and allocentric SN performance is partially mediated by EC thickness, providing a new insight into a complexity of human SN. Our findings underscore the importance of SN assessment in subjects at risk of Alzheimer's disease.
Disclosure: Nothing to disclose

EPR1013

Clinical utility of cerebrospinal fluid dementia biomarkers in the diagnosis of early-onset Alzheimer's disease in comparison to existing clinical diagnostic standards in the United Kingdom

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Background and aims: Diagnosis of Early-Onset Alzheimer's Disease (EOAD) can be challenging, particularly in early stages of the disease, due to the variability in cognitive phenotypes, a high burden of confounding affective comorbidity, and imaging findings with low diagnostic certainty. To ascertain the role of CSF dementia biomarkers in the diagnosis of EOAD, we conducted an analysis on data derived from our practice.
Methods: A retrospective study was conducted on 80 patients, <65 years, referred to the Cognitive Neurology Service at Maidstone Hospital who had CSF analyses, structurl imaging and neurocognitive testing.
Results: 40 received a diagnosis of EOAD (31 with dementia, 9 with MCI). 20 EOAD patients had no evidence of atrophy on structural MRI. The absence of atrophy on MRI had poor positive predictive value (PPV 42.2%) for ruling out the presence of dementia. Presence of selective hippocampal and medial temporal atrophy demonstrated very low sensitivity (23.8% and 25%) although high specificity (94.7% and 95%) for CSF biomarker-pattern for AD and for a clinical diagnosis of AD, respectively. Compared to Free Recall Memory testing, Recognition Memory demonstrated lower sensitivity but higher specificity for abnormal CSF biomarker and for a clinical diagnosis of AD.
Conclusion: Current diagnostic standards in the UK used in the assessment of Young Onset Dementia possess inferior diagnostic accuracies for EOAD as compared to the use of CSF dementia biomarkers. This should be considered in future guidelines as early accurate diagnosis could have significant implications on future practice in the advent of potential disease modifying treatment for AD.
Disclosure: Nothing to disclose

EPR1014

The pattern of inheritance and genetic status in early onset Alzheimer's disease and frontotemporal dementia

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Background and aims: Early-onset dementia (EOD) is conventionally considered to include patients with disease onset before 65 years of age. Alzheimer's disease (AD) and frontotemporal dementia (FTD) are two most common forms of degenerative EOD. Our aim was to investigate the patterns of inheritance and gene mutation status in consecutive degenerative EOD patients.
Methods: 207 consecutive patients diagnosed according to the current clinical criteria for AD and FTD spectrum were recruited from the Neurology Clinic, Clinical Centre of Serbia from 01.04.2012. until 01.04.2017.
Results: One third of AD and FTD patients had familial form of dementia, while the autosomal dominant inheritance pattern existed in 4.7% and 7.7% of probands with AD and FTD, respectively. The gene mutations were identified in 7.3% familial AD (a third of AD patients with autosomal dominant inheritance pattern) and in 1.2% sporadic AD patients; 25% familial FTD patients were gene mutation carriers (half of FTD patients with autosomal dominant inheritance pattern) along with 7% of sporadic FTD patients. Only 3.1% of the total population of AD and 10.3% of FTD possessed known gene mutations.
Conclusion: EOD does not appear to be a strongly inherited autosomal dominant condition. The majority of patients were sporadic. Common gene mutations do not explain the total autosomal dominant burden.
Disclosure: Nothing to disclose

Cerebrovascular diseases 1

EPR1015

Stroke onset to needle delay: where are these golden hours are lost? An Egyptian center experience

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Background and aims: The use of intravenous recombinant tissue plasminogen activator (IV r-tPA) in early acute ischemic stroke (AIS) management faces a lot of difficulties in developing countries due to lessened guideline development with consecutive pre- and intra- hospital delay.
Objectives: To identify the barriers facing the proper utilization of IV r-tPA for AIS in Tanta University Hospitals.
Methods: The study was conducted on 4124 AIS patients eligible to use IV r-tPA divided to group-I consisted of 442 arrived the hospital within less than 3.5 hour from the stroke onset and group-II consisted of 3682 arrived after 3.5 hours from the stroke onset. The former group was further subdivided to 238 received IV r-tPA (group-Ia) and 204 did not receive IV r-tPA (group-Ib) due to different obstacles.
Results: Main causes of prehospital onset to arrival delay were stroke unawareness, long travel time, incorrect believes, non-available neurologists, stroke onset during sleep and multiple causes (18.2%, 20.5%, 12.7%, 9.1%, 16% and 23.5% of cases respectively). Causes of non-administration of IV r-tPA in eligible patients prolonged door to needle time, financial restraints, minor strokes, unavailable beds and fear of complications (41.2%, 26%, 12.7%, 11.3% and 8.8%, respectively).
Conclusion: Increasing the chance of utilizing IV r-tPA for AIS patients' needs regular updating of the stroke chain of survival system to get the highest benefits from the available resources.
Disclosure: Nothing to disclose

EPR1016

Early screening of unilateral neglect (UN) in acute stroke: contribution of a new test

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Background and aims: UN is common in right-hemispheric stroke (about 85%) and leads to poor functional recovery. Because of its multidimensionality, its assessment remains difficult, unreproducible and time-consuming. The aim is to generate and validate a new test to quickly assess UN in patients with acute stroke in order to set up early appropriate rehabilitation.
Methods: The RUNS test (Rapid Unilateral Neglect Screening) covered 8 clinical fields of UN. To validate it, we included 70 healthy subjects and all consecutive patients with right-hemispheric stroke. Those with a history of cognitive impairment or other focal lesion were excluded. UN was assessed first by two physicians simultaneously using the RUNS, and after by a ergotherapist using the BEN from GEREN as reference test. Each assessment was blind from the others.
Results: Healthy subjects had 0.02/20 mean score. To this day, 42 acute stroke patients were included: none refuse the test. The mean between-examiners variability was 0.2 points. UN was underestimated with the NIHSS compared to the BEN (33% of false negative). The RUNS assessment was faster than the reference test (3.7 min vs 30.8 min, $p<0.001$). Matched results between the two tests were observed in 88%.
Conclusion: The RUNS is an acceptable and reproducible tool to assess UN in acute stroke in order to drive and improve rehabilitation. Through its quick and easy use, it can be integrated in other neurological fields. Validity, reliability, sensitivity and specificity will be subsequently available (patients recruitment still in progress).
Disclosure: Nothing to disclose

EPR1017

Effects of previous warfarin, NOAC or antiplatelet therapy on hemorrhage volume and mortality among patients with intracerebral hemorrhage

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Background and aims: Intracerebral hemorrhage (ICH) related to previous anticoagulation or antiplatelet therapy (APT) is increasing. Although prior APT-related ICH risk is controversial, warfarin has a recognized increased risk of ICH, hemorrhage volume expansion and death. Limited data on new oral anticoagulant (NOAC) related ICH are available in the literature. We aimed to compare hemorrhage volume and mortality in patients taking warfarin, NOAC or APT prior to ICH.
Methods: Retrospective analysis of all patients with ICH and prior anticoagulation or APT admitted at a regional hospital from May 2013 to December 2017. We divided the patients in three groups: warfarin patients, NOAC patients and APT patients. We compared the three groups using a univariate analysis.
Results: We included 137 patients: 21.1% were taking warfarin, 13.4% NOAC and 62% APT. NOAC patients had more dyslipidemia ($p=0.05$) and more atrial fibrillation ($p<0.01$) than APT patients; additionally, no significant differences were noted in hemorrhage volume and mortality between these groups. Warfarin patients had more atrial fibrillation ($p<0.001$), more renal disease ($p=0.03$), more infratentorial ICH ($p=0.027$) and less basal ganglia ICH ($p=0.045$) than APT patients. Warfarin patients had higher one-year ($p=0.001$) and cumulative mortality ($p=0.015$) than APT patients. No significant differences were noted when comparing NOAC patients to warfarin patients.
Conclusion: In this single-center cohort of ICH patients with prior antithrombotic therapy, we did not find significant differences in hemorrhage volume neither in mortality between NOAC and warfarin patients. Although warfarin patients had a higher one-year and cumulative mortality than APT patients, NOAC patients had similar outcomes compared to APT.
Disclosure: Nothing to disclose

EPR1018

Genome-wide association study and exome screen of ischemic stroke phenotypes in the Norwegian HUNT-Study

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Background and aims: Ischemic stroke has a partly genetic basis, and previous genome-wide association studies (GWAS) have identified several specific risk loci. We performed three GWAS of ischemic stroke phenotypes in the ethnically homogenouos, population-based Nord-Trøndelag Health Study (HUNT), Norway in order to validate previous findings, identify population-specific genetic risk loci, and to examine rare, exonic, functional variants not targeted by standard GWAS.
Methods: In total 71,860 participants from the population-based HUNT Study, Norway were genotyped using the Illumina HumanCoreExome array. Data were imputed with reference to 2,201 whole-genome sequences HUNT samples and to the Haplotype Reference consortium release 1.1, yielding >20 million variants for analysis. Based on diagnoses from hospital discharge and the Norwegian Stroke Register we identified 4,818 cases hospitalized with ischemic stroke. These were analyzed against 24,599 controls who were ≥70 years of age and did not self-report or have hospital admission for stroke. We subsequently performed separate analyses for cases with (n=937) and without (n=3,681) atrial fibrillation (AF).
Results: Previously reported risk loci for ischemic stroke showed association also in our study, validating previous reports. The strongest association was found for ischemic stroke with AF (rs2634074 on chromosome 4, p=3.71 x10-10), a locus previously associated to AF. We also identified several novel, potentially population-specific risk loci. No rare, genotyped, exonic variant reached genome-wide significance ($p <5x10-8$).
Conclusion: We validated previously reported genetic risk loci for ischemic stroke, and discovered several novel, potentially population specific risk loci. These will need to be replicated in independent studies.
Disclosure: The K.G. Jebesen center for genetic epidemiology is financed by Stiftelsen Kristian Gerhard Jebsen, Faculty of Medicine and Health Sciences Norwegian University of Science and Technology (NTNU) and Central Norway Regional Health Authority.

EPR1019

Psychiatric features of CADASIL: a pilot case-control study

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Background and aims: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) results from a NOTCH3 mutation and is the most common monogenic cause of cerebral small vessel disease (SVD). Psychiatric features, namely mood disorders, are known to be part of its clinical spectrum but have only been reported unsystematically. We aim to compare specific psychiatric features of a CADASIL cohort with non-CADASIL SVD patients.

Methods: We included patients followed in a tertiary hospital between July 2017 and December 2018 that carried a typical NOTCH3-gene mutation and age-and-sex matched SVD negative for NOTCH3 mutations. Patients were evaluated with Montreal Cognitive Assessment (MoCA), Mental Health Inventory (MHI), Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Young Mania Rating Scale and the Yale-Brown Obsessive-Compulsive Scale(Y-BOCS). Demographic data was collected. Groups were compared with Mann-Whitney tests.

Results: 29 CADASIL patients and 29 controls were enrolled. Groups were similar in terms of age (CADASIL 52.26±12.77 vs. Controls 50.96±12.04), education (12.0±4.6 vs. 12.0±4.7 years) and MoCA scores (24.8±5.2 vs. 23.3±3.8). CADASIL patients scored better in terms of global MHI (70.5±16.2 vs. 61.7±16.9; p=0.038) and its subscales anxiety (71.0±16.0 vs. 59.4±21.0; p=0.033), loss of control (78.9±19.6 vs. 70.9±19.9; p=0.048) and positive affect (59.3±16.6 vs. 51.1±14.8; p=0.048). Other scales' scores showed no significant differences between the two groups.

Conclusion: Patients with CADASIL are equally or even less affected by the studied psychiatric changes than matched controls with SVD. These changes(specifically mood disorders) are considered to be features of CADASIL, but they may be nonspecific.

Disclosure: Nothing to disclose

EPR1020

Subclinical peripheral arterial disease in patients with acute ischemic stroke: a study with an ultrasonography

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Background and aims: Peripheral arterial disease (PAD) is an advanced form of atherosclerosis. The presence of PAD affects the clinical outcome of ischemic stroke, which was defined by abnormal ankle brachial index (ABI). However ABI has no information of the location of atherosclerosis. Here, we investigated the clinical implication of PAD confirmed by lower extremity ultrasonography (LEUS) with consideration of its location.

Methods: Acute ischemic stroke patients who admitted to our stroke center received LEUS during admission and were enrolled. Patients with and without atherosclerosis observed from the LEUS was categorized to PAD+ and PAD- patients, respectively. PAD+ patients were further divided to those with PAD at the proximal part (femoral artery; PADP) and at the distal part (popliteal artery; PADD). The clinical outcome was compared between PAD+ and PAD- patients, and between PADP and PADD.

Results: Among 289 patients enrolled, PAD was observed from 108 (37.4%) patients. PAD+ patients were slightly older (72.2±9.7 vs 65.7±11.6, p<0.001) and had more significant carotid artery stenosis (32.4% vs 12.7%, p<0.001). There was no difference in terms of vascular risk factors or stroke subtypes. Patients with PAD+ had poor 3-month functional outcome (modified Ranken Scale: 2.5±1.8 vs 2.0±1.6, p=0.031). Significant carotid artery stenosis was more prevalent in those with PADP than PADD (32.4% vs 12.7%, p<0.001, respectively).

Conclusion: Our study suggested that subclinical PAD diagnosed based on LEUS is associated with poor functional outcome at 3 months after stroke onset. The presence of PAD, especially PADP was associated with the presence of significant stenosis at the carotid artery.

Disclosure: Nothing to disclose

EPR1021

CT perfusion changes without arterial occlusion in acute neurological deficits

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Background and aims: Perfusion CT (pCT) has become established in most stroke centres as a critical imaging tool to differentiate penumbra brain tissue from the infarct core. However, in the absence of arterial occlusion, interpretation of pCT may be challenging.

Methods: Retrospective, observational study analyzing patients admitted with acute neurological deficits (<24h) and pCT changes, without arterial occlusion, in our tertiary hospital (2017-2018). Patients were classified depending on pCT findings as hyperperfusion or hypoperfusion and clinical variables were analyzed.

Results: 53 patients were included, 7 with hyperperfusion and 46 with hypoperfusion, without significant differences in age or sex between groups. In patients hyperperfusion group, mean baseline NIHSS was 6±5.6, and 1 patient received alteplase. NIHSS at discharge was 1±1.7, and median mRS at 3 months was 0 (0-1). 2 (28.6%) patients had a final diagnosis of stroke and 5 (71.4%) of seizures. In hypoperfusion group, mean NIHSS was 4.9±4.9, and 15 (32.6%) patients received alteplase. No symptomatic bleeding was reported. 2 patients experienced worsening of their symptoms (NIHSS>4). NIHSS on discharge was 1.3±2.7, and median mRS at 3 months was 0 (0-4). Stroke was the final diagnosis in 39 (84.7%) patients, while migraine was in seven (15.2%).

Conclusion: In our experience, most patients with acute neurologic deficit without arterial occlusion and CTp changes had a good clinical outcome at 90 days, although a trend towards worse prognosis in hypoperfusion group was observed. Alteplase was safe in cases of hypoperfusion without vascular occlusion. CTp may be helpful differentiating stroke mimics (including seizures or migraine).

Disclosure: Nothing to disclose

Cerebrovascular diseases 2

EPR1022

C-reactive protein in patients with acute ischemic stroke treated with reperfusion therapies

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Background and aims: The aim of this study is to verify in a cohort of ischemic stroke patients, treated with thrombolysis and/or thrombectomy, the association between C-reactive protein (CRP) levels and outcome at 3 months, mortality and symptomatic intracranial haemorrhage.

Methods: 537 consecutive patients, treated with acute intravenous, endovascular and/or combined treatment, admitted in our Stroke Unit, from March 2005 to December 2017, were included in an open database. In our analysis, the median CRP value, between 24 and 72 hours after stroke onset, was 12mg/l.

Results: Patients with higher CRP values were more likely to experience worse functional dependence and death than those with lower CRP values (p<0.001) [TABLE 1].

In multivariate analysis increased levels of CRP were associated with poor outcome (modified Rankin Scale mRS 3-6) OR 1.93 (1.49-3.23) p=0.012 and 3-month mortality OR 2.58 (1.37-4.89) p=0.004 [TABLE 2]. We have not observed a statistical association between CRP values and symptomatic intracranial haemorrhage. Area under ROC curve for poor outcome (mRS 3-6) and CRP levels reached C-statistic value of 0.72 (95% IC 0.65-0.78), p<0.001 [ROC Curve image].

TABLE 1

TOTAL	*mRS 0-2* 270	*mRS 3-5* 175	*mRS 6* 91	*p*	*p* eta adjusted	*sICH*	*p sICH*
Men	180 (67%)	82 (47%)	46 (51%)	<0.001	<0.001	13 (62 %)	0.82
Diabetes	34 (13%)	35 (20%)	25 (28%)	0.001	0.002	8 (38 %)	0.019
Hypertension	142 (53%)	125 (71%)	74 (81%)	<0.001	<0.001	17 (81 %)	0.108
CAD	23 (9%)	30 (17%)	27 (30)	<0.001	<0.001	7 (33 %)	0.03
Previous Stroke	12 (4%)	13 (7%)	4 (4%)	0.383	0.118	0 (0 %)	0.62
Atrial Fibrillation	31 (12)	36 (21 %)	21 (23 %)	0.004	<0.001	3 (14 %)	1
Statine	49 (18%)	55 (31 %)	28 (32 %)	0.001	<0.001	9 (43 %)	0.06
Infections <48h	12 (4%)	25 (14%)	19 (21 %)	<0.001	0.006	9 (43 %)	<0.001
Infections >48h	22 (9 %)	70 (45%)	36 (47 %)	<0.001	<0.001	8 (38 %)	0.11
*Age**	67 (57-77)	72 (64-80)	78 (71-85)	<0.001	-	71 (63-79)	0.693
*NIHSS**	8 (5-11)	17 (12-22)	18 (14-22)	<0.001	<0.001	17 (10-23)	0.185
*Glucose**	120 (98-142)	125 (102-148)	139 (103-175)	<0.001	<0.001	145 (112-178)	0.03
Leucocytes	8.6 (6.6-10.6)	8.2 (6.5-9.9)	9.1 (6.6-11.6)	<0.001	<0.001	9.6 (7.7-11.7)	0.534
C-Reactive Protein	12 (8.8-15.2)	20 (8.8-28.8)	32(16.7-47.3)	<0.001	<0.001	23 (15-31)	0.830

* median

TABLE 1 - Univariate analysis

TABLE 2

Multivariate analysis

Poor outcome

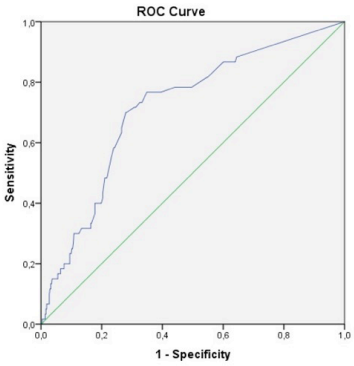
Poor outcome (mRS 3-6)	OR	95% IC		
NIHSS	1,22	1,17	1,27	<0.001
Age	1,31	1,08	1,59	0,006
24-72 hours CRP (log transformed)	1,93	1,49	3,23	0.012

3-month mortality

3 month mortality (mRS 6)	OR	95% IC		
NIHSS	1,14	1,08	1,20	<0,001
Age	1,99	1,46	2,71	<0,001
24-72 hours CRP (log transformed)	2.58	1,37	4,89	0,004

TABLE 2 - Multivariate analysis

ROC CURVE



Area under curve – poor outcome (mRS 3-6) and CRP levels C-statistic 0,72 (95% IC 0,65-0,78), p<0,001.

IMAGE - Area under ROC curve

Conclusion: C-reactive protein value is an independent prognostic factor for poor outcome (mRS 3-6) and 3-month mortality in patients suffering from acute ischemic stroke who received reperfusion therapies.

Disclosure: Nothing to disclose

EPR1023

Paroxysmal left sided numbness from extensive cortical siderosis in setting of spontenous resolving posterior parietal dural arteriovenous fistula

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Background and aims: Cortical siderosis is an increasingly recognized neuroimaging marker of amyloid angiopathy and may be associated with an increased risk of intracranial hemorrhage. Focal cortical siderosis can present with transient focal neurologic symptoms.
Methods: This case was evaluated at a tertiary referral medical center in the Southwest United States.
Results: A 67-year-old male presented with brief, recurrent paroxysmal spells of left-sided hemibody numbness. Investigations included a head CT, transthoracic echocardiogram, and transcranial doppler which were unremarkable. Brain MRI and MRA revealed extensive right hemispheric superficial siderosis secondary to a potential dural arterovenous fistula (AVF) seen predominantly within the right frontal and parietal vertex along the right cerebral hemisphere, although extended into the right temporal and occipital lobes. There was also involvement of the left cerebral hemisphere, along the vertex although to a lesser extent. Neurosurgery was consulted and he underwent a diagnostic cerebral angiography which confirmed a Type III dural AVF in the left posterior parietal paramedian location above the lambdoid sutures. The patient was placed on magnesium oxide to help with potential cortical spreading depression. Interestingly, he had one prior isolated episode which was investigated for stroke several months prior to his admission. He was ultimately diagnosed with transient ischemic attack. At 6-month follow-up with neurosurgery, he was symptom-free. A repeat brain MRA showed spontaneous resolution of the dural AVF but unchanged cortical siderosis. The mechanism was suspected self-obliterated dural AVF.
Conclusion: Our case highlights a unique presentation of cortical siderosis in the setting of a spontaneously resolving dural AVF.
Disclosure: Nothing to disclose

EPR1024

Acute ischemic stroke, atrial fibrillation and early DOAC-treatment: 30-day risk of recurrent ischemic stroke, intracranial hemorrhage in a multi-centre individual patient data meta-analysis

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Background and aims: We aimed to investigate recurrent ischaemic stroke (IS) and symptomatic intracranial haemorrhage (ICH) early after a recent cerebral ischaemia in patients with atrial fibrillation (AF) and their time course in relation to the initiation of direct oral anticoagulants (DOACs).
Methods: International, individual patient data meta-analysis from 8 cohort studies. We included patients with acute IS or TIA, non-valvular AF, and a DOAC within 30 days. We excluded patients with symptomatic intracranial haemorrhage (ICH) within 24 hours of endovascular recanalization therapy (n=2), or not started on a DOAC within 30 days. The endpoints were recurrent IS (re-IS) and ICH within 30 days.
Results: We included 2555 patients (median age: 77 years, IQR 70-84), of which 2460 had IS (96.5%). The median NIHSS was 5 (IQR 2-10). DOAC were started after a median of 5 days (IQR 2-10). Re-IS occurred, after a median of 6 days (IQR 2-15), in 37 patients (1.4%); 16 of these re-IS (43%) occurred prior to DOAC-start. ICH occurred, after a median of 10 days (IQR 7.5-14), in 11 patients (0.4%); 6 of these ICH (55%) occurred after DOAC-start.
Conclusion: Among patients with acute IS and AF, nearly half of the re-IS occurred prior to DOAC-start, i.e. were potentially preventable. The number of ICH potentially attributable to early start of DOAC was very low. Ongoing randomized clinical trials will show whether an earlier DOAC-start can further reduce the risk of re-IS while keeping the risk of ICH low.
Disclosure: Nothing to disclose

EPR1025

Remote ischemic post-conditioning protects against experimental stroke by modifying characteristics of endogenous extracellular vesicles

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Background and aims: Remote ischemic post-conditioning (rPostC) has been shown to reduce cell injury in experimental stroke models. Indeed, rPostC ameliorates post-stroke brain injury in rodents as has been shown by our group and others. Although previous data has shown that rPostC might affect post-stroke immune responses, the underlying mechanisms have not yet been understood. Since recent evidence suggests a role of extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) to be involved in the process of post-stroke immunomodulation, we analyzed whether or not rPostC affected secretion profiles of endogenous MSC-derived EVs.
Methods: Using a well-established protocol, adult male C57BL6 mice underwent middle cerebral artery occlusion (MCAO) followed by repeated cylces of non-traumatic rPostC. EVs were isolated from MSCs derived from stroke mice using polyethylene glycol precipitation. For some experiments, mice underwent MCAO and received EVs obtained from MSCs derived from mice that had been exposed to both MCAO and rPostC.
Results: Using nanotracking analysis, enrichment of EVs derived from stroke mice treated with rPostC was significantly increased in comparison to control stroke mice. Along with this, the TLR4 regulator miR-1906 was significantly increased in EVs derived from rPostC mice. Likewise, brain expression levels of TLR4 were significantly decreased in mice treated with rPostC, resulting in reduced post-stroke inflammatory levels. Interestingly, infusion of MSC-EVs derived from rPostC mice into mice exposed to MCAO only significantly improved neurological outcome in these animals.
Conclusion: rPostC mediates its protective mechanisms via modifying secretion patterns of MSC-derived EVs.
Disclosure: Nothing to disclose

EPR1026

Brain imaging signs and response to intravenous trombolysis in posterior circulation stroke

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Background and aims: Intravenous thrombolysis (IVT) is a standard treatment for both anterior circulation ischemic stroke (ACIS) and posterior circulation ischemic stroke (PCIS). The most of the previously published studies have been focused on basilar artery occlusion only. Our aim was to evaluate the predictors for a good clinical outcome and intracerebral haemorrhage (ICH) in the posterior circulation IVT patients from the initially performed CT / MR imaging.
Methods: The set consisted of 1644 consecutive acute ischemic stroke patients (1400 ACIS, 203 PCIS cases) who underwent IVT with rt-PA in standard dose 0,9 mg/kg. ICH classified according to ECASS I and 90-day clinical outcome assessed using the modified Rankin scale (mRS). Early ischaemic sings (tissue hypoattenuation, lesion size – PC ASPECTS, swelling, hyperattenuated artery) and pre-existing structural signs (old infarcts - PC ASPECTS, ASPECTS, leukoaraiosis– Fazekas, Swieten, atrophy) were assessed. The role of following factors was taken into account: presenting characteristics, common stroke risk factors, pre-medication, stroke severity, admission blood glucose level, blood before and during IVT, occlusion of arteries, recanalization rate, time to treatment.
Results: Good clinical outcomes (mRS0-2) were noted in 59.6% PCIS patients with mortality rate 13.3%. Intracerebral haemorrhage was noted in 8.3% and large haemorrhage (parenchymatous hematoma 1 and 2) was found in 2.4%. Some early ischaemic sings and pre-existing structural signs on initial CT/MR imagingcorrelates significantly with 90-day clinical outcome and risk for IVT.
Conclusion: Early ischaemic sings and pre-existing structural signs should be considered during the assessment of PCIS patients eligible to intravenous thrombolysis.
Disclosure: This study was conducted on an academic basis and was supported by the AZV CR - Health Research Council of the Czech Republic No. 17-29452A, and 17-30101A; by the institutional support of the Ministry of Health of the Czech Republic MH CZ – DRO (FNOL, 00098892) – 2017, 2018 and by a grant from the Internal Grant Agency of Palacky University IGA_LF_2018_017 and IGA_LF_2019_010.

EPR1027

Thrombectomy in acute ischemic stroke patients with NIHSS 5 or lower

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Background and aims: It remains unclear whether patients presenting with large vessel occlusion strokes and mild symptoms benefit from mechanical thrombectomy (MT). The purpose of the present study was to compare outcomes in acute ischemic stroke patients with intracranial vessel occlusions and minor stroke symptoms (NIHSS 5 or lower) treated with MT with those who treated with intravenous thrombolysis (IVT) alone.
Methods: In a prospective observational study at Oslo University Hospital, we assessed the outcome in patients admitted with minor stroke (NIHSS 5 or lower), premorbid modified Rankin Scale 0-2, middle cerebral-M1/M2, intracranial carotid, anterior cerebral or basilar artery occlusions. Groups receiving MT and IVT only were compared. Clinical outcome with improvement of NIHSS from baseline to 24 hours and modified Rankin Scale at 3 months were compared as well as MT safety. All patients were assessed with perfusion imaging before MT.
Results: Among 323 consecutive patients treated with EVT in 2017-18,48 (15.1%) had mild strokes with NIHSS 5 or lower at admission. Median NIHSS was 1 after 24 hours and median mRS after three months was 0 (range 0-3) in patients with NIHSS 5 or lower who were treated with MT. In the group of consecutive patients with NIHSS 5 or lower who were treated with IVT, median NIHSS after 24 hours was 1 (range 0-5) and median mRS 0 (range 0-3).
Conclusion: Thrombectomy in selected patients with low NIHSS is safe and can increase the chance of excellent clinical outcome after 3 months. Larger prospective studies are needed.
Disclosure: Nothing to disclose

EPR1028

Functional connectivity during task fMRI in patients with cerebral small vessel disease

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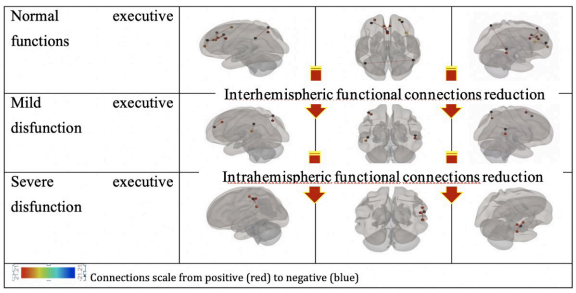
Background and aims: Cerebral small vessel disease (SVD) is a very prevalent condition associated with brain diffuse ischemic damage which can lead to fronto-subcortical circuits disruption and executive dysfunction (ED). The aim of our study was to evaluate functional connectivity in SVD patients with different severity of ED during task fMRI.
Methods: 51 patients (60±6.7 years) with SVD according to STRIVE criteria and 20 healthy volunteers (age and education matched) underwent fMRI on 3T scanner with serial count task. According to TMT B-A test results all patients were divided into three groups – normal executive functions (EF), mild and severe ED. Pre- and postprocessing of fMRI data were performed using SPM12 and CONN17.a.
Results: FMRI analysis showed reduction of interhemispheric functional connections in patients with mild ED and intrahemispheric functional connections in patients with severe ED between the structures of the salience and executive-control networks (fig. 1).



Functional connectivity in the salience and executive-control networks during task fMRI in SVD patients with different severity of ED

Conclusion: Gradual reduction of inter- and intra-hemispheric functional connections between the structures of EF networks in patients with SVD supposed to be fMRI equivalent of disconnection syndrome. The main cause of the disconnection syndrome in these patients is the white matter tracts disruption caused by SVD which disturbs communication between crucial neural networks responsible for normal EF. Multimodal structural and functional neuroimaging studies can reveal mechanisms of cognitive impairment in SVD and explain the clinical variation.
Disclosure: Nothing to disclose

Epilepsy 1

EPR1029

Can folic acid reduce risk of pregnancy complications in women with epilepsy?

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Background and aims: Women with epilepsy, especially those treated with antiepileptic drugs (AEDs), have an increased risk of pregnancy complications. Some studies suggest that in women in general, folic acid supplementation may reduce the risk of such complications. We aimed to investigate the effect of folic acid supplementation and maternal plasma folate concentrations on the risk of preterm birth, fetal growth restriction, and hypertensive disorders of pregnancy in women with epilepsy.
Methods: Women and singleton children in the Norwegian Mother and Child Cohort Study (MoBa) were included. Information was collected from MoBa questionnaires and linked with the Medical Birth Registry of Norway. Folate and AED concentrations were measured in maternal plasma in week 17-19 and in the umbilical cord after delivery (AED concentrations only).
Results: Women with epilepsy using AEDs (n=333) were compared with women without epilepsy (n=109,276). For women not using folic acid supplement periconceptionally, the adjusted odds ratio (aOR) for preterm birth in the epilepsy group compared to controls was 3.1 (95%CI 1.5–6.3, p=0.002); small for gestational age was 2.0 (95%CI 0.9–4.3, p=0.07); and any hypertensive disorder of pregnancy was 1.3 (95% CI 0.4–3.5, p=0.70). For women with folic acid supplementation periconceptionally, the corresponding aORs were 1.2 (95% CI 0.7–2.0, p=0.58); 1.5 (95% CI 1.0–2.4, p=0.058); and 1.7 (95% CI 1.1–2.6, p=0.017). The relationship between maternal plasma folate and pregnancy outcomes will be presented.
Conclusion: Periconceptional folic acid supplementation was associated with a lower risk of preterm birth in women with epilepsy using AEDs.
Disclosure: The study is part of a Nordic project funded by NordForsk.

EPR1030

Progressive encephalomyelitis with rigidity and myoclonus – case report

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Background and aims: Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a rare disorder of subacute onset presenting as limb and truncal rigidity, muscle spasms, brainstem signs, and hyperekplexia Life-threatening, it is part of the spectrum of stiff-person syndrome (SPS) with anti-glutamic acid decarboxylase (GAD) antibodies.
Methods: The case is presented of a previously healthy 38-year-old woman with a rapidly form of PERM developing over 7 months.
Results: A 38-year-old woman was referred for subacute onset of severe and progressive gait disturbance associated with painful muscular rigidity and spasms of the trunk and lower limbs, unstable posture, followed by involuntary movement of the legs with propagation to myoclonic limb jerks with hyperekplexia. Symptoms appeared 4 months before with few tonic-clonic seizures. Brain and spinal imaging were normal. EEG with theta-delta dysrythmia, evoked potential was normal. Tumor and bone markers were all in referent levels. Anti Aquaporin 4–IgA and IgM, Yo and NMDA receptors antibodies, IgM viral markers, antidsDNA, c-ANCA, ANA, cuprum, ceruloplasmin, were all negative. CSF was negative. Neuropsychological testing did not show any deflection. GAD (glutamate decarbox.) antibodies was 33.6 (<10), and she was also positive to Hu D and Ri antibodies. A first and second cycle of IVIG was completed with good clinical response.
Conclusion: This case displayed not only the clinical features of PERM, previously associated with both Hu and Ri antibodies, but also some of the features associated with GAD antibodies. This unusual combination of antibodies may be responsible for the particularly progressive course, but good response to IVIG.
Disclosure: Nothing to disclose

EPR1031

Cell specific DNA methylation and gene expression changes in early epileptogenesis

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Background and aims: Mesial Temporal Lobe Epilepsy (MTLE) is characterized by time dependent cellular changes of both neurons and glia, also referred as to epileptogenesis. No causative treatment options, apart from surgery, are available.
DNA methylation (DNAm) is a potentially important upstream mechanism in epileptogenesis and may serve as a novel therapeutic target.
This is the first study to investigate DNAm, gene expression and their possible correlation in neurons and glia separately.
Methods: We used the intracortical mouse model of MTLE, as described by Bedner P. et al, Brain, 2015.
At 24hrs post status epilepticus, hippocampi from 8 kainate- and 8 saline injected mice were extracted, shock frozen and separated into neurons (NeuN+) and glial (NeuN-) cells via flow cytometry. DNAm and gene expression changes were analysed via RRBS and RNA-sequencing.
Results: Our preliminary results hint at significant changes in both DNA methylation and gene expression in both neurons and glia at 24 hours after status epilepticus.
Conclusion: In our model, we found significant neuron and glia specific changes in both DNA methylation and gene expression in early epileptogenesis. These results refine current understanding of DNAm, gene expression and their possible correlation in epilepsy.
Disclosure: The EU-GliaPhD project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 722053.

EPR1032

Switching from carbamazepine and oxcarbazepine to eslicarbazepine: reasons and results

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Background and aims: Eslicarbazepine (ESL) is a third-generation antiepileptic drug (AED) approved as an adjunctive treatment for focal seizures. It belongs to carboxamide group, like other AEDs such as carbamazepine (CBZ) and oxcarbazepine (OXC). Switching from one of these old treatments to ESL is frequent for different reasons. The aim of this study it to evaluate the reasons and results of this switching.
Methods: This is a retrospective, non-interventional study of epileptic patients under conditions of normal clinical practice. All of them switched from CBZ or OXC to ESL for different reasons. Follow-up period was 12.7±0.5 months. Baseline demographics, reasons for switching, adherence, medical history, CBZ, OXC and ESL dosage, side effects and reasons for discontinuation were evaluated.
Results: A total 112 patients were enrolled (age 46.6±7.9 years old; 59 men, 53 women). Reasons for switching were: hyponatremia (30.4%), hypercholesterolemia (28.6%), lack of adherence (28.9%), lack of efficacy (11.6%) and other side effects (3.6%). Adherence was 91.9±9.1%, ESL dosage was 1102±135 mg/day. ESL was generally well tolerated, side effects were present in 13 patients (11.6%), and only 4 patients abandoned the treatment.
Conclusion: ESL seems to be an effective and well tolerated AED to treat patients previously treated with CBZ and OXC. ESL provides a better side effects profile than old carboxamides and it is hardly associated to hyponatremia and hypercholesterolemia, two of the most important reasons for this switching. This treatment option should be considered for those patients experiencing side effects with old carboxamides.
Disclosure: Nothing to disclose

EPR1033

Mortality in children born to mothers with and without epilepsy

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Background and aims: The overall mortality in young people with epilepsy is increased compared with persons without epilepsy and recent studies suggest that the mortality in the subset of women with epilepsy who are pregnant, is also very high. However, the mortality in offspring born to women with epilepsy has not been studied in great detail.
Methods: This was as cohort study of 1,845,911 singletons born in Denmark between 1987 and 2016. Exposure and outcome data was retrieved from Danish Health Registers. Maternal epilepsy was treated as time-varying exposure. Models were adjusted for calendar time, sex, and maternal psychiatric disease.
Results: Compared to the offspring of women without epilepsy, the Relative Risks (RR) of dying in offspring of women with epilepsy according to age were 1.68 (95% CI: 1.29-2.19) in children 1-28 days after birth, 1.42 (95% CI: 1.01-2.00) in children 29-365 days after birth, 1.36 (95% CI: 0.88-2.09) in children 1-4 years of age, 1.23 (95% CI: 0.78-1.93) in children 5-15 years of age, and 1.64 (95% CI: 1.22-2.22) in persons 16-30 years of age.
Conclusion: Offspring of women diagnosed with epilepsy have an increased mortality even after adjusting for co-morbid psychiatric disease. Further studies should clarify the reasons for this increased risk as well as identify preventive efforts to reduce the offspring mortality.
Disclosure: Dr. Christensen has received honoraria from UCB Nordic and Eisai

EPR1034

One-year clinical experience with brivaracetam in spain: Study of the efficacy and tolerability

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Background and aims: To analyse the efficacy and tolerability of brivaracetam (BRV) at 6 and 12 months in daily clinical practice conditions.
Methods: Patients who started on BRV in two different Spanish hospitals were included. Data were collected at 6 and 12 months. The following data were collected: age, gender, age at onset of epilepsy, seizure and epilepsy types, aetiology, monthly seizure frequency, adverse events and number of previous anti-epileptic drugs (AEDs). Response was analysed in 6 and 12 month completers and defined as a >50% reduction in monthly seizure frequency compared with the baseline
Results: 219 patients were included in the study. 90.6% fulfilled the criteria of drug-resistant epilepsy. After 6 months 203 patients (92.9%) continued on BRV therapy and 179 (81.7%) at month 12. Median number of AEDs used in the past was 5 and median number of concomitant AEDs was 2.84 (38.5%) patients switched from levetiracetam (LEV) to BRV. Median BRV dose was 150 mg and 200 mg at months 6 and 12, respectively. The responder rate was 38.8% and 39.2% at both follow up points. Seizure freedom at month 12 was achieved in 23 (10.6%). 41.7% of patients switching from LEV to BRV were responders at the last follow-up visit. Adverse events were experienced by 64 (29.2%) and resulted in withdrawal in 26 (11.5%). The most common adverse events were somnolence and dizziness.
Conclusion: In this long term study, BRV showed efficacy in 39.2% of patients in daily clinical practice conditions. Tolerability was good in this drug-resistant population.
Disclosure: Nothing to disclose

EPR1035

Retention in the first two months of eslicarbazepine acetate adjunctive treatment: data from four phase III clinical trials in adults with focal seizures

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Background and aims: To evaluate treatment discontinuation in the first two months of adjunctive eslicarbazepine acetate (ESL) treatment for focal seizures in adults.

Methods: This post-hoc analysis included data pooled from four phase III, randomized, double-blind, placebo-controlled trials (BIA-2093-301, -302, -303, -304; CNS Neurosci Ther 23,961-972,2017) of adjunctive ESL treatment in adults with focal seizures. ESL discontinuation was assessed during two treatment periods (1-30 days and 31-60 days), considering two main reasons for withdrawal: exacerbation of seizures (increased seizure frequency >100% vs baseline) and treatment-emergent adverse events (TEAEs) leading to treatment discontinuation; remaining reasons were grouped in category "other".

Results: Retention rates for 1-30 days vs. 31-60 days periods were: 94.3%, 99.0%, 90.4% and 83.9% vs. 90.1%, 94.4%, 87.0% and 76.5% in the placebo, ESL 400, 800 and 1200mg groups, respectively. ESL discontinuation due to exacerbation of seizures occurred very rarely in both time periods (≤1%). The incidences of TEAEs leading to treatment discontinuation during 1-30 days were 1.2%, 0.5%, 6.4% and 10.6% in the placebo, ESL 400, 800 and 1200mg groups, respectively with dizziness, ataxia, vomiting and nausea being the most frequent. Decrease in the incidence of TEAEs leading to treatment discontinuation was observed during 31-60 days period for ESL 800 and 1200 mg groups (1.4% and 4.7%, respectively); dizziness, nausea, diplopia and vomiting were the most frequent TEAEs.

Table 1. Treatment discontinuation rates

			ESL		
		Placebo	400 mg	800 mg	1200 mg
Total number of patients (N,(%))*		513 (100)	196 (100)	500 (100)	490 (100)
Time of discontinuation	Reason for treatment discontinuation				
1-30 days	Exacerbation of seizures**	1(0.2)	0	0	0
	TEAEs leading to discontinuation	6(1.2)	1(0.5)	32(6.4)	52(10.6)
	Other reasons	22(4.3)	1 (0.5)	16(3.2)	27(5.5)
31-60 days	Exacerbation of seizures	1(0.2)	2(1.0)	0	1(0.2)
	TEAEs leading to discontinuation	6(1.2)	6(3.1)	7(1.4)	23(4.7)
	Other reasons	15(2.9)	1(0.5)	10(2.0)	12(2.4)

*Safety population (pooled 301-304 studies)
** increased seizure frequency >100% vs baseline

Treatment discontinuation

Table 2: Safety analysis of TEAEs leading to discontinuation

			ESL		
Time of discontinuation		Placebo	400 mg	800 mg	1200 mg
1-30 days	TEAEs leading to discontinuation, N(%)*				
	Dizziness	2 (33.3)	0	16 (50.0)	22 (42.3)
	Ataxia	0	0	7 (21.9)	14 (26.9)
	Vomiting	0	0	6 (18.8)	13 (25.0)
	Nausea	0	0	4 (12.5)	12 (23.1)
	Headache	3 (50.0)	0	1 (3.1)	3 (5.8)
	Partial seizures	2 (33.3)	0	0	0
31-60 days	TEAEs leading to discontinuation, N(%)*				
	Dizziness	1(16.7)	0	2(28.6)	11(47.8)
	Nausea	0	0	1(14.3)	11(47.8)
	Diplopia	0	1(16.7)	0	5(21.7)
	Vomiting	0	0	1(14.3)	5(21.7)
	Partial seizures	2(33.3)	0	0	0

*At least 20% of patients in any treatment group

Safety analysis of TEAEs leading to discontinuation

Conclusion: Retention rate was high (≥77%) during the first two months of adjunctive ESL treatment. The overall incidences of TEAEs leading to treatment discontinuation decreased over two months period.

Disclosure: JM, RC, NS, HG: Bial Portela & Ca

Epilepsy 2

EPR1036

Epilepsy and driving: differences in law enforcement and behaviour in Europe

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Background and aims: To describe the driving behaviour of Spanish epileptic patients. To compare it with recently available published data in German population (Willems et al, 2018). To analyze differences between laws in both countries and European Directives.
Methods: A prevalence study of 135 epilepsy patients having a medical follow up at our Neurology unit. They filled in a self-administered anonymous questionnaire.
Results: In our population (the mean age was 44.4 years and 35.8% were males), 47.4% of epileptic patients had a driving license. Among them 68.8% usually drove. 50.4% of patients had uncontrolled epilepsy. 14.7% of patients with uncontrolled epilepsy recognized they kept driving, even one of them worked as professional driver. Only 21.5% of epileptics declared to know the law governing them in driving.
Conclusion: In Spain there are less epileptic patients who have a driving license, with a similar amount of patients with uncontrolled seizures. The percentage of patients with uncontrolled epilepsy who drove was similar (14.7% and 15.1% respectively in Spanish and German population). In any case, a relevant amount of epileptic patients without seizures control admitted driving, infringing the law.
Spanish law is as restrictive or even more than German law, depending on the situation (a table will be shown in order to summarize requested time without seizures to drive in each case in both countries). European directives lead comparables laws in Spain and German. Nevertheless, in Spain a system supported by the health service would be necessary in order to evaluate the ability to drive and inform the epileptic patients.
Disclosure: Nothing to disclose

EPR1037

The seizure reduction effect of Vagus Nerve Stimulation (VNS) increases over time

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Background and aims: Implantation of VNS is a treatment option which is offered to people with pharmacoresistant epilepsy who are not suited to or have failed epilepsy surgery. Previous studies of the effect of VNS show responder rates (≥50% reduction of seizure frequency) in 30-50% of the patients. However, many studies have small number of patients or short follow-up. The aim of this study is to evaluate the long-term effect of VNS in patients who were operated between 1993 and 2012.
Methods: Data was collected from the VNS quality register at the Special Hospital for epilepsy (SSE) in Norway. Descriptive methods and cross-tabulation with chi square testing were used for the analysis.
Results: 463 patients (47.2% children <18 years) were implanted with VNS in the designated time period, whereas 320 (69%) had >5 years of follow-up. Mean duration of epilepsy was 16,7 years (1-65). Mean age at implantation was 23 years (1-67). 54% of the patients had focal, 43% had generalised and 3% had epilepsy which could not classified. Responder rates after 6 months and 5 years was respectively 30% and 53.1% ($p<0.0001$). Among patients who didn't change or reduced their medication while being treated with VNS (n=130) had a responder rate of 63.8% at 5 years compared to 46.1% among patients who changed their medication. The percentage of seizure free patients increased significantly in both groups between 6 months and 5 years.
Conclusion: VNS is a good treatment option for patients with pharmacoresistant epilepsy. The effect increases over time.
Disclosure: Nothing to disclose

EPR1038

The role of miR-146a, a negative regulator of inflammation in mesial temporal lobe epilepsy

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Background and aims: Neuroinflammation is emerging as an important epileptogenic process and its regulatory mechanisms may be of particular interest in the development of new treatments. MiR-146a, a dominant negative regulator of inflammatory responses, has been widely described as upregulated in Mesial Temporal Lobe Epilepsy (MTLE) patients. Expression and/or function of miR-146a is highly influenced by genetic variations, some of which have already been associated with MTLE susceptibility. We sought to study the importance of miR-146a in MTLE development, analysing its circulating levels and rs57045329 and rs2910164 polymorphisms in a Portuguese population.

Methods: A cohort of 208 MTLE patients (116F, 92M; 44.9 12.2 years, age at onset=13.5±10.1; 111 with FS antecedents) and 275 healthy controls was studied. MiR-146a circulating levels in 89 MTLE patients and 81 healthy controls.

Results: Genotypic frequencies of rs2910164 (GG: 54.4% vs 57.9%; GC: 44.2% vs 36.0%; CC: 4.3% vs 6.9%) and rs57045329 (AA: 92.3% vs 94.6%; AG: 7.7% vs 5.1%; GG: 0.0% vs 0.0%) polymorphisms were similar in MTLE patients and controls. No correlations were observed with clinical data. MiR-146a serum levels were 2 fold higher in MTLE-HS patients than in controls (p=0.001).

Conclusion: It has been argued that the miR-146a upregulation in MTLE is a compensatory mechanism to overcome the exacerbated inflammatory response caused by seizure-induced damage. Our genetic and expression results support that hypothesis suggesting that in MTLE miR-146a overexpression is not genetically determined but may rather be a reflex of the ongoing inflammatory responses. This could pave new avenues for seizure treatment.

Disclosure: Financial Support: BICE Tecnifar

EPR1039

Overactivation of the inflammasome / ILβ axis in the hippocampus and anterior temporal cortex of drug-resistant mesial temporal lobe epilepsy (MTLE) patients

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Background and aims: Mounting evidence suggests that neuroinflammation is paramount in epileptogenesis. We have already shown that MTLE-HS have a genetic predisposition to produce higher IL-1β. This genetic evidences have been proven in brain tissue where activated HLA-DR+ microglia and IL-1β overexpression was observed (Leal et al., 2017)

Seizure-induced cell death leads to the endogenous release of HMGB1 and ATP resulting in inflammasome activation and IL-1β production via TLR4 and P2X7R activation, respectively.

Methods: Here, we investigated the genetic and epigenetic expression of inflammasome / IL-1β axis key players in a cohort of 342 controls and 196 MTLE-HS patients, 24 of which underwent amigdalo-hippocampectomy.

Results: TLR4 and P2X7R are overexpressed in the hippocampus and anterior temporal lobe of MTLE-HS patients. We detected a reduction in serum levels of the miR-22, a P2X7R expression suppressor in drug-refractory MTLE-HS patients.

Conclusion: Our data suggest that the pathogenesis of human MTLE-HS is associated with a pro-inflammatory profile underlying significant changes in the purinergic signalling pathway. Additionally, we showed that these alterations are not limited to the hippocampal formation, but are also evident in the anterior temporal lobe which might facilitate seizures propagation. Knowing that the mechanisms that modulate the complex interplay between the purinergic signalling cascade, neuroinflammation and neurotransmission require further investigations, the results presented here prompted us to hypothesize that targeting these pathways may constitute a valuable novel approach for the treatment of refractory MTLE.

Disclosure: Financial support: BICE Tecnifar

EPR1040

Retinal structural changes in photosensitive epilepsies: evaluation with ocular coherence tomography

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Background and aims: Photosensitivity (PS) is the most frequently reflex trait associated with Genetic Generalized Epilepsies (GGE). The role of the retina and the retinal nerve fiber layer (RNFL) thickness in the mechanisms underlying PS has been previously explored, mainly in relation to the use of antiepileptic drugs.
Objective of the study is to assess RNFL thickness in the peripapillary and macular areas in the eyes of patients with photosensitive epilepsy as compared to a group of controls by means of ocular coherence tomography (OCT).
Methods: We enrolled patients with a diagnosis of epilepsy with documented photosensitivity. For all patients, a 21-channel EEG recording was performed using a standard intermittent photic stimulation protocol.
All patients underwent OCT examination using OCT-HD (Cyrrus 5000, Carl Zeiss Meditec, Dublin, CA, USA) with OCT-4 software. The following parameters were measured for right eye (RE) and left eye (LE): RNFL thickness of the peripapillary area, single quadrants analysis, foveal thickness (FT), macular volume (MV), ganglion cell layer (GCL) and choroidal thickness (CT).
Results: 30 patients with photosensitive epilepsy and 28 controls were enrolled. Mean age was 30.2±9.1 years in patients [M=8 (26.7%)] and 30.5±3.7 in controls [M=7 (25%)]. Significant differences were found between patients and controls in the following parameters: for RNFL (in RE 97.8±15.7 vs 107.3±7.7; p=0.01; in LE 99±14.6 vs 108.1±7.6; p=0.03), MV (in RE 9.6±0.5 vs 6.9±0.3; p<0.001; in LE 9.6±0.51 vs 7±0.4; p<0.001), GCL (in RE 81.1±5.5 vs 86.5±4.2; p=0.0001; in LE 82.6±5.0 vs 86.2±5.1; p=0.0087).
Conclusion: The results of our study show significant retinal alterations in patients with photosensitivity.
Disclosure: Nothing to disclose

EPR1041

Immunophenotyping of autoimmune epilepsy by mass cytometry

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Background and aims: The concept of 'autoimmune epilepsy' is not well-defined. Seizures observed with forms of autoimmune encephalitis are considered a prototypical example of an immune-mediated epilepsy and can respond well to immunotherapy. However, the clinical significance of autoantibodies in more common forms of epilepsy has not been clearly established, and an evidence base to support the use of immunotherapies in such patients is lacking. We hypothesise that a phenotypic signature of peripheral blood leucocytes could distinguish between true autoimmune and non-autoimmune epilepsy – we aim to detect this with mass cytometry, a novel single-cell proteomic method.
Methods: Sera and peripheral blood mononuclear cell (PBMC) samples were obtained from epilepsy patients and controls. Sera were screened for autoantibodies on cell-based assays and primary neuronal cultures. Cryopreserved PBMC samples were stained with a 29-antibody panel targeting all major immune cell populations prior to mass cytometry. Data was analysed using a standardised, supervised method (Gemstone) and with unsupervised clustering-based methods, including DepecheR.
Results: Sera and PBMCs from 50 individuals (epilepsy patients and healthy controls) have been collected. Antibody screening is complete. Mass cytometry experiments will be completed by March 2019. Figure 1 is an example of a 2-dimensional representation of mass cytometry data for one of the healthy control subjects.

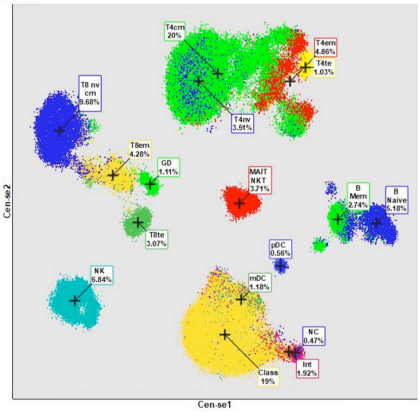

Figure 1: Cen-se' map (dimensionality reduction plot) of PBMCs from a healthy control subject shows good separation of the major immune cell types, including different developmental stages of B and T cell subsets.
B mem, memory B-cells; *B naïve*, naive B-cells; *Class*, classical monocytes; *Gd*, gamma delta T-cells; *Int*, intermediate (transitional) monocytes; *MAIT NKT*, mucosal associated invariant T-cells & natural killer T-cells; *mDC*, myeloid dendritic cells; *NC*, non-classical monocytes; *NK*, natural killer cells; *PBMC*, peripheral blood mononuclear cells; *pDC*, plasmacytoid dendritic cells; *T4 cm*, central memory CD4 T-cells; *T4 em*, effector memory CD4 T-cells; *T4 nv*, naive CD4 T-cells; *T4 te*, terminal effector CD4 T-cells; *T8 em*, effector memory CD8 T-cells; *T8 nv cm*, naive & central memory CD8 T-cells; *T8 te*, terminal effector CD8 T-cells.

Figure 1

Conclusion: The immunocellular phenotype of autoimmune epilepsy is unexplored. Mass cytometry is a method well-suited to identifying distinguishing immunophenotypic characteristics. This work could aid diagnostic clarification and decision-making regarding immunotherapy, potentially improving clinical outcomes.
Disclosure: Supported by the University of Oxford-UCB Alliance.

EPR1042

Interleukin 18 and its binding protein IL-18Ba – possible new markers of low-grade systemic inflammation in epilepsy patients.

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Background and aims: Inflammation seems to have an important role in epileptogenesis independent of the underlying cause. Nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome produces IL-1β and IL-18, and whereas IL-1β has been suggested to be involved in epileptogenesis, there are no data on IL-18. The purpose of the study was to assess if IL-18 and its binding protein IL-18Ba could be related to the presence of epilepsy.
Methods: In our cross-sectional study we analysed circulating levels of IL-18 and IL-18Ba among 121 epilepsy patients, of all types, and 80 healthy controls. Participants completed questionnaires on epilepsy and comorbidity. Three different antiepileptic drugs (AEDs) were used by patients participating in the study: carbamazepine (CBZ) (n=55), lamotrigine (LTG) (n=51), levetiracetam (LEV) (n=15). Regression models were used to analyse associations with risk factors.
Results: The patients had significantly higher level of IL-18 (p=0.003) and IL-18Ba (p=0.008) in comparison to the control group. The groups differed in sex, age and weight, but even after correction for these potential confounders both markers were still significantly elevated in the patient groups. Subgroup analyses showed higher level of both IL-18 (0.019) and IL-18Ba (0.029) in LTG treated patients, and IL-18 (0.016) in CBZ group. Multivariate regression showed no association between level of IL-18 and IL-18Ba related to epilepsy duration, severity or seizure type.
Conclusion: Our findings show significantly higher concentrations of IL-18 and IL-18Ba among epilepsy patients regardless of the epilepsy type and AED suggesting low-grade systemic inflammation involving IL-18 mediated mechanisms in these patients.
Disclosure: Nothing to disclose

Headache and pain 1

EPR1043

Impact of fremanezumab on headache-related disability in patients with migraine and documented inadequate response to 2-4 classes of migraine preventive medications in the international, multicentre, randomised, placebo-controlled FOCUS study

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Background and aims: Migraine is the second leading global cause of years lived with disability. Fremanezumab, a fully-humanised monoclonal antibody (IgG2Δa) that selectively targets calcitonin gene-related peptide (CGRP), has proven efficacy for preventive treatment of migraine in adults. The FOCUS study of fremanezumab was the first and largest study of a migraine preventive treatment in a difficult-to-treat population of adults with episodic or chronic migraine (EM or CM) who had documented inadequate response to 2-4 classes of migraine preventive medications. Headache-related disability, assessed using the 6-item Headache Impact Test (HIT-6) and Migraine Disability Assessment (MIDAS) questionnaire, was an exploratory endpoint.
Methods: During 12 weeks of double-blind, placebo-controlled treatment, patients were randomised (1:1:1) to monthly fremanezumab (Month 1: CM, 675mg; EM, 225mg; Months 2 and 3: 225mg), quarterly fremanezumab (Month 1: 675mg; Months 2 and 3: placebo), or matched monthly placebo. Changes in HIT-6 and MIDAS scores from baseline during the 4 weeks after administration of the third dose of study drug were compared using analysis of covariance models.
Results: 838 patients were randomised. With both fremanezumab regimens, reductions from baseline in the disability score, as measured by both HIT-6 and MIDAS, during the 4 weeks after the third dose of study drug were significantly greater compared with placebo (all P≤0.0002; Table).

Table. LSM (SE) Change From Baseline and LSMD (SE) in Change From Baseline Versus Placebo in Disability Scores Measured by HIT-6 and MIDAS During the 4 Weeks After the Third Dose of Study Drug

	Placebo (n=278)	Monthly fremanezumab (n=283)	Quarterly fremanezumab (n=276)
Disability score measured by HIT-6			
LSM (SE) change from baseline	−2.2 (0.54)	−6.1 (0.54)	−5.2 (0.55)
LSMD (SE) vs placebo		−3.8 (0.58)[a]	−3.0 (0.58)[a]
Disability score measured by MIDAS			
LSM (SE) change from baseline	−7.0 (3.24)	−24.7 (3.24)	−19.7 (3.29)
LSMD (SE) vs placebo		−17.7 (3.43)[a]	−12.7 (3.45)[b]

LSM, least-squares mean; SE, standard error; LSMD, least-squares mean difference; HIT-6, Headache Impact Test; MIDAS, Migraine Disability Assessment.
[a]*P*<0.0001 versus placebo (based on analysis of covariance model).
[b]*P*=0.0002 versus placebo (based on analysis of covariance model).

Table

Conclusion: Monthly or quarterly fremanezumab was associated with significant improvements in headache-related disability, based on HIT-6 and MIDAS scores, versus placebo in patients with migraine and documented inadequate response to 2-4 classes of migraine preventive medications.
Disclosure: This study was funded by Teva Pharmaceuticals.

EPR1044

Pain attributed to a lesion or disease of nervus intermedius: clinical characteristics of a series of 12 new cases

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Background and aims: Pain attributed to Nervus Intermedius (NI) is a rare disorder. International Classification of Headache Disorders (ICHD-III) classifies it as NI neuralgia or painful NI neuropathy depending on the predominant presence of pain paroxysms or continuous pain. NI Neuralgia may be related to vascular compression and painful NI neuropathy attributed to herpes zoster. We aimed to describe characteristics of a series of patients attended in a tertiary hospital.
Methods: From January 2008 we have registered all patients attended in an outpatient headache clinic. We prospectively gathered their characteristics and headache codified accordingly to ICHD. We have retrospectively reviewed patients with pain attributed to Nervus Intermedius from January 2008 to January 2019.
Results: We present 12 patients (3 males, 9 females) out of 6161 (0.19%) included in our registry. Magnetic resonance imaging was obtained in all cases with no vascular compression and contrast enhancement of geniculate ganglion in one patient. Mean age at onset was 53±19.6 years (29-94). In four cases there was an oppressive background pain with intensity of 4.7±0.5 (4-5) (NI neuropathy phenotype), and in 8 stabbing paroxysms rated as 7.2±1.5 (5-9) (NI neuralgia phenotype). In five cases (3 presented as neuralgia and 2 as neuropathy) facial paresis appeared, but only in one a herpetic eruption was observed. In 9 patients medical therapy was needed and in 7 (4 neuralgias and 3 neuropathies), amitriptyline achieved a total response.
Conclusion: In our series, pain related with NI is not attributed to vascular compression or herpes zoster. Amitriptyline is an effective therapy regardless of phenotype.
Disclosure: Nothing to disclose

EPR1045

Anatomical landmarks for localizing the otic ganglion, a possible new treatment target for headache disorders

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Background and aims: The otic ganglion (OG) is a parasympathetic ganglion located in the infratemporal fossa under the foramen ovale, adjacent to the medial part of the mandibular nerve. Parasympathetic innervation of intracranial vessels from the OG has been shown in animal and human models. Evidence suggests that the OG plays an important role in the cranial vasomotor response. We review the evidence that positions the OG as a viable target for headache disorders. The OG is a small structure not detectable on medical imaging. The foramen ovale is easily identifiable on CT-scans and the mandibular nerve on MRI. The position of the OG may be predicted if the mean distance from the foramen ovale is known.
Methods: 21 high definition photographs of 21 infratemporal fossae from 18 cadavers were analysed. The distance between the inferior edge of the medial part of the foramen ovale to the OG was measured.
Results: Four photographs of infratemporal fossae of 4 patients were excluded due to the inability to localize the inferior edge of the foramen ovale. A total of 15 infratemporal fossae from 17 patients were measured. The mean distance from the foramen ovale to the OG was 4.5 mm (SD 1.7), range 2.1 – 7.7 mm.
Conclusion: We have described the average distance from the OG to an easily identifiable anatomical landmark that is visible in CT-scans, the foramen ovale. This anatomical study may aid in the development of strategies to localize the OG in order to explore its role as a therapeutic target for headache disorders.
Disclosure: Nothing to disclose

EPR1046

Effects of on-call work on residents' headache

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Background and aims: 24 hours on-call work requires the physician to work at any time during this period. It involves sleep deprivation and it is a stress factor. Our aim is to assess the effects of on–call work on primary headaches in medical residents (MR).
Methods: We collected demographic data from MR in their first year of residency (age, sex, history of headache) who had never performed on-call work before and we administered the Migraine Disability Assessment (MIDAS) questionnaire, the Headache Impact Test (HIT–6) questionnaire, the Hospital Anxiety and Depression Scale (HADS) and the Pittsburg Sleep Quality Index (PSQI) before and six months after the beginning of on-call work.
Results: 43 MR completed the study. 67.4% were women with mean age of 25.7 [±2] years. 20.9% had history of migraine and 39.5% had history of tensional headache, no history of cluster headache was found. Before starting on – call work the mean scores were 9.4 [±7.7] in PSQI, 7.4 [±5.2] in HADS, 44.9 [±11.59] in HIT-6 and 2.5 [±2.5] in MIDAS. Six months after, mean scores were 9.4 [±6.8] in PSQI, 10.8 [±9.6] in HADS, 43.7 [±14.27] in HIT-6 and 10.42 [±12.5] in MIDAS. A statistically significant worsening in HADS scores was found (p=0,001). An increase in migraine–related disability was also found, increasing MIDAS score from 2.5 (little or no disability) to 10.42 (mild disability).
Conclusion: There was an increase in depressive and anxious symptoms and an increase in migraine – related disability in medical residents after starting 24 hours on-call work.
Disclosure: Nothing to disclose

EPR1047

Oral preventive response in nummular headache: an observational study in a series of 127 patients

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Background and aims: Nummular headache (NH) is a primary headache included in the International Classification of Headache Disorders (ICHD). No randomized control trials have been done. The possible therapeutical options include neuromodulators, tricyclic antidepressants, OnabotulinumtoxinA. We aim to describe responses to oral preventives in a NH series.

Methods: Observational descriptive study with a prospective cohort design. We included patients diagnosed of NH according to ICHD criteria that received oral preventive treatment. The study period was from January 2008 to January 2018, including all consecutive cases evaluated in our Headache Clinic. We present data as percentage, median and standard deviation. We considered response if the reduction of headache-days per month was at least 50%.

Results: During the study period 5,515 patients were evaluated and 127 included. Age of onset was 50.3 (18.7) and 68.5% were female patients, with a mean evolution time of 32.6 months (72.4). In 69.2% of patients, no prior preventive treatments had been used. The most used treatment was gabapentin in 78%, followed by lamotrigine (19.7%), amitriptyline (12.6%) and pregabaline (5.5%). 83 patients (65.4%) presented >50% response. We did not found a higher percentage of responders among those patients that had received prior preventive treatment or those with a shorter evolution of the headache.

Conclusion: Oral preventive drugs seem to be effective in NH, but factors associated with response to treatment are still unknown. Knowledge about this headache should be improved in order to shorten time to diagnosis and percentage of untreated patients.

Disclosure: Nothing to disclose

EPR1048

Sustained efficacy of lasmiditan: Results from phase 3 randomized clinical trials for acute treatment of migraine

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Background and aims: Sustained pain freedom is an important attribute of acute migraine therapies, particularly to patients. Efficacy of the centrally-penetrant, highly selective, 5-HT1F agonist, lasmiditan, on sustained pain freedom is reported. Also reported is an additional analysis of modified sustained pain freedom based on definition by Ferrari et. al. in a meta-analysis of triptans.

Methods: Data from similarly designed, Phase 3, double-blind studies, SAMURAI (NCT02439320) and SPARTAN (NCT02605174), were pooled. Patients with Migraine Disability Assessment Score ≥11 were randomized equally to lasmiditan 50mg (SPARTAN only), 100mg, or 200mg, or placebo, and were to take study drug within 4 hours of onset of migraine pain. Sustained pain freedom was defined as pain freedom at 2 hours and 24/48 hours postdose without use of additional medications; patients with missing data were assumed to not be pain free. Modified sustained pain freedom was defined for patients with available data as pain freedom at 2 hours and no moderate-to-severe headache at 24 hours postdose, without use of additional medications, as defined by Ferrari et. al.

Results: Sustained pain freedom was significantly higher in patients treated with lasmiditan versus placebo at 24 and 48 hours. Modified sustained pain freedom at 24 hours was observed in significantly higher proportions of lasmiditan-treated patients versus placebo (Table 1).

	Placebo N=1063	LTN 50mg[b] N=556	LTN 100mg N=1035	LTN 200mg N=1046
Pain Freedom at 2 hours	18.3%	28.6%*** (1.6 [1.2, 2.0])	29.9%*** (1.9 [1.5, 2.3])	35.6%*** (2.5 [2.0, 3.0])
Sustained pain freedom at 24 hours	10.3%	17.4%** (1.6 [1.2, 2.1])	16.9%*** (1.8 [1.4, 2.3])	21.2%*** (2.3 [1.8, 3.0])
Sustained pain freedom at 48 hours	9.6%	14.9%* (1.5 [1.1, 2.1])	15.2%*** (1.7 [1.3, 2.2])	18.4%*** (2.1 [1.6, 2.7])
Modified sustained pain freedom at 24 hours[a]	12.9%	21.7%** (1.6 [1.2, 2.1])	21.7%*** (1.9 [1.5, 2.4])	27.0%*** (2.5 [2.0, 3.2])

[a]Denominators for calculating percentages for modified sustained pain freedom were: Placebo: N=996; LTN 50mg: N=506; LTN 100mg: N=916; LTN 200mg: N=926. [b]SPARTAN only. *p<0.05, **p<0.01 and ***p<0.001, for comparisons versus placebo. Odds ratios [confidence intervals] are shown in parentheses. Abbreviation: LTN: lasmiditan

Table 1. Proportions of patients experiencing pain freedom at 2 hours, sustained pain freedom at 24 and 48 hours, and modified sustained pain freedom at 24 hours following dosing with placebo, lasmiditan 50mg, 100mg or 200mg.

Conclusion: Sustained pain freedom at 24 and 48 hours was noted in significantly more patients treated with lasmiditan versus placebo, and is consistent with findings from a meta-analysis of triptans. These findings are valuable when considering patient-centric approaches to migraine care.

Disclosure: The study was sponsored by Eli Lilly and Company.

Motor neurone diseases 1

EPR1049

Value of AVXS-101 for spinal muscular atrophy type 1: improved survival and motor function, lower use of pulmonary support with decreased hospitalization and associated costs

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Background and aims: Spinal muscular atrophy type 1 (SMA1) is a rapidly progressing, debilitating neurodegenerative disease resulting from bi-allelic survival motor neuron 1 (SMN1) gene deletion/mutation. This study assessed the impact of onasemnogene abeparvovec (AVXS-101) on survival, ventilatory support, motor milestone achievement, and total hospitalizations in SMA1 patients contrasted with those treated with nusinersen.
Methods: SMA1 patients (two SMN2 copies) were treated with AVXS-101 (CL-101; NCT02122952; cohort 2; N=12) or nusinersen (ENDEAR; NCT02193074; N=80). Survival (composite endpoint of time to death or permanent ventilation), ventilatory support, motor milestones, and hospitalization were contrasted (CL-101, ≥24 months post-dose; ENDEAR, ≥14 months of age). Costs were determined using published claims analysis data, itemized costing derived from literature and expert opinion using a multi-state Markov model.
Results: The proportion of patients alive without permanent ventilation was 66% in nusinersen-treated patients and 100% in AVXS-101-treated patients. In nusinersen-treated patients, 19% required permanent assisted ventilation, whereas no AVXS-101-treated patient required such support. In nusinersen-treated patients, 8% sat independently and 1% stood; 92% of AVXS-101-treated patients sat unassisted, 17% stood with assistance, and 17% walked independently. The mean unadjusted annualized rate of hospitalizations (total hospitalizations/total number of subject-years followed) was 4.5 for nusinersen-treated patients and 2.1 for AVXS-101-treated patients; 5-year direct medical costs of nusinersen-treated patients were $74,265 higher than AVXS-101-treated patients.
Conclusion: Patients treated with a single dose of AVXS-101 have improved survival and motor milestone achievement, and lower healthcare utilization (reduced ventilatory support and hospitalization), resulting in decreased estimated direct medical costs compared to nusinersen.
Disclosure: This study is funded by AveXis, Inc. (USA)

EPR1050

Intra-oral pressures and body myometries as tools to track weakness progression in SBMA and in ALS

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Background and aims: Amyotrophic lateral sclerosis (ALS) and Spinal bulbar muscle atrophy (SBMA), also known as Kennedy disease (KD), are two neuromuscular progressive disorders, characterised by limb and bulbar muscle wasting and weakness, with a very different prognosis. Clinical scales to evaluate the progression of disease are not accurate in detecting early onset of symptoms and their progress. We evaluated onset and progression of bulbar and limb impairments using Iowa-Oral-Performance-Instrument (IOPI) and muscle myometries.
Methods: We enrolled 50 KD, 20 ALS and 25 controls and assessed functional rating scales (FRSs), tongue and left and right perioral strength, using IOPI, and limb region strength by Medical-Research-Council (MRC) rating scale and hand-held dynamometer. Follow-up was performed at six months and one year. We analysed data using t-test, ANOVA and Cox regression analysis.
Results: FRS-bulbar subdomains and intra-oral pressure measurements showed a statistically significant correlation ($p<0.001$) in ALS and in SBMA. Furthermore, intra-oral pressures were able to detect changes in ALS and in SBMA patients with no apparent symptoms and changes on the FRSs. Conversely, FRSs-limb subdomains didn't correlate with limb myometries. Finally, myometries perform better than FRSs and the MRC-scale in measuring weakness progression in both ALS and SBMA.

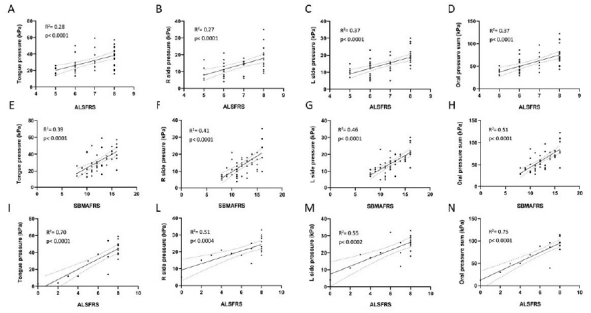

Fig. 1 Relationship between functional rating scales (ALS-FRSr and SBMA-FRS) and intra-oral pressures in ALS and SBMA patients
(A-H) All these graphs show an important correlation between each intra-oral measure (tongue pressures, left and right perioral pressures and their sum) and both ALS-FRSr and SBMA-FRS scales in SBMA patients. (I-N) All these graphs show an important correlation between each intra-oral measure and ALS-FRSr in ALS patients.
ALSFRSr: ALS Functional Rating Scale Revised; SBMAFRS: SBMA Functional Rating Scale. Oral pressure sum: sum of tongue pressure plus left perioral pressure plus right perioral pressure.

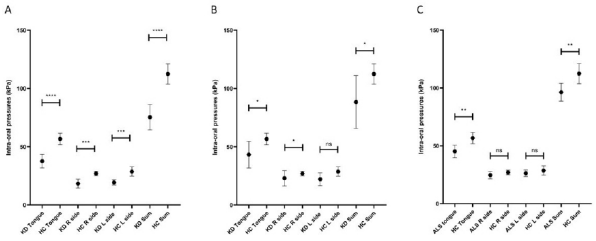

Fig. 2 Comparison of intra-oral pressures between KD with normal bulbar functions and healthy controls (HC).
(A) KD patients with normal ALSFRS-bulbar score show an important reduction of intra-oral pressures compared to HC. (B) KD patients with normal SBMA-FRS-bulbar score show statistically significant differences of intra-oral pressures compared to HC, except for left-side pressures. (C) ALS patients with normal FRS-bulbar score show a statistically important reduction of tongue and total pressure Error bars indicate 95% CIs.
R side: right side perioral pressure; L side: left side perioral pressure. Sum: sum of tongue pressure plus R-side pressure plus L-side pressure.

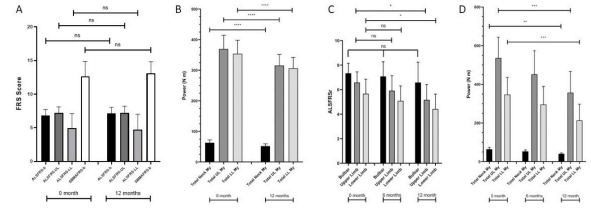

Fig. 3 Comparison between FRS scores and Myometries in evaluation of disease progression in ALS and SBMA patients
(A) In SBMA patients both ALSFRS and SBMA sub-scores didn't change after one year, while (B) myometries show an important reductions in all districts. (C) In ALS patients almost FRS-subscores didn't significantly change between 0 to 6 months and 6 to 12 months. A light change is present between 0 to 12 months in upper and in lower sub-scores. Contrarily myometries (D) show an important reduction in all sub-scores between 0 to 6 months and 6 to 12 months.
ALSFRS-b: ALSFRSr-bulbar sub-score; ALSFRS-UL: ALSFRSr-upper limb sub-score; ALSFRS-LL: ALSFRS-lower limb sub-score; Total Neck My: sum of neck muscles strength; Total UL My: sum of upper limb muscles strength; Total LL My: sum of lower limb muscles strength.

Conclusion: This study shows that intra-oral pressures are a sensitive measure for detecting pre-symptomatic bulbar involvement in ALS and SBMA. Further, myometries perform better than FRSs and the MRC-scale to measure progression of weakness in ALS and SBMA. In conclusion, intra-oral pressures and myometries are useful clinical tools to evaluate disease progression in ALS and in SBMA.
Disclosure: Nothing to disclose

EPR1051

Cognitive impairment progression across ALS clinical stages: a population-based study

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Background and aims: To assess the association of the degree of severity of motor impairment to that of cognitive impairment in a large cohort of ALS patients.
Methods: This is a population-based cross-sectional study on ALS patients incident in Piemonte, Italy, between 2007 and 2015. Cognitive status was classified according to the revised ALS-FTD Consensus Criteria. The King's and the Milano Torino Staging (MiToS) systems were used for defining the severity of motor impairment.
Results: Of the 797 patients included in the study, 163 (20.5%) with ALS-FTD, 38 (4.8%) with cognitive and behavioral impairment (ALScbi), 132 (16.6%) with cognitive impairment (ALSci), 63 (7.9%) with with behavioral impairment (ALSbi), 16 (2.0%) with non-executive impairment, and 385 (48.2%) cognitively normal. According to King's staging, the frequency of cases with ALS-FTD progressively increased from 16.5% in stage 1 to 44.4% in stage 4; conversely the frequency of ALSci, ALSbi and ALScbi increased from King's stage 1 to King's stage 3 and decreased thereafter. A similar pattern was observed with the MiToS staging. ALS-FTD was more frequent in patients with bulbar involvement at time of cognitive testing. Patients with C9ORF72 expansion (n=61) showed more severe cognitive impairment with increasing both King's and MiToS stages.
Conclusion: Our findings suggest that ALS motor and cognitive components may worsen in parallel over time, and that cognitive worsening becomes more pronounced when bulbar function is involved.
Disclosure: Nothing to disclose

EPR1052

Exploring the 18F-FDG-PET metabolic correlates of ALS King's stages: an evidence of lesions spreading

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Background and aims: It has been postulated that in amyotrophic lateral sclerosis (ALS) lesions spread across the CNS through a cortico-efferent spreading model. We aimed at evaluating the changes of metabolic patterns across King's stages through brain 18F-FDG-PET.
Methods: We collected 406 ALS cases who underwent brain 18F-FDG-PET at diagnosis and for whom the King's stage at PET from 1 to 4 (4a and 4b where considered together) was derived from ALSFRS-R. The King's stage was regressed against brain metabolism using the multiple regression model of SPM 12. The two-sample t-test was used for group comparisons (we excluded stage 4 for small size). Age at PET and sex were included as covariates in all the analyses (height threshold $p<0.001$; $p<0.05$ FWEcorrected at cluster level).
Results: In the multiple regression brain metabolism negatively correlated with the King's stage in Brodmann Areas (BAs) 3,4, and 6 bilaterally. The comparison between patients with King's stage 1 and 2 showed no differences. Patients with King's stage 3 showed relative hypometabolism in BAs 4 and 6 bilaterally and in right BA 8 compared to a group including both King's 1 and 2 stages.
Conclusion: Brain metabolism of motor regions tends to decrease with the increase of King's staging. The gap seems to be more relevant between stages 2 and 3 than between stages 1 and 2. The metabolic correlates of King's stage 4 need further investigations.
Disclosure: Nothing to disclose

EPR1053

Modulation of selected miRNAs in ALS models for the development of novel therapeutics.

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Background and aims: Motor Neurons (MNs) degeneration is the hallmark of Amyotrophic Lateral Sclerosis (ALS). Its underlying mechanisms remain elusive, even though a disruption of RNA metabolism involving micro RNAs (miRNAs) seem to play a pivotal role in ALS-related genetic pathways and MNs survival. We aim at determining whether the modulation of disease-relevant miRNAs can halt MNs neurodegeneration in vitro and in an ALS mouse model (SODG93A).
Methods: We generated iPSCs reprogramming ALS and control fibroblasts and differentiated them into spinal MNs. The MNs miRNA transcriptome was profiled using the TaqMan® Low Density Array. We transfected ALS IPS-derived MNs with specific miRNA mimic against selected candidates. Finally, we silenced an ALS-relevant miRNA downregulating the RNA-binding protein ELAVL4/HuD by injecting morpholino antisense oligonucleotides (MO) into SOD1G93A mice (MO-SOD1 mice) evaluating survival, MNs function and neuropathology.
Results: We obtained a transcriptome of human ALS MNs and demonstrated that selected deregulated miRNAs implicated in MNs survival, synapsis and neurogenesis can be modulated by miRNA mimic in vitro. We proved that MO intracerebroventricular injection increases survival and muscle strength in MO-SOD1 mice compared with scramble-treated mice. Considering MNs survival and neuromuscular junction (NMJ) denervation, we documented an increase in MNs life-span and in the number of fully innervated NMJs in MO-SOD1 mice. This improvement correlated with an up-regulation of the miRNA-target HuD demonstrated by qPCR and western blot.
Conclusion: The exogenous regulation of miRNAs in vivo can modify genetic pathways involved in complex neurodegenerative diseases such ALS in an effective manner contributing to the identification of novel therapeutics and biomarkers.
Disclosure: Nothing to disclose

EPR1054

Patient reported outcome measures in Amyotrophic Lateral Sclerosis

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Background and aims: Patient Reported Outcome Measures (PROMs) are growing components of healthcare practices and are considered valuable outcome measures, because the information gathered from patients is not modified by interpretation of physician. There has been little data on the application of PROMs in Amyotrophic Lateral Sclerosis (ALS) practices: we examined the feasibility of PROM collection in an ALS academic center and the correlations between the obtained scores and clinical outcome measures as recorded by healthcare providers in the routine clinical care.
Methods: We collected iPad-based surveys which included two validated PRO instruments: A: PROM Information System (PROMIS-10) which generates Mental Health, Physical Health and neuro-ABC Balance scores, and B: Neuro Quality of Life fatigue short form (NeuroQoL). We tested the associations between PROM scores and clinical outcome measures (e.g. ALSFRS-R score, vital capacity (VC), ambulatory status, use of BiPAP/G-Tube).
Results: A total of 291 ALS patients completed PROMs. The mean physical health score was 45.1 (SD:9.7), the mean mental health score was 48.4 (SD:9.8) and the mean neuro-ABC score was 72.9 (SD:28.9). The mean NeuroQoL fatigue score was 48.9 (SD:11.9). The PROMIS-10 scores demonstrated significant positive correlation with the ALSFRS-R score and VC ($p<0.05$). Moreover, we obtained higher Physical and Mental scores in patients able to walk and a lower Physical score in patients with BiPAP.
Conclusion: We obtained that the physical health assessments, as reported by patients, are strongly correlated with physical health assessments as recorded by healthcare providers, especially with essential outcomes as ALSFRS-R and VC.
Disclosure: Nothing to disclose

EPR1055

Nusinersen experience in teenagers and young adults with spinal muscular atrophy (SMA): Results from CS2/CS12 and SHINE

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Background and aims: Nusinersen has shown clinically meaningful efficacy in presymptomatic and symptomatic infants/children with SMA. Here, we report outcomes in symptomatic teenagers treated with nusinersen.
Methods: This case series includes five participants (SMA Type II, participant 1; Type III, participants 2–5) who were 14 or 15 years at treatment initiation in CS2 (Phase 1b/2a), received intrathecal nusinersen 12 mg in CS12 (open-label extension), and were 17 or 19 years at last CS12 visit (Day 715) having transitioned to SHINE (long-term extension; NCT02594124).
Results: At CS2 baseline, participants 2, 4 and 5 were ambulatory. Participant 1 achieved improvement on HFMSE and maintained stable ULM scores from CS2 baseline to CS12 Day 715. HFMSE scores in participants 2–5 remained stable or slightly improved; ULM scores in participants 3 and 4 remained unchanged at the scale maximum to Day 715. 6MWT distance increased from CS2 baseline to Day 715 in participants 2 and 5; participant 4 walked independently for short distances without support in CS2 (6MWT=0m), and walked unaided during CS12 visits (23–74m). The majority of participants experienced stable/slightly improved health-related quality of life (HRQoL) scores. The most common adverse events were related to the lumbar puncture. Additional data from the SHINE study will be presented.
Conclusion: In contrast to the decline in motor function documented in previous SMA natural history studies, nusinersen-treated teenagers in this case series demonstrated stable or improved outcomes as determined by motor

function and HRQoL measures. Additional data from the SHINE study will elaborate further on these improved clinical trajectories.

Disclosure: This study was funded by Biogen (Cambridge, MA, USA) and Ionis Pharmaceuticals Inc. (Carlsbad, CA, USA); medical writing support was provided by Excel Scientific Solutions (Horsham, UK) and funded by Biogen.

Movement disorders 1

EPR1056

Development of an unsupervised analysis pipeline for human microelectrode recordings in Parkinson's disease

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Background and aims: Deep brain stimulation (DBS) is a common treatment for advanced Parkinson's disease (PD). Intra-operative microelectrode recordings (MER) along pre-planned trajectories are often used for accurate identification of subthalamic nucleus (STN), a common target for DBS-PD. However, this identification can be difficult in regions of transition and misidentification can lead to suboptimal location of the lead and inadequate clinical outcomes.
Methods: Tools for unsupervised analysis and spike-sorting of human MER were developed. A machine-learning classification model for high-accuracy identification of STN was programmed, using MER time and frequency properties. Neurophysiological characteristics of segregated STN segments were compared by dividing the STN in dorsal and ventral portions, which present higher probability of being motor and non-motor regions respectively. Ongoing work will refine the results using anatomical gold standard through lead trajectory reconstruction, fused with an STN functional subdivision atlas.
Results: Using leave-one-subject-out validation, classification accuracy for STN-DBS recordings is 96.3±3.15% (30 trajectories, 5 patients; compared to human expert classification). Significant differences between STN segments (357 STN neurons in 5 subjects) were found, as higher burst and firing rate of dorsal STN neurons (median(interquartile range) of 1.8 (1.5) vs 1.15 (0.05) bursts/s, p=0.001 and 21.4 (16.85) vs. 15.3 (14.33) spikes/s, p=0.013 respectively).
Conclusion: We've developed tools for human MER analysis, that provided good results in STN classification and are fast and generalizable for other brain regions. In line with the literature, preliminary activity differences were found in functionally segregated STN segments. Ongoing anatomical work can further validate its' usefulness in optimizing electrode placement and research purposes.
Disclosure: Nothing to disclose

EPR1057

Dual-task in Parkinson's disease: a gait analysis and functional MRI study

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Background and aims: To study gait parameters and fMRI patterns during dual-task in Parkinson's disease patients with postural instability and gait disorders (PD-PIGD).
Methods: 20 PD-PIGD patients performed Timed-Up-and-Go (TUG) test, and TUG with motor (TUG-MOT) and cognitive (TUG-COG) dual-tasks. TUG-MOT consisted of TUG while holding a glass full of water, while TUG-COG consisted of TUG while counting backwards by threes starting from 100. Six cameras SMART-DX7000 optoelectronic system was used to obtain peak and mean velocity during the turning phase. Patients performed two fMRI tasks: i) motor-task (foot anti-phase movements); ii) dual-task (foot anti-phase movements while counting backwards by threes starting from 100).
Results: PD-PIGD patients showed increased total time of execution and slower turns during TUG-MOT and TUG-COG relative to simple TUG. During fMRI dual-task relative to motor-task, patients showed increased activation of the fronto-temporo-parietal regions and decreased activity of the sensorimotor areas. Correlation analysis showed that: i) better TUG performance correlated with increased recruitment of the cortical/cerebellar motor areas, fronto-striatal circuit and occipital lobe during the motor-task; ii) better TUG-MOT/TUG-COG performance correlated with increased activity of motor areas and decreased recruitment of superior/middle frontal and temporal gyri, superior/inferior parietal gyri, occipital areas and right pallidum during the dual-task.
Conclusion: Dual-task resulted in a slower gait performance particularly during turning, a challenging situation for PD-PIGD patients. This pattern might reflect an increased dynamic postural instability when high cognitive load is requested. FMRI results suggest that an optimized recruitment of motor and cognitive networks is associated with a better dual-task performance.
Disclosure: Nothing to disclose

EPR1058

Transcranial ultrasound in atypical parkinsonism: how reliable is it in real clinical practice? A multi-centre comprehensive study

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Background and aims: Substantia nigra hyperechogenicity (SN+) in transcranial ultrasound (TUS) is frequent in Parkinson's disease (PD), while lenticular nucleus hyperechogenicity (LN+) and III ventricle enlargement (IIIV+) are common in Atypical Parkinsonism (AP). However, there are no studies assessing the diagnostic yield of all TUS biomarkers in AP (progressive supranuclear palsy, PSP, multiple system atrophy, MSA, corticobasal degeneration, CBD). Previous references lack homogeneous criteria and data are incomprehensive (Table1).

Methods: Analysis of TUS performed in routine clinical practice in AP and PD patients from two tertiary hospitals. Expert recommendations were strictly followed. Previous literature was critically analysed.

Results: 155 AP (98 PSP, 40 MSA, 14 CBD), 254 PD, 145 control subjects were included (Figure1). We confirmed good sensitivity for SN+ in PD (80%), but specificity was lower than reported (61%) (Table2). LN+ and IIIV+ had moderate sensitivity for AP and PSP diagnosis respectively (65%, 63%), but specificity was higher than reported (87%, 91%). We confirmed high specificity and positive predictive value of the combination SN/LN (98%, 93% AP; 83%, 86% PD). The combinations of two or three echofeatures, previously unreported, showed high specificity but lower sensitivity (SN/IIIV: 75% sensitivity, 87% specificity PD; 42% sensitivity, 98% specificity PSP) (SN+LN+: 79% sensitivity, 86% specificity CBD) (SN/IIIV/LN: 67% sensitivity, 89% specificity PD; 29% sensitivity, 99% specificity PSP; 41% sensitivity, 95% specificity MSA; 57% sensitivity 91% specificity CBD).

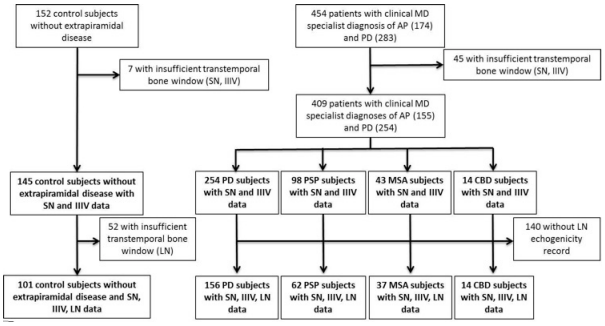

Figure 1. Study flowchart. AP: atypical parkinsonism. CBD: corticobasal degeneration, IIIV: third ventricle, LN: lenticular nucleus, MD: movement disorders, MSA: multiple system atrophy, PD: Parkinson's Disease, PSP: progressive supranuclear palsy, SN: substantia nigra

	Echofeature			PD			PSP			MSA			CBD			MIXED AP		
	SN	LN	III	n SN	n LN	n III	n SN	n LN	n III	n SN	n LN	n III	n SN	n LN	n III	n SN	n LN	n III
Walter 2003	+	+	+	25	22	25	7	7	7	16	15	14	-	-	-	-	-	-
Walter 2004	+	+	+	-	-	-	11	10	11	-	-	-	8	6	8	-	-	-
Behnke 2005	+	+	-	88	88	-	18	18	-	32	32	-	-	-	-	-	-	-
Walter 2007	+	+	+	134	125	134	20	19	20	21	20	21	-	-	-	-	-	-
Okawa 2007	+	-	-	63		-	13	-	-	11	-	-	-	-	-	-	-	-
Gaenslen 2008	+	+	-	43	39	-	4	NA	-	6	NA	-	3	NA	-	-	12	-
Ebenthover 2010	+	-	+	-	-	-	34	-	34	-	-	-	-	-	-	-	-	-
Bione 2012	+	-	-	371	-	-	NA	-	-	NA	-	-	-	-	-	18	-	-
Bouwmans 2013	+	-	-	102	-	-	6	-	-	8	-	-	4	-	-	-	-	-
Kostic 2013	+	+	+	-	-	-	32	32	32	-	-	-	-	-	-	-	-	-
Sastre Bataller 2013	-	-	+	-	-	39	-	-	13	-	-	-	-	-	-	-	-	-
Bartova 2014	+	-	-	29	-	-	5	-	-	2	-	-	-	-	-	-	-	-
Sadowski 2014	+	+	-	-	-	-	20	20	-	-	-	-	12	11	-	-	-	-
Sanzaro 2015	+	±	-	30	-	-	3	3	3	2	2	2	-	-	-	-	-	-
Fujita 2016	+	-	-	64	-	-	9	-	-	15	-	-	-	-	-	-	-	-
Li 2017	+	+	±	22	22	-	-	-	-	21	21	-	-	-	-	-	-	-
Zhou 2018	+	-	-	147	-	-	-	-	-	86	-	-	-	-	-	-	-	-
Monaco 2018	+	+	-	121	121	-	-	-	-	-	-	-	-	-	-	92	92	-
				1239	**417**	**198**	**182**	**109**	**120**	**220**	**90**	**37**	**27**	**17**	**8**	**110**	**104**	**0**

Table 1. Literature review of studies of TUS in AP. Echofeatures analysed in each study (present: +; absent: -; present but not fully disclosed as to allow analysis: ±), and subjects of each diagnostic category available for analysis are disclosed. NA: non assessable, whenever data of the echofeature was given as the addition of 2 or more APs without distinction of diagnostic category (disclosed in "Mixed AP").

Table 1. Literature review of studies of TUS in AP. Echofeatures analysed in each study

					AC et al. (2019)				Previous literature analysis			
Diagnostic category A vs. B		SN	IIIV	LN	Sample size	Sensitivity	Specificity	PPV	Sample size	Sensitivity	Specificity	PPV
PD	PSP/MSA/CBD	+			254 vs. 155	0.80 [0.75;0.85]	0.61 [0.52;0.68]	0.77 [0.72; 0.82]	1239 vs. 539	0.77 [0.75;0.80]	0.81 [0.77;0.84]	0.90 [0.88;0.92]
	PSP/MSA/CBD	+		-	156 vs. 113	0.75 [0.67;0.82]	0.83 [0.75;0.90]	0.86 [0.80; 0.92]	88 vs. 50			0.91
	PSP	+	-		254 vs. 98	0.75 [0.69;0.80]	0.87 [0.78;0.93]	0.94 [0.90;0.97]				
	PSP/MSA/CBD	+	-	-	156 vs. 113	0.67 [0.59;0.75]	0.89 [0.81;0.94]	0.89 [0.83;0.95]				
PSP	PD/MSA/CBD		+		98 vs. 311	0.63 [0.53;0.73]	0.91 [0.88;0.94]	0.70 [0.66; 0.79]	113 vs. 229	0.63 [0.51;0.72]	0.75 [0.69;0.80]	0.55 [0.47;0.64]
	PD/MSA/CBD	-	+		98 vs. 311	0.42 [0.32;0.52]	0.98 [0.96;0.99]	0.89 [0.80;0.98]				
	CBD	-		+	62 vs. 14	0.42 [0.30;0.55]	0.93 [0.66;1.00]	0.96 [0.89;1.00]	20 vs. 11	1.00	0.67	1.00
	PD/MSA/CBD	-	+	+	62 vs. 207	0.29 [0.18;0.42]	0.99 [0.97;1.00]	0.90 [0.77;1.00]				
MSA	PD/PSP/CBD	-	-		43 vs. 366	0.63 [0.47;0.77]	0.81 [0.76;0.85]	0.28 [0.19;0.37]				
	PD/PSP/CBD	-	-	+	37 vs. 232	0.41 [0.25;0.58]	0.95 [0.92;0.98]	0.58 [0.39;0.77]				
CBD	PD/PSP/MSA	+		+	14 vs. 255	0.79 [0.69;0.95]	0.86 [0.81;0.90]	0.23 [0.11; 0.35]				
	PD/PSP/MSA	+	-	+	14 vs. 255	0.57 [0.29;0.82]	0.91 [0.87;0.94]	0.26 [0.10;0.41]				
	PSP	+	-		14 vs. 98	0.57 [0.29;0.82]	0.87 [0.78;0.93]	0.38 [0.17;0.59]	8 vs. 10	0.83	1.00	1.00
PD/CBD	PSP/MSA	+			268 vs. 141	0.81 [0.75;0.85]	0.65 [0.57;0.73]	0.82 [0.77; 0.86]	1266 vs. 512	0.77 [0.75;0.80]	0.83 [0.80;0.87]	0.92 [0.90;0.94]
PSP/MSA/CBD	PD			+	113 vs. 156	0.65 [0.56;0.74]	0.87 [0.81;0.92]	0.79 [0.76; 0.87]	320 vs. 417	0.74 [0.69;0.78]	0.84 [0.80;0.87]	0.79 [0.75;0.83]
PSP/MSA	PD	-		+	99 vs. 156	0.42 [0.33;0.51]	0.98 [0.94;1.00]	0.93[0.86;1.00]	39 vs. 125 50 vs. 88	0.59	1.00 0.96	1.00

Table 2. Diagnostic reliability of each echofeature for each diagnostic category. Data are disclosed as sensitivity, specificity and positive predictive value with 95% confidence intervals between brackets

Conclusion: We present a large comprehensive study of TUS, confirming its usefulness and certain limitations in AP diagnosis. Adherence to consensus criteria is critical to implement TUS for clinical and research purposes.

Disclosure: Nothing to disclose

EPR1059

Evolution of prodromal parkinsonian features in a cohort of GBA mutation positive individuals: a 6-year longitudinal study.

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Background and aims: GBA mutations are the most frequent risk factor for Parkinson disease (PD). The aim of this study is to evaluate clinical features in a group of GBA mutation positive individuals (GD and Het GBA carriers) at risk of developing PD over 6-years follow-up.
Methods: This is a longitudinal study on a cohort of GBA positive carriers. At baseline, we enrolled 30 GD Type1 patients (mean age 52.4 years), 30 Het GBA (mean age 59 years) carriers and 30 mutation negative controls (HC). We assessed motor and non-motor prodromal signs of PD in all subjects, by means of clinical questionnaires and scales (MoCA, UPSIT, RBDsq, UPDRS-III, UMSARS, and BDI). At 6 years, we repeated the assessment and collected venous blood samples to measure GCase activity.
Results: After 6 years, 1 GD patient developed a clinically defined PD syndrome. Over the 6-year follow-up, we observed a significant worsening in UMSARS, RBDsq, UPDRS-III and BDI scores compared to baseline scores in both the GD and HetGBA groups. Intergroup comparisons showed that GD subjects had significantly worse scores in UPSIT, UMSARS, MoCA and UPDRS-III than HC, while Het GBA displayed worse outcomes in UPSIT and UPDRS-III compared to HC. In GBA mutation positive individuals (Het GBA and GD), an UPSIT score of 23 at baseline was correlated with worse outcome at 6 years in UPSIT, MoCA, UPDRS-III and BDI.
Conclusion: In this 6-year longitudinal study, GBA mutation positive subjects showed a worsening in motor and non-motor prodromal PD features.
Disclosure: Nothing to disclose

EPR1060

Ventilatory impairment in Parkinson's disease: a 5-years follow-up study

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Background and aims: Pulmonary dysfunction is related among axial and non-motor symptoms of Parkinson's Disease (PD). It impacts the quality of life and could affect the prognosis. However, most of the studies assessed it in advanced PD patients without any prospective follow-up. The aim of our study was 1) to assess the evolution of lung volumes and respiratory muscles strength after a 5 years follow-up; 2) to determine the prognostic factor of the ventilatory disorder in PD.
Methods: 27 early-stage PD patients (mean age at inclusion (V0)=67.3±7.6; mean disease duration (V0)=1.9 years (±1.6)) were included and followed up during 5 years. Neurological examination and pulmonary function testings were performed at V0, repeated 2 years (V2) and 5 years later (V5).
Results: At V5, the vital capacity (p=0.001), the forced expiratory volume in 1 second (p=0.006), the functional residual capacity (p=0.0003) and the total lung capacity (p=0.0008). The sniff nasal inspiratory pressure increased and cough expired volume significantly increased (p=0.002 and p=0.001, respectively). Pulmonary function testing data at V0 were not associated with a worse outcome at V5.
Conclusion: We demonstrated for the first time that the lung volumes decreased after 5 years of disease progression. We need to confirm the results on a larger population in order to determine the prognostic value of this global ventilatory disorder.
Disclosure: Nothing to disclose

EPR1061

Differentiating Parkinson's disease patients from healthy controls based on 3D kinematics signature

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Background and aims: Classical assessment of Parkinson's disease rests on clinical observation. Inertial measurement units (IMUs) have been explored as a tool for objective movement assessment. Using physics-based biomechanical models, IMUs data could be a fast and cheap tool to complement regular clinical assessment.
Methods: We have recruited 18 Patients with Parkinson's diseases on the On state (PwPD, 8 Female, age at evaluation: 69.3±6.7 years, disease duration: 69.9±53.1 months of disease duration) and 10 age-matched controls (5 female). Subjects were instrumented with 7 IMUs sensors skin-mounted over the pelvis, thighs, shanks and feet. The raw data collected from IMUs accelerometer, gyroscope and magnetometer during a 20 meter walk was used to fed a 3D lower limb biomechanical model based on which subjects' gait spatiotemporal variables, joint angles and velocities were calculated and compared between groups. Significance was set at a level of 0.05.
Results: PwPD presented a consistent (and significantly different from controls) pattern of reduced speed, cadence and step length, while increasing the double-support, stride and step duration. A decision tree classifier with 5-fold cross-validation achieved an accuracy of 0.84 when distinguishing PwPD and controls. Sagittal plane lower limb peak joint velocities, step length and duration, and foot clearance were found to be the most important kinematic features in the distinction.
Conclusion: IMU-based 3D kinematics revealed bradykinesia-evocative features in PwPD. It disclosed the gait feature that better distinguished PwPD and controls. These assessment tools can complement clinical practice guiding longitudinal in-office subject assessment and therapeutic decisions. Future studies will be directed at this.
Disclosure: Matias is the cofounder of the company Kinetikos, Portugal

EPR1062

Frequency of impulse control disorder in Parkinson's disease: insights from the Luxembourg cohort

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Background and aims: To establish the frequency of impulse control disorder (ICD) in idiopathic Parkinson's disease (IPD) and analyze contributing factors.
Methods: Within the Luxembourg cohort (Hipp et al., 2018), IPD patients were annually evaluated for the presence of ICD (score ≥1 on item 1.6 of the MDS-UPDRS I rating scale) and medication use and compared to age-matched healthy controls (HC). Calculations were done with a Mann-Whitney U Test.
Results: 1106 subjects were eligible for the study: 512 IPD patients with 1 to 3 visits (V1-V3) and 594 HC with 1 baseline visit. 50 IPD (9.7%) patients scored positive for ICD in contrast to 34 HC (5.7%) (p=0.01). Among 236 IPD patients without dopamine agonist (DA) use, only 13 (5.5%) scored positive for ICD, in contrast to 37 (13.1%) among 276 patients with use of DA (p=0.004). Male sex or concomitant use of amantadine did not influence the presence of ICD. Frequency of ICD increased from V1 to V3 (p=0.005).
Conclusion: In this observational study, without recruitment bias of a tertiary care center and thus more representative for the general PD population, IPD patients without use of DA agonists show a frequency of ICD comparable to HC. Thus ICD risk is not disease-inherent, however frequency significantly increased with the use of DA. There is no protective effect of amantadine nor sex preference. Our study confirms and extends previous reports on ICD in IPD (Cormier-Dequaire et al., 2018). IPD patients should be informed about ICD risk before initiating DA treatment.
Disclosure: Fonds national de la Recherche de Luxembourg Michael J Fox Foundation European Union's Horizon2020 research and innovation program

Movement disorders 2

EPR1063

Intrinsic functional connectivity changes in drug-naïve Parkinson's disease patients with mild cognitive impairment

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Background and aims: Mild cognitive impairment (MCI) is a common nonmotor symptom in Parkinson's disease (PD) and it is considered a risk factor for developing dementia. Using resting-state functional MRI, we investigated intrinsic brain networks connectivity correlates of MCI in a cohort of drug-naïve patients with PD.

Methods: 3T MRI images of 40 drug-naïve non-depressed PD patients (PD-MCI and PD-noMCI), and 20 matched healthy controls (HCs) were analyzed. MDS Task Force Level II diagnostic criteria were applied to determine the presence of MCI. Single-subject and group-level independent component analysis was used to investigate intra and inter-network functional connectivity differences within the major neurocognitive networks (i.e. frontoparietal network, FPN, default-mode network, DMN, ventral and dorsal attention network, VAN and DAN, and salience network, SN) between patients sub-groups and HCs. Finally, linear regression analysis was used to investigate correlations between imaging and clinical data.

Results: Compared to PD-noMCI patients, PD-MCI patients showed decreased connectivity within the right FPN, the DMN and the VAN. Inter-network connectivity between DMN/DAN and DMN/VAN were significantly positive in PD-MCI patients compared to PD-noMCI. Functional connectivity measures among these neurocognitive networks were found to be correlated with neuropsychological outcomes.

Conclusion: Our findings demonstrate the presence of a specific intrinsic functional connectivity pattern involving the most important neurocognitive networks in early PD patients with MCI. We hypothesize that this functional architecture may reflect the presence of diffuse neuropathological changes, which may be present at the diagnosis and represent a potential early biomarker for developing clinically significant cognitive impairment over time.

Disclosure: Nothing to disclose

EPR1064

Circulating neuron-specific microRNAs as novel biomarkers for the detection and differentiation of idiopathic and familial Parkinson's disease

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Background and aims: A minimally invasive test for early detection and monitoring of Parkinson's disease (PD) is a highly unmet need for drug development and planning of patient care. MicroRNAs are endogenous, single-stranded RNA molecules that control gene expression by binding to the 3'UTR of target mRNAs. Through this action, microRNAs oversee most intracellular regulatory pathways including those of cell division and differentiation. Importantly, several of them are secreted in appreciable amount into the circulation and because of their high stability in both blood and urine, they are investigated for their use as biomarkers for disease screening. In PD, microRNAs have been implicated in the regulation of critical genes for the development of the disease such as alpha-synuclein (SNCA) and beta-glucocerebrosidase (GBA) as well as of protein-clearing pathways including autophagy. Towards this, we explored the expression profile of 21 neuron-specific microRNAs in PD patients and normal controls.

Methods: We analyzed 100 idiopathic PD patients, 25 PD carriers of the SNCA A53T mutation, 25 PD carriers ofdifferent GBA mutations, and 100 neurologically normal controls, matched by sex and age, using Real Time PCR in the plasma samples of control and PD patients.

Results: We observed a different molecular signature of microRNA expression between the 4 groups. Interestingly, many of the differentially expressed microRNAs were previously reported to be deregulated in patients withneurodegenerative disease.

Conclusion: These results suggest that plasma neuronal microRNAs discriminate idiopathic PD from familial and healthy controls and may be considered as non-invasive biomarkers for differential diagnosis and potentially therapeutic efficacy.

Disclosure: Nothing to disclose

EPR1065

Arterial spin labelling detects striatal hypoperfusion in early drug-naïve patients with Parkinson's disease

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Background and aims: Early drug-naïve Parkinson's disease (PD) patients offer a crucial insight into the earliest pathological changes manifesting at disease onset. Previous studies, using arterial spin labelling (ASL), provided evidence that in PD treated with levodopa, cerebral blood flow (CBF) is increased in the striatum. Preclinical and clinical evidence showed that dopaminergic treatment can modulate brain perfusion increasing the CBF levels in striatum. This modulation showed relatively greater effects in patients exhibiting L-dopa-induced dyskinesia. No studies have been performed in early drug-naïve PD patients. In this study, we evaluated regional CBF in a cohort of early drug-naïve PD patients, exploring the reciprocal relationship between CBF, using ASL MRI, and the integrity of dopaminergic terminals, using [123I]FP-CIT SPECT scan.
Methods: 33 de novo PD patients and 23 age- and gender-matched healthy controls underwent an ASL MRI and a [123I]FP-CIT SPECT scan.
Results: Compared to healthy controls, PD patients showed lower ASL CBF in the putamen ($P=0.001$), pallidum ($P=0.011$), substantia nigra ($P=0.034$), thalamus ($P<0.001$) and occipital lobe ($P<0.001$). Lower ASL CBF correlated with lower [123I]FP-CIT SPECT binding in the putamen ($rho=0.558$; $P=0.006$).
Conclusion: Our findings provide evidence that there is an interaction between vascular and dopaminergic pathology in early PD, thus ASL MRI has the potential to serve as an early biomarker to assess PD pathology in drug-naïve patients with a short disease duration.
Disclosure: Nothing to disclose

EPR1066

Cognitive improvement after six-week action observation and motor imagery training in patients with Parkinson's disease

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Background and aims: To test whether six-week Action Observation and Motor Imagery Training (AOT-MI) improves cognitive functions in patients with Parkinson's disease (PD); and to detect the relationship between cognitive and functional MRI (fMRI) activity changes.
Methods: 20 PD patients were randomized into two groups: AOT-MI-group performed a 6-week (W6) gait/balance training consisting of AOT-MI combined with practicing the observed-imagined exercises; LANDSCAPE-group performed the same exercises combined with watching landscape videos. Patients underwent pre- and post-treatment fMRI scans while performing a dual-task. Neurological, physiotherapeutic and neuropsychological evaluations were performed at study entry, after training (W6), and after 14 weeks from baseline (W14). Cognitive changes over time were evaluated through computer-based sessions. The effect of training on cognitive performance and the relationship between cognitive and fMRI activity changes were assessed.
Results: At W6, only AOT-MI patients improved performances in subtests assessing the attention switching and the visuospatial localization, and at W14 in subtests assessing the spatial working and recognition memory. In AOT-MI patients, cognitive improvement was related with a greater functional recruitment of fronto-occipital brain areas and affective-cognitive sub-regions of cerebellum and with a reduced recruitment of thalamus and motor sub-regions of cerebellum.
Conclusion: In the AOT-MI group only, a cognitive improvement was observed after a six-week training and persisted after a relatively long-term period. In the AOT-MI group, the greater involvement of extra-motor and the lower involvement of the motor areas after training seem to be crucial for obtaining high cognitive performance, likely reflecting the integration between these circuits.
Disclosure: Nothing to disclose

EPR1067

Rhythmic disorders in idiopathic RBD: a potential new marker for future PD?

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Background and aims: The development of neuroprotective drugs in Parkinson's disease (PD) increases the need for early markers of the disease. At prodromal stage, REM sleep behaviour disorder seems to be the most robust predictor for PD. However, this sleep disorder is not present in all patients. Other markers such as olfactory deficits, visual changes, and autonomic and depressive symptoms exist but lack specificity.
Patients with PD suffer from timing distortions in the perception and production of rhythmic events. These rhythmic skills abnormalities are easy to detect with a rhythmic test, implemented on a tablet application.
The aim of our study was to compare rhythmic skills in patients with idiopathic RBD (IRBD), healthy controls, and patients with PD, to identify potential rhythmic markers related with other early markers of PD.
Methods: Clinical characteristics, rhythmic skills, depressive and olfaction measures were compared in 21 patients with IRBD, 38 patients with Parkinson's disease and 38 control subjects matched for age and sex and educational level. Patients with IRBD also had dopamine transporter imagery.
Results: Subjects with IRBD tapped faster and with greater variability at unpaced tapping and at tapping with music, and had impaired anisochrony detection with music compared to controls. They did not differ from patients with PD. Unpaced tapping variability was correlated with olfaction and dopamine uptake measures.
Conclusion: There is evidence of rhythmic disorders in subjects with IRBD; this impairment is correlated with other early markers for PD. Testing rhythmic skills with simple and inexpensive tasks may be promising for screening for potential future PD.
Disclosure: CGS-MERRI University of Montpellier

EPR1068

Neuroanatomical and clinical predictors of pain in patients with early de novo Parkinson's disease

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Background and aims: Pain is a common and troublesome symptom encountered by Parkinson's disease (PD) patients. We investigated associations between clinical features, neuroanatomical changes and pain in early de novo PD patients.
Methods: The Parkinson's Progression Markers Initiative database was utilised to identify 421 patients. They were grouped based on the presence of persistent pain - defined as pain at all assessments (follow up range 3-60 months). We explored neuroanatomical differences between those with (n=53) and without (n=368) persistent pain using voxel-based morphometry (VBM) performed on their baseline MRI brain scan. Furthermore, associations between baseline clinical features and persistent pain were evaluated.
Results: The presence of persistent pain was associated with areas of volumetric loss. The regions of strongest correlation were the raphe nuclei (r=-0.164; P=0.001), pontis oralis (r=-0.158; P=0.002), and locus coeruleus (r=-0.131; P=0.01). These results remained significant with age as a covariate. Persistent pain was associated with increased severity of fatigue (r=0.240; P<0.001), light headedness (r=0.147; P=0.003), sleep disturbance (r=0.133; P=0.006) and apathy (r=0.127; P=0.009) at baseline assessment. There was no correlation with baseline motor assessment.
Conclusion: This study demonstrates that PD patients with persistent pain have atrophy in the raphe nuclei, pontis oralis and locus coeruleus. These brain regions have known importance for the descending control of pain. They are also important for sleep regulation, which is of particular interest given the association between early sleep disturbance and persistent pain identified in this study. Identifying predictive factors for the development of chronic pain in PD could enable targeted management for at risk patients.
Disclosure: Data was obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). PPMI is sponsored by the Michael J. Fox Foundation for Parkinson's Research (MJFF) and is co-funded by MJFF, Abbvie, Avid Radiopharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Covance, Eli Lilly & Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Merck, MesoScale, Piramal, Pfizer and UCB. Industry partners contribute through financial and in-kind donations and provide feedback on study parameters through the Industry Scientific Advisory Board, which is positioned to inform the selection and review of potential progression markers that could be used in clinical testing.

EPR1069

Cerebellar brain inhibition as a diagnostic marker for Progressive Supranuclear Palsy

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Background and aims: Progressive Supranuclear Palsy (PSP) diagnosis still remains problematic, and there is urgent need for diagnostic markers to differentiate PSP from other neurodegenerative disorders. Transcranial Magnetic Stimulation (TMS) studies have previously suggested an impairment of cerebellar-brain-inhibition (CBI) in PSP patients. The rationale of CBI assessment, evaluating cerebello-cortical connectivity, relies on the well-demonstrated cerebellar abnormalities in PSP. The objective of this work is to determine whether the impairment of the dentato-thalamo-cortical pathway, evaluated with TMS, may be a reliable diagnostic marker of Progressive Supranuclear Palsy (PSP).

Methods: Paired pulse TMS was used to investigate cerebellar brain inhibition (CBI), in patients with PSP, atypical parkinsonisms and dementia. The primary outcome measures were sensitivity and specificity of CBI, derived from receiver operator curve analysis in discriminating PSP from other neurodegenerative disorders.

Results: A total of 150 participants met inclusion criteria. We diagnosed 19 PSP, 26 Parkinson's disease, 25 dementia with Lewy bodies, 15 corticobasal syndrome, 25 frontotemporal dementia and 15 Alzheimer's disease patients, and 25 healthy controls. We found that PSP patients were characterized by a specific impairment of CBI (0.99±0.08) compared to the healthy control group and other neurodegenerative disorders (mean CBI range=0.63-0.80, all p-values<0.001). Using the best cut-off index, CBI differentiated PSP from other diagnoses with an overall sensitivity of 100%, a specificity of 94%, and an accuracy of 97%.

Conclusion: TMS is a non-invasive procedure which reliably distinguishes PSP from other neurodegenerative disorders and, if these findings are replicated in larger studies, could represent a useful additional diagnostic tool to be used in clinical practice.

Disclosure: Nothing to disclose

Movement disorders 3

EPR1070

Grey matter atrophy in Parkinson's disease with long-duration response

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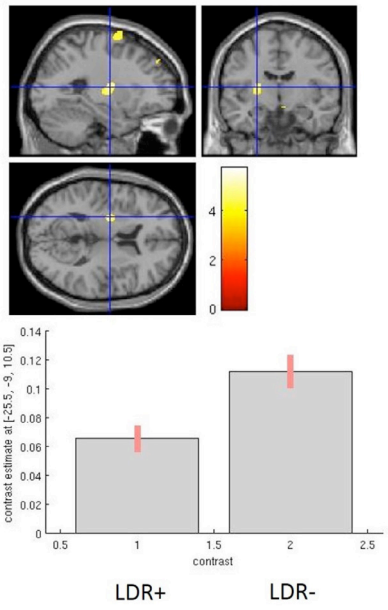
Background and aims: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the response to L-dopa, that still remains the best available symptomatic treatment for PD. The therapeutic response to L-dopa consists of two components: the short-duration response (SDR), an improvement of the clinical condition following the administration of a single dose of L-dopa, and the long-duration response (LDR), a sustained benefit deriving from prolonged administration of L-dopa. Aim of the study is to investigate neuroanatomical correlates of LDR using structural magnetic resonance imaging (MRI) and voxel-based morphometry analysis.

Methods: Drug-naïve patients with a new diagnosis of PD according to Brain Bank criteria were consecutively enrolled. They underwent an acute challenge with 250/25 mg of L-dopa. Then, a treatment with 250/25 mg every 24 hours was started and, after two weeks, LDR was evaluated. Structural brain MRI data were acquired using a 3D T1-weighted sequence and VBM analysis of MRI data was performed.

Results: 24 patients were enrolled. After two weeks of therapy, 15 patients (62.5%) showed LDR (PD-LDR+), while 9 patients (37.5%) showed no LDR (PD-LDR-). VBM analysis between PD-LDR+ and PD-LDR- showed decreased GM density in left putamen and in superior frontal gyrus in PD-LDR+ ($p<0.001$ uncorrected).

	PD de novo N=24	PD-LDR+ N=15	PD-LDR- N=9	p-value
Sex, Men (%)	16 (66,6%)	9 (60%)	7 (77,7%)	0,8**
Age	64,3 ± 7,1	62,4 ± 7,9	67,4± 4,0	0,09*
Disease duration	2,1 ± 1,1	2,2 ± 1,1	1,8 ± 1,2	0,5*
UPDRS-ME	26,1 ± 9,4	24,7 ± 10,3	28,9 ± 7,2	0,3*
Structural MRI features				
WM	560,5 ± 55,6	563,7 ± 69,4	555,1 ± 20,3	0,7*
GM	504,4 ± 61,8	512,7 ± 72,5	490,5 ± 38,1	0,4*
CSF	270,8 ± 50,6	264,9 ± 56,5	280,6 ± 40,1	0,4*
ICV	1335,7 ± 134,9	1341,3 ± 167,2	1326,3 ± 56,7	0,8*

Demographics and clinical characteristics of PD de novo patients



Decreased GM density in left caudate nucleus in PD-LDR+

Conclusion: This study showed the presence of atrophy in cortical and subcortical areas in PD patients who showed LDR after two weeks of continuative levodopa therapy with 250/25 mg every 24 hours. The presence of basal ganglia atrophy could induce a compensation mechanism, improving connectivity and leading to a sustained response to dopaminergic therapy.

Disclosure: Nothing to disclose

EPR1071

The BeyoND study: design and baseline characteristics of an international, multicentre study evaluating the long-term safety of ND0612 for Parkinson's disease

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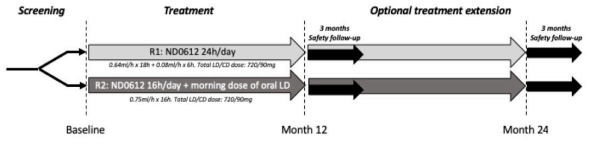
Background and aims: ND0612 is a drug-device combination that continuously delivers liquid levodopa/carbidopa by subcutaneous infusion to reduce motor complications in fluctuating Parkinson's disease (PD). This ongoing, open-label, one-year safety study (NCT02726386) aims to establish the long-term safety profile of ND0612.
Methods: Adult (>30 years old) patients with a diagnosis of PD (Hoehn & Yahr ≤3 during ON) taking ≥4 levodopa doses/day and ≥1 other PD medications were included. Patients had to have ≥2 hours of OFF time per day with predictable early-morning OFF periods. Patients were assigned to open-label treatment with ND0612 for either 24 hours or 16 hours + morning dose of oral levodopa (Figure). Adjunct oral PD medications can be taken as needed. Safety/tolerability is assessed through adverse events and percentage of early discontinuations. At study end, patients can opt to continue on their allocated treatment for an additional 2-years.



BeyoND study design

Results: 214 patients have been enrolled (24-hour regimen: n=91; 16-hour regimen: n=123) at 46 sites (8 countries). Overall, 66% of patients are male and the mean±SD age is 64.1±8.76 years. Patients have an average time (mean±SD) from PD diagnosis of 9.5±4.9 years and have had motor fluctuations for 5.2±4.2 years. The mean±SD LD dose is 1060±665mg, with 52.2% of patients taking ≥900mg LD/day. The mean duration of daily OFF time at baseline is 5.47±2.72 hours and the mean baseline UPDRS motor score is 27.4±12.5.
Conclusion: This is the first study to evaluate the long-term safety of ND0612 in PD patients experiencing motor fluctuations.
Disclosure: Funded by NeuroDerm

EPR1072

withdrawn

EPR1073

Correlation between structural neuroimaging and clinical outcomes in a small sample of patients with early Huntington's disease

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Background and aims: Scores on the symbol digit modalities test (SDMT), Stroop word-reading, Total Motor Score (TMS) and composite UHDRS (cUHDRS) are correlated with disease progression and brain changes in large samples of patients with Huntington's disease (HD). Here we sought to correlate the clinical measures in HD with atrophy rates and brain volumes in a small sample of early manifest patients.
Methods: Participants were recruited from the PADDINGTON study and comprised 49 early HD patients from 4 sites. Statistical analysis was performed using Stata version 12.0. The boundary-shift integral (BSI) was used to calculate change over 15 months in whole brain, caudate and ventricular volumes. Baseline grey matter (GM), white matter (WM), whole-brain (WB) volumes and voxel-based morphometry (VBM) analysis were performed using SPM12. VBM results were considered significant at $p<0.001$.
Results: Ventricular BSI correlated with SDMT ($p=0.038$), Stroop ($p=0.005$), TMS ($p=0.026$) and cUHDRS ($p=0.006$). GM volume showed statistically significant correlations with SDMT ($p<0.001$), Stroop ($p=0.03$), TMS ($p=0.001$) and cUHDRS ($p=0.045$). WB volume correlated with SDMT ($p<0.001$), Stroop ($p=0.045$), TMS ($p=0.02$). Brain BSI showed correlations with Stroop ($p=0.03$) and cUHDRS ($p=0.03$), all results shown at an uncorrected level. VBM showed correlations between baseline GM volumes of several subcortical nuclei with all clinical measures. (shown below in Image 1)
Conclusion: There were statistically significant associations between clinical measures and change over time in brain volumes, suggesting that clinical decline is closely linked to ongoing pathology in HD.

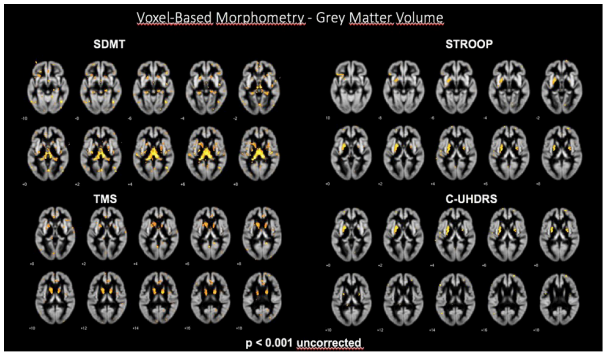

Image 1

Disclosure: Nothing to disclose

EPR1074

Depressive symptoms are associated with lower locus coeruleus volumes in Parkinson's disease

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Background and aims: Depression associated with Parkinson's disease (PD) has a different symptom profile to endogenous depression, with high frequency and severity of anxiety. The aetiology of depression in PD remains uncertain though abnormal noradrenergic neurotransmission could play a role. We aimed to assess the integrity of locus coeruleus function via in vivo neuromelanin-sensitive MRI in antidepressant-naïve patients with PD.
Methods: 34 patients with PD were enrolled and underwent a full clinical battery including the patient-reported Beck Depression Inventory-II (BDI-II), the clinician-reported Hamilton Rating Scale for Depression (HRSD), and the structured clinical interview for DSM-IV Axis I Disorders (SCID-I). All subjects underwent a 3T neuromelanin-sensitive MRI.
Results: 10 of 34 patients with PD (29.4%) had BDI-II and HRSD scores above the discriminative cut-off for PD depression though only half of these patients could be classed on SCID-I criteria as having an anxiety/mood disorder. Patients with PD with the highest scores for depression symptoms showed significantly lower volume of locus coeruleus ($P<0.05$) on neuromelanin-sensitive MRI compared to low score cases, and lower volume of locus coeruleus was correlated with higher BDI-II ($r=0.671$, $P<0.001$) and HRSD scores ($r=0.751$, $P<0.001$).
Conclusion: Depressive symptoms in antidepressant-naïve patients with PD correlate with lower volume in the locus coeruleus possibly reflecting lower extracellular noradrenaline levels. Our data are compatible with a key role of abnormal noradrenergic neurotransmission contributing to the pathophysiology of PD depression.
Disclosure: Nothing to disclose

EPR1075

Efficacy responders to opicapone among Parkinson's disease patients with 'early' motor fluctuations: data from the BIPARK-I double-blind experience

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Background and aims: To evaluate, in levodopa-treated Parkinson's disease (PD) patients with 'early' motor fluctuations, the proportion of patients (i.e., responders) achieving at least one hour of OFF-time reduction or one hour of ON-time increase. Opicapone (OPC), a once-daily COMT inhibitor, proved effective in the treatment of motor fluctuations in PD patients in two large, pivotal, multinational trials (BIPARK-I and II) [1,2].
Methods: Double-blind, 14- to 15-week, placebo- and active-controlled study [1]. 'Early fluctuators' (EF) were defined as subjects with onset of motor fluctuation within <2 years of study baseline. This post-hoc analysis investigated ON- and OFF-time responders of OPC-50mg compared with entacapone (ENT) and placebo (PLC) in EF levodopa-treated PD patients.
Results: In total, 359 patients were randomized to PLC (n=121), OPC-50mg (n=116) or ENT (n=122); 206 patients were EF (PLC, n=66; OPC-50mg, n=70; ENT, n=70). Overall, in the OPC-50 mg group, proportions of OFF-time (70% vs. 48%; p=0.001) and ON-time (65% vs. 46%; p=0.003) responders were significantly higher than PLC. For EF, in the OPC-50 mg group, proportions of OFF-time (69% vs. 47%; p=0.0157) and ON-time (66% vs. 42%; p=0.0061) responders were significantly higher than PLC. No significant differences were noted in proportions of OFF- and ON-time responders for ENT versus PLC in overall (58% vs. 58%) and EF (56% vs. 56%) populations.
Conclusion: OPC-50 mg was effective in reducing motor fluctuations in 'early fluctuators', resulting in a significant proportion of responders, similar to total population.
1. Ferreira et al., Lancet Neurology 2016; 15(2):154-165.
2. Lees et al., JAMA Neurol. 2017; 74(2):197-206.
Disclosure: This study has been supported by BIAL - Portela & C[a], S.A.

EPR1076

Elevated iron load in globus pallidus in patients with cervical dystonia

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Background and aims: The pathophysiology of idiopathic cervical dystonia (CD) is still poorly understood. Increased brain iron levels have been described in several movement disorders. The objective of this study was to determine the presence of basal ganglia iron abnormalities in CD compared to healthy controls (HC).
Methods: We included 37 patients with clinically diagnosed CD (15 M/ 22 F; age 57.6±14 years; mean disease duration 16.6±10. 8 years) and 37 age- and sex-matched HC. All subjects underwent a 3T cerebral MRI protocol, as well as detailed clinical examinations. For quantitative iron measurement we performed R2*-relaxometry and Quantitative Susceptibility Mapping (QSM). As regions of interest we defined caudate nucleus, thalamus, putamen, globus pallidus and substantia nigra. Group differences were calculated by t-test (for normally distributed variables), otherwise by Mann-Witney-test and results were corrected with Bonferroni correction for multiple comparisons. For clinical correlations we performed Spearman correlations.
Results: CD patients showed significantly higher R2* ($p=0.025$) and QSM ($p=0.015$) values in bilateral GP. There were no significant group differences in other basal ganglia regions. There was no significant correlation between R2* or QSM in GP and disease duration, Burke-Fahn-Marsden scale and TSUI score.
Conclusion: We found elevated R2* levels and for the first time susceptibility changes in the GP using QSM, which is regarded as more sensitive to iron. Future (longitudinal) studies need to clarify if the pallidal iron accumulation represents a pivotal event or an epiphenomenon in the pathophysiology of CD.
Disclosure: Nothing to disclose

MS and related disorders 1

EPR1077

Reduced rate of brain atrophy after 5 years of ocrelizumab treatment in patients with PPMS from the Phase III ORATORIO Trial

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Background and aims: Analyses of ORATORIO and ORATORIO open-label extension (OLE) demonstrated ocrelizumab reduced the risk of 24-week confirmed disability progression versus placebo in the double-blind period (DBP) by 25% (p=0.037), and had consistent and sustained benefits over 5 years of DBP/OLE favouring earlier and continuous treatment. For whole brain volume (WBV), a 17.5% (p=0.02) relative reduction of brain volume loss from Week 24 to 120 was demonstrated in the DBP. These analyses assessed efficacy of switching to or maintaining ocrelizumab on brain atrophy in the OLE of ORATORIO (NCT01194570) in primary progressive multiple sclerosis (PPMS) through 5 years of follow-up.

Methods: At the end of the ORATORIO DBP, patients remained on randomised treatment until the trial outcome was ascertained. Patients entered the OLE ~3–9 months after DBP cut-off and either continued ocrelizumab or switched from placebo to ocrelizumab. Changes in WBV are reported for Week 120 of the DBP and Week 96 of the OLE.

Results: At week 120, percentage change from baseline in WBV was –1.472%/–1.304% for placebo/ocrelizumab (Δ=0.168%; p=0.085). For week 96 of the OLE, corresponding percentage change from original study baseline was –2.960%/–2.595% (Δ=0.366%; p=0.043). Consistent trends were observed for cortical grey and white matter volumes.

Conclusion: ORATORIO demonstrates a long-term reduction in brain atrophy with continuous ocrelizumab versus placebo-ocrelizumab switch in PPMS, measured over 5 years of DBP/OLE. Reduced rates of brain atrophy were observed for whole brain, cortical grey and white matter volume in patients receiving ocrelizumab earlier and continuously compared with when ocrelizumab initiation was delayed.

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

EPR1078

Predictive value of conventional MRI parameters in first spinal attacks of neuromyelitis optica spectrum disorder

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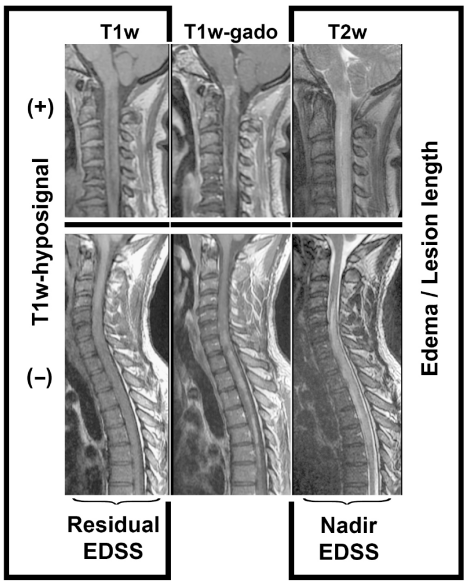
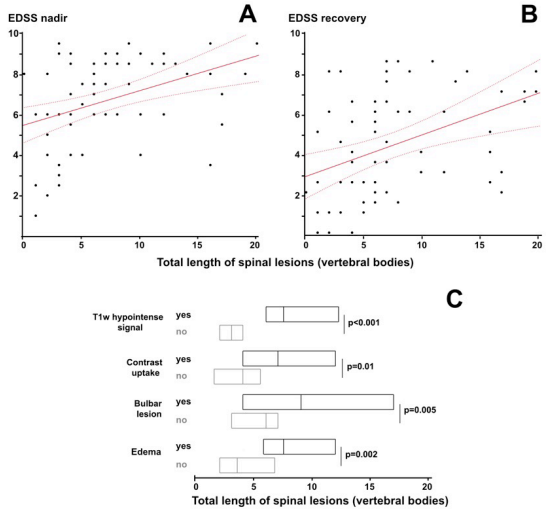
Background and aims: While spinal cord (SC) attacks of neuromyelitis optica spectrum disorder (NMOSD) are often devastating, signs predictive of their poor clinical outcome have been elusive until now, except for the delay in initiating plasma exchange (PE).
We studied the correlation between conventional non-standardized MRI parameters, PE treatment and clinical data obtained at nadir and recovery.
Methods: Retrospective monocentric study of first SC attacks of NMOSD.
Results: 69 Afro-Caribbean NMOSD patients were included (AQP4-antibodies positive in 65%). Median nadir and residual EDSS were respectively 7.5 and 4.0. In bivariate analysis, all conventional MRI parameters were highly correlated with nadir and residual EDSS. In multivariate analysis, nadir EDSS strongly correlated with lesion length and edema, whereas residual EDSS correlated with T1w hypointense signal. Contrast uptake was not associated with outcome.



Relation between MRI parameters with clinical prognosis.



Correlation between MRI parameters and EDSS. (A) Correlation between lesion length and nadir EDSS ($r=0.44$; $p<0.001$), (B) and residual EDSS ($r=0.47$; $p<0.001$). Best fit straight lines with confidence intervals. (C) Correlation between lesion length and other MRI parameters (hypointensity-T1, T1-enhancement, bulbar lesion and edema).

Conclusion: A specific pattern of lesions in conventional MRI data is differentially associated with nadir and residual EDSS. Lesions associated with poor prognosis should prompt highly efficient treatment.
Disclosure: Nothing to disclose

EPR1079

Sys4MS: Multiple sclerosis genetic burden score in a systems biology study of MS patients from four countries

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Background and aims: Multiple Sclerosis (MS) is an auto-inflammatory disease affecting the nervous system resulting in different neurological deficits of varying degree. A systems biology study (Sys4MS) was initiated in 2015, studying the complex interplay between genetic and environmental risk factors in MS. We aim to combine integrative omics, imaging and clinical data, in order to develop personalized healthcare for MS patients. We present the genetic risk score analysis in this abstract.

Methods: Four participating centres included 328 MS patients and 90 healthy controls. Genotypes were obtained for 152 out of 200 MS-associated single nucleotide polymorphisms (SNPs) as well as for 17 out of 32 MS-associated HLA loci. The sum of the MS genetic burden (MSGB) per individual was calculated.

Results: The patients (71% women) had a mean age of 43 years. The median expanded disability status scale (EDSS) score was 2.0 (range 0-8.0). The MSGB of patients was significantly higher as compared to the healthy controls (respectively 4.23 vs 3.20, p-value 3.4*10-8, Figure 1). We observed several significant differences in the MSGB between patients from the participating centres (Norway, Germany, Spain and Italy, Figure 2) indicating that genetic background is an important factor in MSGB-based analyses.

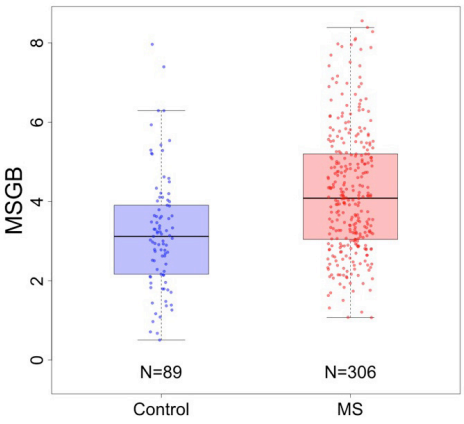

Figure 1. Boxplots of the MS genetic burden score of controls (blue) and MS patients (red). Dots represent individual scores. The boxes delimit 25% and 75% of the values; the horizontal bars represent the median value. The whiskers represent values that do not exceed a distance of 1.5 times the interquartile range from the middle 50% of the data.

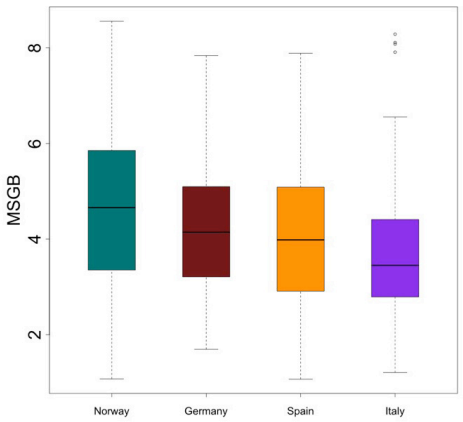

Figure 2. Boxplots of the MS genetic burden for MS patients only by country (Green - NOR, Brown - GER, Yellow - ESP, Purple - ITA). Boxes delimit 25% and 75% of the values; horizontal bars indicate the median value. The whiskers represent values that do not exceed a distance of 1.5 times the interquartile range from the middle 50% of the data.

Conclusion: In line with previous studies, MS patients had higher a MSGB as compared to healthy controls. We hypothesize that genetic background may influence the observed difference in MSGB between different countries, stressing the importance of correction for genetic ancestry in subsequent analyses applying the MSGB.

Disclosure: This project is funded by the EU-program ERACoSysMed.

EPR1080

withdrawn

EPR1081

Impairment of neurotransmitter networks in patients with Multiple Sclerosis: Clinical implications

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Background and aims: Neurons communicate through the release of neurotransmitters modulating their activity. There is mounting evidence regarding the role of neurotransmitter networks in neurodegenerative diseases, such as Parkinson's and Alzheimer's disease, however the role of neurotransmitter networks in Multiple Sclerosis (MS) has not been thoroughly assessed. We investigated the changes in the modulatory neurotransmitter networks including the serotonergic, noradrenergic, cholinergic and dopaminergic systems.
Methods: We applied resting-state functional connectivity and graph theory to evaluate neurotransmitter network dysfunction within these networks, and their association with clinical disability in MS. Twenty-nine MS patients and 24 age- and gender-matched healthy controls performed clinical and cognitive assessments including the expanded disability status score, symbol digit modalities test and Hamilton Depression rating scale.
Results: We demonstrated a diffuse reorganization of network topography ($P<0.01$) resulting in damage of serotonergic, cholinergic, noradrenergic and dopaminergic networks in patients with MS. Serotonergic, noradrenergic and cholinergic network impairment was associated with disease duration, EDSS and depressive symptoms ($P<0.01$). Serotonergic, noradrenergic, cholinergic and dopaminergic network impairment was associated with cognitive abilities ($P<0.01$). Disease severity, assessed through the MS severity score was associated with both noradrenergic and serotonergic network impairment ($P<0.01$).
Conclusion: The identification of in vivo functional changes and neurotransmitter network reorganization in MS could provide opportunities to develop novel neurotransmitter-targeting symptomatic treatments. Furthermore, our results indicate that the assessment of resting-state neurotransmitter networks might be a useful tool in predicting disability burden over time, and could serve as a surrogate endpoint regarding treatment efficacy in clinical trials with novel disease modifying drugs.
Disclosure: Antonio Carotenuto, Heather Wilson, Beniamino Giordano, Silvia P. Caminiti, Zachary Chappell, George Dervenoulas, Steven C.R. Williams and Alexander Hammers declare no potential conflicts of interest with respect to the research, authorship and/or publication of this abstract. Dr Eli Silber and Peter Brex received funding to attend lectures, advisory board and for lecturing from Biogen, Merck, Teva, Genzyme and Roche. Professor Marios Politis research is supported by Parkinson's UK, Lily and Edmond J. Safra Foundation, Michael J Fox Foundation (MJFF) for Parkinson's research, and CHDI Foundation.

EPR1082

In vivo evaluation of Multiple Sclerosis pathology with combined perfusion and diffusion MR imaging.

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Background and aims: Inflammation, demyelination, perfusion changes and axonal degeneration are the pathological changes in Multiple Sclerosis (MS). Lesions detected through T2-weighted images might show either hyper- or hypo-perfusion suggesting that they can be acute, sub-acute or chronic. The combination of perfusion and diffusion imaging might be a useful tool to classify lesions according to their stage, possibly detecting the residual inflammatory activity even in presence of an intact blood-brain barrier.

Methods: 25 relapsing-remitting MS patients (EDSS=3.18±1.42 and annualized relapse rate=0.63±0.34), and 22 age- and gender-matched healthy controls (HCs) were enrolled. All participants underwent clinical assessments and MRI scans, including diffusion tensor imaging to measure fractional anisotropy (FA) and arterial spin labeling to measure the cerebral blood flow.

Results: Compared to HCs' white matter, the outer and the inner T2 perilesional layer (8 to 4 mm and 4 to 0 mm from lesion border, respectively), T2 and T1 lesions showed reduced cerebral blood flow (-15.8%, -21.6%, -28.7% and -31.2%, respectively; $P<0.001$). Highly perfused T2 lesions showed a lower FA compared to T2 lesions with a reduced perfusion (0.29±0.11 and 0.32±0.11, respectively; $P=0.004$).

Conclusion: Combined perfusion and diffusion imaging approach might differentiate chronic lesions from lesions with an on-going residual inflammatory process even in the absence of a disrupted BBB and gadolinium enhancement. This finding might be used to evaluate drug efficacy toward neuroinflammation in MS with the ultimate goal to prevent their evolution toward a chronic and irreversible stage.

Disclosure: Antonio Carotenuto, Heather Wilson, Beniamino Giordano, Zachary Chappell, George Dervenoulas, Steven C.R. Williams and Alexander Hammers declare no potential conflicts of interest with respect to the research, authorship and/or publication of this abstract. Dr Eli Silber and Peter Brex received funding to attend lectures, advisory board and for lecturing from Biogen, Merck, Teva, Genzyme and Roche. Professor Marios Politis research is supported by Parkinson's UK, Lily and Edmond J. Safra Foundation, Michael J Fox Foundation (MJFF) for Parkinson's research, and CHDI Foundation.

EPR1083

Direct comparison between T1/T2-weighted ratio MRI and [18F] florbetaben PET imaging as measures of myelin integrity in multiple sclerosis

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Background and aims: Cortical demyelination in multiple sclerosis correlates with physical and cognitive disability. In vivo imaging tools are limited in their ability to detect cortical demyelination. Both T1-w/T2-w ratio images and PET imaging using β-amyloid targeting tracers were proposed as specific tools for myelin imaging. We performed a direct comparison between T1-w/T2-w ratio and [18F]florbetaben PET imaging to test the ability of T1-w/T2-w ratio in detecting demyelination.
Methods: 12 multiple sclerosis patients and age- and gender-matched healthy controls were enrolled. All subjects underwent one hybrid PET-MRI scan. Distribution volume ratio, calculated using supervised cluster analysis, was used to assess [18F]florbetaben binding. T1- and T2- weighted images were used to construct the T1-w/T2-w ratio. PET and T1/T2-w ratio cortical grey matter Z-score maps were calculated for each individual MS patient selecting cortical gray matter and compared using a voxel-wise analysis (one-sample t-test performed with two images per subject, P-value threshold at 0.05 family wise errors corrected).
Results: T1-w/T2-w ratio was higher compared to PET imaging in detecting cortical demyelination in several cortical areas, including cerebellar cortex (all $P<0.001$). Lower mean T1-w/T2-w ratio values were detected only for the intralesional layers (all $P<0.05$) compared to healthy controls' white matter, whereas lower diffusion volume ratio values were detected in both perilesional and intralesional layers ($P<0.001$).
Conclusion: When compared with [18F]florbetaben PET imaging, T1-/T2-weighted ratio underestimates demyelination in both grey and white matter. Therefore, caution should be used when assessing demyelination and, eventually, remyelinationin clinical trials through T1-/T2-weighted.
Disclosure: This research was financially supported by Piramal Imaging Ltd. Dr Eli Silber and Peter Brex received funding to attend lectures, advisory board and for lecturing from Biogen, Merck, Teva, Genzyme and Roche. Professor Marios Politis research is supported by Parkinson's UK, Lily and Edmond J. Safra Foundation, Michael J Fox Foundation (MJFF) for Parkinson's research, and CHDI Foundation.

MS and related disorders 2

EPR1084

Fingolimod versus glatiramer acetate in patients with relapsing-remitting multiple sclerosis – ASSESS study results

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Background and aims: The ASSESS, rater- and dose-blinded study, evaluated whether fingolimod (0.5mg and 0.25mg) has superior efficacy compared with glatiramer acetate (GA) 20mg in reducing disease activity over 12 months in patients with relapsing-remitting multiple sclerosis.

Methods: Eligible patients were randomised to receive once-daily oral fingolimod 0.5mg (N=345), 0.25mg (N=366), or subcutaneous GA 20mg (N=324). Superiority of the fingolimod doses was tested hierarchically: 0.5mg versus GA followed by 0.25mg versus GA. The primary endpoint was reduction in annualised relapse rate (ARR), and secondary endpoints were MRI measures of disease activity at 12 months. Safety and tolerability were assessed.

Results: Over 12 months, fingolimod 0.5mg significantly reduced ARR versus GA (relative reduction, 40.7%; p=0.0138); reduction with fingolimod 0.25mg was not significant versus GA. Compared with GA, fingolimod 0.5mg and 0.25mg doses significantly reduced the number of new/newly enlarged T2 lesions (p<0.0001 for both) and gadolinium-enhancing (Gd+) T1 lesions (p=0.0167 and p=0.0011, respectively). T2 lesion volume was significantly reduced with both fingolimod doses (p<0.0001 and p=0.0060, respectively), whereas reduction in Gd+ T1 lesion volume was significant with fingolimod 0.5mg dose (p=0.0052). The effect of fingolimod doses on brain volume changes was similar to GA. Adverse events reported with both fingolimod doses were consistent with the known safety profile.

Conclusion: Fingolimod 0.5mg showed superior efficacy versus GA in reducing the disease activity. Fingolimod 0.25mg has shown numerically similar effect on ARR and better effect on MRI lesion counts versus GA. Safety findings were consistent with the established safety profile of fingolimod.

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

EPR1085

Functional brain network organisation predicts cognitive decline in multiple sclerosis: a longitudinal magnetoencephalography study

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Background and aims: Disruptions in functional brain network organisation seem to be important underlying mechanisms of cognitive impairment in multiple sclerosis (MS). However, little is known about its longitudinal predictive value and its unique value beyond structural brain pathology.

This longitudinal study aimed to investigate the importance of disruptions in functional brain network organisation as a predictor of cognitive decline in MS patients, and to explore its unique value irrespective of structural pathology.

Methods: Magnetoencephalography (MEG) recordings and magnetic resonance imaging (MRI) were analysed in 100 MS patients at baseline. Neuropsychological assessments were obtained at baseline and after 5 years. Brain network organisation was computed using network properties of the Minimum Spanning Tree (MST; i.e. backbone of the functional brain network). Correlational and regression analyses were performed to relate these measures to cognitive decline, and to explore their effects beyond grey matter and white matter lesion volume.

Results: Cognitive decline was best predicted by both a disintegrated network (i.e. a loss of network complexity) in the delta band and a more integrated network (i.e. a larger chance of hub overload) in the beta band at baseline (MEG model: R2=21%). These network measures remained independent predictors of cognitive decline (p<0.05) when structural brain measures were included (combined model: R2=27%).

Conclusion: In conclusion, disruptions in functional brain network organisation can serve as predictive markers of cognitive decline in MS patients. These disruptions in functional brain network organisation may be responsible for cognitive decline irrespective of the accumulation of structural damage.
Disclosure: Nothing to disclose

EPR1086

Rapid reduction of lesion accumulation in specific white matter tracts as assessed by lesion mapping in RR-MS patients treated with IFN beta-1a

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Background and aims: In relapsing-remitting multiple sclerosis patients, interferon beta-1a (IFNbeta-1a) reduces brain lesion accumulation over time, as assessed by magnetic resonance imaging (MRI). We aimed to identify treatment-specific spatio-temporal areas using lesion probability mapping (LPM).
Methods: Post-hoc analysis of MRI data from the IMPROVE study, comparing patients treated with subcutaneous IFNbeta-1a (44micrograms) three times weekly (n=120) versus placebo (n=60). MRI examinations were acquired at weeks 4, 8, 12 and 16 to build lesion probability maps (LPMs) of cumulative combined unique active (CUA) lesions. Lesion location differences were assessed in several white matter (WM) tracts using predefined anatomic WM atlases. Voxel-wise comparisons assessed differences in lesion frequencies between IFNbeta-treated and placebo groups within general linear model framework using nonparametric permutations ($p<0.05$, cluster-corrected).
Results: IFNbeta-treated patients presented 50% reduction in CUA lesions compared with placebo group (treated: 41cm^3 at week 4; 95cm^3 at week 16; mean 24cm^3/month; placebo: 62cm^3 at week 4; 196cm^3 at week 16; mean 48cm^3/month) (fig 1). Tract analysis showed similar results; 50% reductions of lesion accumulation with IFNbeta in the cortico-spinal tract (CST), 52% in anterior thalamic radiation (ATR) and 65% in superior longitudinal fasciculus (SLF) (fig 2). At voxel-wise analysis, LPM of treated patients showed lower frequency of CUA lesions versus placebo from week 4. This was pronounced at week 16 in the left CST ($p<0.005$), left ATR ($p<0.005$) and right SLF ($p<0.02$) (fig 3).

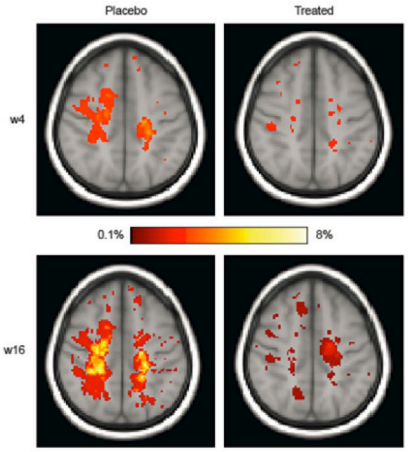

Fig 1: Follow-up LPM (week 4-16) of the spatial distribution of cumulative CUA lesions in the Placebo and Treated groups. The intensity corresponds to the probability, for that voxel, that a new lesion occurs.

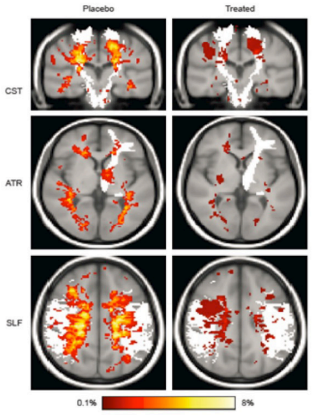

Fig 2: Follow-up LPM (week 4-16) of the spatial distribution of cumulative CUA lesions at the level of WM tracts in the Placebo and Treated groups. The intensity corresponds to the probability, for that voxel, that a new lesion occurs.

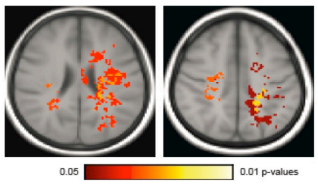

Fig 3: LPM showing clusters of significant lower frequency of CUA lesion occurrence in Treated with respect to Placebo at week 16. At each voxel, the color intensity corresponds to the p-value.

Conclusion: IFNbeta-1a reduces lesion accumulation in specific WM tracts versus placebo. Highest local differences were along regions involved in clinical manifestations such as CST, SLF and ATR.
Disclosure: This study was sponsored by Merck Serono S.p.A., Rome, Italy, an affiliate of Merck KGaA, Darmstadt, Germany.

EPR1087

Improvements with Alemtuzumab in clinical and MRI disease activity outcomes in RRMS patients across age groups: CARE-MS I and II 8-year follow-up

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Background and aims: In the 2-year (y) CARE-MS studies (NCT00530348; NCT00548405), alemtuzumab (12 mg/day; baseline: 5 days; 12 months later: 3 days) significantly improved outcomes versus SC IFNB-1a in RRMS patients. Efficacy was maintained through Y8 in 2 consecutive extensions (NCT00930553; NCT02255656 [TOPAZ]). We show 8-y alemtuzumab efficacy/safety in pooled CARE-MS patients stratified by age.

Methods: Patients were stratified by age at core study baseline: ≤25y (137/811 [17%]); >25 – ≤35y (350/811 [43%]); >35 – ≤45y (238/811 [29%]); >45y (86/811 [11%]).

Results: Through Y8, 590/811 (73%) alemtuzumab-treated patients remained on study; 50% received no additional alemtuzumab or other DMT. Patients received additional alemtuzumab for relapse only (18%–26%), MRI activity only (7%–10%), and relapse/MRI activity (9%–18%). At Y2 across age groups, alemtuzumab improved outcomes versus SC IFNB-1a (ARR: 0.22–0.24 versus 0.38–0.51, all P≤0.05; 6-month confirmed disability worsening-free [CDW-free]: 85%–92% versus 62%–88%; 6-month confirmed disability improvement [CDI]: 20%–31% versus 13%–25%; MRI disease activity-free: 70%–86% versus 42%–63%, all P≤0.001). Through Y8 in alemtuzumab-treated patients, ARR was stable, and CDW-free rates decreased with age, whereas CDI rates showed less variability. Across age groups, 61%–86% of alemtuzumab-treated patients were MRI disease activity-free at Y8, and median annual brain volume loss was ≤0.26% annually in Y3–Y8. Safety findings were generally balanced across age groups.

Conclusion: Alemtuzumab significantly improved outcomes versus SC IFNB-1a through Y2 in all age groups. Efficacy was maintained through Y8, with safety balanced across age groups, suggesting prolonged alemtuzumab benefit irrespective of age.

Disclosure: study support by Sanofi and Bayer HealthCare Pharmaceuticals.

EPR1088

Disease activity following fingolimod withdrawal in relapsing remitting multiple sclerosis: a monocentric Italian study

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Background and aims: Fingolimod (FTY) is a highly effective and well tolerated second-line drug approved for relapsing-remitting multiple sclerosis (RRMS). Nonetheless, a proportion of FTY-treated patients stops the drug during the first years due to side effects (SE) or lack of efficacy (LoE). We analyzed the different therapeutic strategies after FTY discontinuation in a monocentric Italian cohort to identify the best approach to be used in this setting.

Methods: Among 367 patients that started FTY before July 2014, 80 discontinued the drug after on average 23.5 months; new disease-modyfing treatments (DMT) were introduced based on treating neurologists and patients' preferences and periodic evaluations and MRI scans were performed according to standard clinical practice.

Results: 44.4% patients discontinued for LoE and 55.6% for other reasons (21% for SE, 34.6% for patient's preference or pregnancy planning). Patients were followed-up on average for 28 months. Overall 75.7% patients experienced disease reactivation during follow-up (44.7% showed a clinical relapse and 66.2% MRI activity), among whom 46% had stopped FTY due to LoE and 54% due to other reasons. Specifically, 31% showed disease reactivation during the first 3 months after FTY stop; among them 65.2% were not treated with any DMT, 17.4% had started a first-line DMT (injectives, teriflunomide or dimethyl-fumarate) and 17.4% were treated with monoclonal antibodies. Among subjects with early reactivation, 60.8% discontinued the drug for LoE, the remaining for other reasons.

Conclusion: FTY discontinuation bears a high risk of disease reactivation and the early start of DMTs is strongly recommended in this setting.

Disclosure: This study was partially funded by FISM (Federazione Italiana Sclerosi Multipla)

EPR1089

Subcutaneous Interferon β-1a: 10 years of the UK Multiple Sclerosis Risk Sharing Scheme

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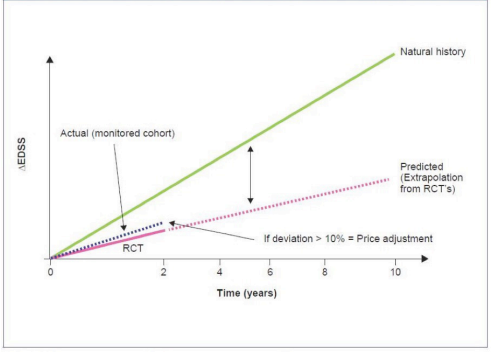
Background and aims: The UK Department of Health (DoH) established the multiple sclerosis Risk Sharing Scheme (RSS), providing patients with relapsing-remitting multiple sclerosis access to disease-modifying treatments (DMTs), whilst maintaining cost-effectiveness. We aim to present final Year-10 RSS results for patients treated with subcutaneous interferon beta-1a (sc IFNbeta-1a).

Methods: NHS patients meeting eligibility criteria and treated with DMTs entered the RSS. Disease progression was assessed biennially by Expanded Disability Status Scale (EDSS). Disease course was modelled based on baseline EDSS and long-term natural history (NH) data (British Columbia). 'Target' hazard ratios (HRs) applied to NH data allowed comparison of actual vs. target health-related quality of life (utility)-weighted EDSS. Shortfalls in treatment benefit exceeding 10% triggered price adjustments to restore cost-effectiveness (Figure 1). HRs producing zero shortfall were deemed 'implied HRs' (HRs <1 indicate treatment benefit).

Figure 1. The UK MS Risk Share Scheme: The basic premise



EDSS, Expanded disability status scale; **MS**, multiple sclerosis; **RCT**, randomised controlled trial.

Results: Analysis involved 1635 sc IFNbeta-1a-treated patients (mean baseline EDSS: 2.92; observed mean Year-10 EDSS: 4.12). Baseline, Year-10 expected untreated, and Year-10 expected with treatment, utility-weighted EDSS was 0.618, 0.486, and 0.535, respectively (actual observed utility-weighted EDSS: 0.534). The actual 2.6% shortfall reduced to zero with an implied HR of 0.77.

Conclusion: UK DoH criteria for cost-effectiveness were fulfilled throughout the 10 years of the RSS. The final Year-10 RSS analysis provides long-term evidence, within the context of a large scale 'real-world' evaluation, of the treatment benefits provided to patients treated with sc IFNbeta-1a.

Disclosure: Funded by Merck KGaA, Darmstadt, Germany

EPR1090

Cortical laminar assessment of T1 and T2* in the cerebellum of MS patients and controls at 7T MRI

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Background and aims: Histopathological studies showed that Multiple Sclerosis (MS) extensively affects the cerebellar white matter and cortex in patients with advanced disease. The aim of this study was to characterize the microstructural cortical changes in the cerebellum of early MS patients by using ultra-high field magnetic resonance imaging (MRI).

Methods: 18 relapsing-remitting MS patients (<5 years disease duration, median EDSS 1.5, range 1-2, 9/18 had very mild cerebellar deficits) and 9 age-matched healthy controls underwent quantitative T1 and T2* at 7T MRI using high-spatial resolution MP2RAGE (0.58 mm3 isotropic) and a ME-GRE MRI (0.7x07x0.9 mm3). The cerebellar cortex was segmented into three layers. Average T1- and T2*-maps were computed for each layer in the hemispheres and vermis and then compared between patients and controls using mixed effects models. False discovery rate was used to correct for multiple comparisons.

Results: In MS subjects, significantly longer T1 values were observed in all vermis layers (p for individual layers <0.01 to <0.02), in the middle and external layer of the cerebellar hemispheres (p<0.03). No between-group differences in T2* values were found.

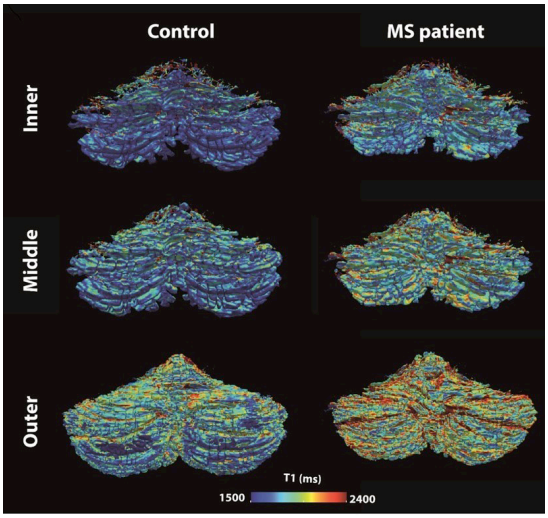

Fig. 1 T_1 maps of the three cerebellar layers in an MS patient and in a healthy control. The middle and the outer layer show significantly longer T_1 in the MS patient compared to the healthy control.

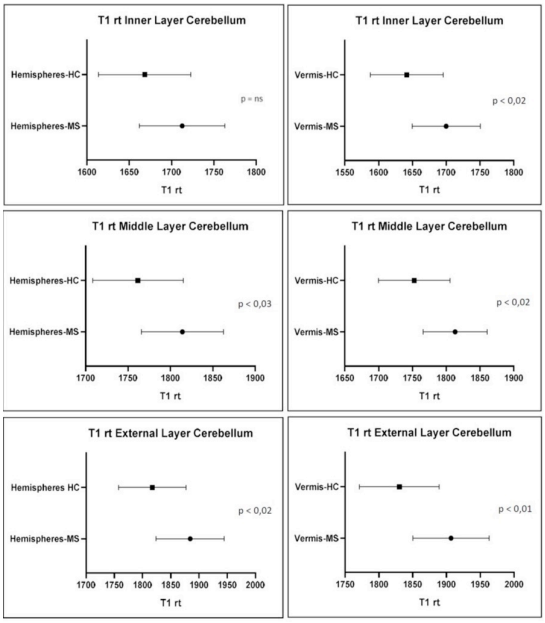

Fig. 2 Quantitative T_1 values in cerebellar vermis and hemispheres, comparison between healthy controls and MS patients. Significantly longer T_1 relaxation times (rt) values are found in MS patients in all three vermis layers ($p < 0.01$ to < 0.02) and in the middle and external layer of the cerebellar hemispheres ($p < 0.03$).

Conclusion: The observed T1 increase in early MS patients suggests significant demyelination of cerebellar cortex. The absence of a measured change in T2* may be due to the lower spatial resolution of the ME-GRE and/or to the lower sensitivity of T2* (compared to T1) to demyelination. Furthermore, the higher sensitivity of T2* to changes other than demyelination (e.g. iron accumulation) could also overshadow the effects of demyelination.

Disclosure: Nothing to disclose

Neurogenetics 1

EPR1091

Genotype-phenotype correlation in Complicated Hereditary Spastic Paraparesis (HSP) with Thin Corpus Callosum (TCC) in a specialized unit in Southern Spain

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Background and aims: To describe patients assessed in our Unit with HSP-TCC and confirmed molecular diagnosis
Methods: We selected patients assessed in our unit with confirmed diagnosis of HSP-TCC. After applied our protocol of study we analyzed different variables such as clinical, radiological and molecular, in order to correlate genotype-phenotype.
Results: We included six cases, three of them are siblings. Five cases presented an early onset. Five cases have positive family history with recessive inherence pattern. We have been able to identified molecular diagnosis in all them: 2 cases with compound heterozygosis in SGP11 gen (SPG11), the 3 sibling share the same DDHD2 homozygosis mutation (SPG54), and one case showed a homozygosis mutation in GBA2 gen (SPG46). They all presented spasticity in the lower limbs. The SPG11 cases did not presented cognitive decline while SPG54 siblings and SPG4 case associated a severe cognitive decline. As other neurological features, SPG46 case showed remarkable cerebellar signs and axonal polineuropathy, while one of SPG11 case showed parkinsonism confirmed with abnormal DAT-scan. Regard cranial MRI, the common feature was the TCC, being remarkable in SPG11 and SPG54 in comparison with SPG46 who associated cerebellar atrophy, the 2 cases of SPG11 also show the characteristic "Ears-of-the-lynx" sign
Conclusion: Hereditary Spastic Paraparesis constitute a heterogeneous group of diseases, becoming diagnosis a challenge, reason why taking in account radiological sings as Thin corpus callosum could be a useful tool in the diagnosis approach. As far as we know, we described the first cases of SPG54 and SP46 in Spain.
Disclosure: Nothing to disclose

EPR1092

Biallelic mutations in PNPLA6 gene in a patient with late-onset ataxia and hypogonadotropic hypogonadism

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Background and aims: Autosomal recessive cerebellar ataxias (ARCAs) are a heterogeneous group of clinical conditions, often associated with non-cerebellar features. Two syndromes combined early-onset ARCA with hypogonadotropic hypogonadism: Boucher-Neuhäuser syndrome, which is associated with chorioretinal dystrophy, and Gordon Holmes syndrome, associated with brisk reflexes. The patatin-like phospholipase domain containing protein 6 (PNPLA6) gene has been correlated with both syndromes. PNPLA6-related disorders present a continuum spectrum of clinical manifestations, including ataxia, spasticity, brisk reflexes, peripheral neuropathy, intellectual, eye and hair abnormalities, hypogonadotropic hypogonadism and hypopituitarism. How mutations in a single gene causes such a wide range of disorders is unknown. Here we report clinical and genetic findings in a patient harbouring compound heterozygous mutations in PNPLA6.
Methods: A 56-year-old man was referred to us for a mild cerebellar ataxia with onset during the third decade of life. Medical history was significant for hypogonadotropic hypogonadism. Family history was unremarkable. Neurological examination showed ataxic-spastic gait, occurrence of central nystagmus, dysmetria and dysdiadochokinesia, pyramidal hypertonia and brisk deep tendon reflexes. Brain MRI displayed white matter hyperintensities in the periventricular and subcortical areas and cerebellar atrophy of superior vermis. Neurophysiologic studies were normal. Intelligence quotient was 77. Ophthalmological examination and Optical Coherence Tomography exam ruled out chorioretinal dystrophy.
Results: Genetic analysis of PNPLA6 gene demonstrated two novel heterozygote mutations (c.2264A>C/p.Q755P and c.3388C>T/p.H1130Y).
Conclusion: Genetic analysis of the PNPLA6 gene should be considered in the screening of all patients with ARCAs associated with hypogonadism. Further studies will help to define how mutations correlate with a broad clinical spectrum.
Disclosure: Nothing to disclose

EPR1093

Non-motor manifestations in premanifest Huntington's disease

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Background and aims: A diagnosis to manifest Huntington's disease (HD) is made when motor signs are unequivocally identified. Cognitive and behavioral symptoms are often present years before but not always recognized as signs of HD in clinical practice.
Our aim is to characterize the nonmotor features in premanifest HD gene carriers.
Methods: We performed an observational study of HD patients in a tertiary center. Two groups were compared: 18 HD mutation carriers without motor signs (Unified HD Rating Scale<4) and 18 controls, in two consecutive evaluations over one year. Nonparametric statistic analysis was conducted to compare neuropsychological score (depression, drive/executive, irritability, psychosis, apathy and suicidal ideation) and cognitive performance (symbol-digit, verbal fluency and stroop interference). A $p<0.05$ was considered statistically significant.
Results: Premanifest HD patients had a median age of 35.18 years, 13 were females, and the majority (72.2%) had cognitive and behavioural manifestations. Only 1 patient presented suicidal ideation. In the two consecutive evaluations, HD premanifest patients had higher scores of depression (11.67 vs 5.94, 9.78 vs 3.12, $p<0.05$) and irritability (5.81 vs 0.94, 5.61 vs 0.82, $p<0.05$) when compared to control group. There were also significant differences in speed of cognitive processing (0.78 vs 0.65, 0.78 vs 0.18, $p<0.05$) and verbal perseveration (1.22 vs 0.24, 1.17 vs 0.41, $p<0.05$) with worse performance in the group of pre-manifest HD.
Conclusion: In our study, nonmotor features, particularly behavioral (depression and irritability) and cognitive (speed of cognitive processing and verbal perseveration), are present in premanifest HD patients. We highlight the need to detect changes in these domains and discuss the inclusion of behavioral and cognitive criteria in clinical diagnosis of HD.
Disclosure: Nothing to disclose

EPR1094

Stimulus-induced paroxysmal cranial dyskinesia and Nail Patella Syndrome co-segregate in a multigenerational family with a novel variant in the LMX1B gene

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Background and aims: Nail Patella Syndrome (NPS) is caused by autosomal dominant mutations in the LMX1B gene (NPS [MIM: 161200]), encoding the transcription factor LMX1B, important for cytoskeletal and kidney development. LMX1B is key in serotonergic and dopaminergic neuron circuit development in mammalian CNS. In a multigenerational Danish family stimulus-induced cranial dyskinesia with paroxysmal blepharospasms and pursing of mouth occurs together with musculoskeletal abnormalities and kidney dysfunction. A genetic linkage study identified the likely cause of this hereditary dyskinesia and its connection with the non-neurological phenomena.
Methods: Genome-wide single-nucleotide polymorphism (SNP) microarray analysis was performed for 13 family members and LOD score calculated. Subsequently, six additional family members were analyzed with short tandem polymorphism (STP) and SNP's and LOD score re-calculated. Whole exome sequencing was followed by Sanger sequencing and Western blotting to confirm presence of a novel variant and gene expression.
Results: Linkage to the 9q32-34.11 locus associated with NPS was found (LOD score Z=4.93). Exome sequencing revealed a novel missense variant (C>G transition) at position chr9: 126693822 (hg38) in LMX1B segregating with the dyskinesia and NPS-features. The transition (CAG>GAG) results in a Q to E amino acid change at position 264 in the protein. SIFT analysis deemed the variant pathogenic. Western blotting confirmed expression of LMX1B in both patients and healthy controls.
Conclusion: Paroxysmal dyskinesia is a hitherto unrecognized part of the clinical spectrum of NPS. The novel variant likely results in a toxic gain-of-function effect. We hypothesize that subsequent disruption of dopaminergic function is the underlying cause of the dyskinesia.
Disclosure: Nothing to disclose

EPR1095

Characterization of a Portuguese cohort of Machado-Joseph disease: besides ataxia

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Background and aims: Background: Machado-Joseph disease (MJD) is a rare autosomal dominant neurodegenerative disorder. Its phenotypical expression is remarkably polymorphic, with pyramidal, extrapyramidal, cerebellar, brainstem, peripheral nerve and cognitive involvement.
Aims: Determine the influence of clinical symptoms on quality of life (QoL).
Methods: A prospective cohort study was performed in MJD patients followed in a tertiary centre. Each patient was characterized in the following domains: ataxia (SARA score), non-ataxia signs (INAS score), cognitive function (MoCA score), QoL (ADL score), sleep (EQ-5D-3L score) and depression (PSQI and PHQ9 scores). Baseline and one-year follow-up evaluation were achieved and compared with a control group. Descriptive and comparative statistical analysis were performed, assuming $p<0.05$ as statistically significant.
Results: We enrolled 33 patients, 54.5% males, with mean CAGs expansion length 71.4 (±4.7) and mean age of symptom onset of 39.4 (±12.2) years. 9.7% of the patients presented SARA score<4 and all showed non-ataxic symptoms (82% pyramidal signs, 82% abnormal oculomotricity, 75% peripheral involvement, 68% extrapyramidal signs and 39% urinary dysfunction). Mean MoCA score does not differ from controls and patients' QoL is lower than controls ($p<0.001$). Patients with worse QoL had more extrapyramidal, urinary and oculomotor abnormalities, and higher scores on sleep and depression questionnaires. In 14 patients with longitudinal assessment, there was no evolution of SARA, QoL and sleep scores, but presented more non-ataxic signs and had lower scores in depression.
Conclusion: In our cohort, non-ataxic symptomatology (pyramidal, extrapyramidal, brainstem, dysautonomic, sleep and depression) negatively influences QoL. We highlight the possible therapeutic intervention in these symptoms.
Disclosure: Nothing to disclose

EPR1096

Expanding the mutation spectrum of Caveolinopathies: a novel heterozygous missense mutation in CAV3 gene causing idiopathic persistent hyperCKemia and dyslipidemia.

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Background and aims: CAV3 gene, which encodes caveolin-3, a muscle-specific membrane protein and the principal component of caveolae membrane in muscle cells in vivo, is the only gene known to cause caveolinopathies. Caveolins are involved in cellular metabolic regulation through calcium signaling but also in glucose and lipid metabolism.

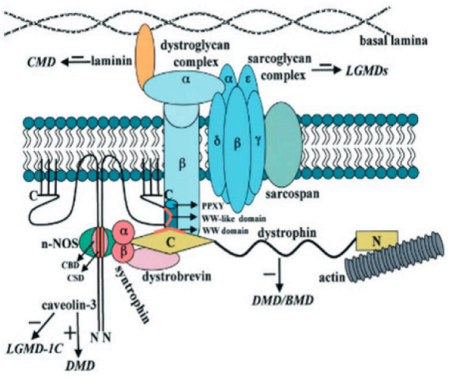

Fig.1 Sarcolemmal proteins. Arrows show diseases caused by the absence () or up-regulation (+) of the indicated gene. Deficience of CAV3 cause LGMD-1C.

Methods: A 45-year-old male patient was admitted to our Department because of persistent increasing creatin kinase (CK) serum levels from the age of twenty (ranging values between 300-500 U/L) and myalgias to lower limbs. His father, a brother and a child had high CK serum levels. He also referred a previous diagnosis of familial dyslipidemia. He underwent to protocol for neuromuscular disease.
Results: Clinical evaluation revealed bilateral corneal arch, neurological examination was neagative. Laboratories disclosed hypercholesterolemia (227 mg/dl), hyperCKemia was confirmed. Cardiological and pneumological assessment were normal. Muscle biopsy showed some "ring fibers" and multimini-core alteration. Immunofluorescence with anti-caveolin-3 antibodies on muscle biopsy showed reduced immuno-reactivity on the plasma membrane. Whole exome sequencing excluded mutation responsable of familial hypercholesterolemia and revealed a novel heterozygous c.130G>A (p.Val44Met) CAV3 missense mutation.

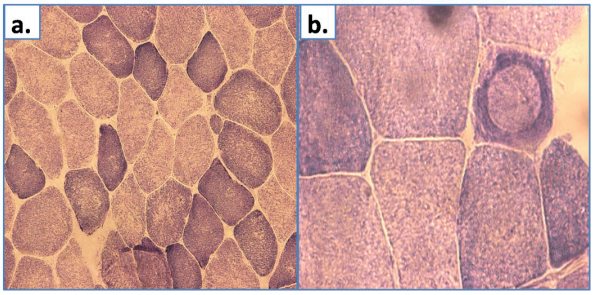

Fig. 2 Muscle biopsy showing multiminicores fibers (a) with NADH staining and ring fibers (b).

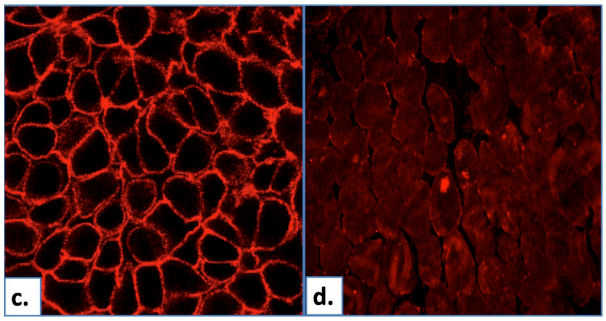

Fig.3 Caveolin3 antibody in muscle control (c), reduced expression of caveolin3 in probans muscle (d).

Conclusion: We describe a novel missense heterozygous mutation of CAV3 gene causing idiopathic persistent hyperCKemia and we propose a possible relationship between CAV deficiency and metabolic alteration. The LDL receptor requires a normal membrane structure to function properly, CAV3 is mainly expressed in muscle, but hepatocytes can also express low but functionally levels of CAV3. Altered expression in hepatocytes could be relevant for hypercholesterolemia. We suggest to do an accurate metabolic screening in this patients.
Disclosure: Nothing to disclose

Neuro-ophthalmology/ neuro-otology

EPR1097

Illusions and visual hallucinations in Parkinson's disase: Is it in the eye?

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Background and aims: Visual hallucinations (VH) (perceptions without object to perceive) and illusions (misperception of an existing object) are frequently reported in Parkinson's disease (PD). Many studies have investigated the pathophysiology of these phenomenoms, yet generally with no distinction between VH and illusions. We hypothesize that illusions could be related to low level visual impairment, while VH could be associated to a more widespread degeneration leading to higher levels visuo-perceptive and cognitive dysfunctions.
Methods: We included 30 PD with VH, 30 PD with illusions and 30 PD without illusions or VH matched for age and sex, and compared retinal thickness between these groups using spectral domain optical coherence tomography. We also compared clinical and demographical data, general ophthalmologic evaluation, sleep, cognitive and visuoperceptive functions, as well as morphologic and resting state MRI between these patients.
Results: Retinal layer thinning was observed in VH group compared to the others in the ganglion cells complex, in the inner temporal section of ganglion cells layer ($p=0.02$) and in the inner superior section of inner plexiform layer ($p=0.05$). Conversely, for the illusions group visual acuity was lower compared to the others ($p=0.04$) and prevalence of curable pathologies of the eyes anterior segment was higher ($p<0.01$).
Conclusion: Illusions in PD could be due to relatively isolated low level visual impairment with "bottom-up" dysfunction, while the thinning of dopaminergic retinal layers observed in VH, could reflect a more widespread degeneration and disease severity involving "top-down" dysfunction. Illusions and VH could have different pathophysiological mechanisms and prognosis.
Disclosure: This research has been granted an institutional support by the "Fondation de France".

EPR1098

Functional-structural assessment of the optic pathways in patients with optic neuritis

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Background and aims: To evaluate whether spectral domain optical coherence tomography (SD-OCT) and multifocal visual evoked potential (mfVEP) are potentially better biomarkers than conventional fuel field visual evoked potential (ffVEP) in diagnosing Optic Neuritis (ON).
Methods: A total of 126 eyes (66 eyes of patients with history of ON and 60 eyes of a sex and age matched healthy control (HC) group) were investigated.Inclusion criteria were normal ffVEP results shown in patients suspected of having a first episode of ON. Both eyes of the patients and controls were systematically investigated with SD-OCT (Cirrus 4000), Visual Acuity, ffVEP and mfVEP.
Results: With regards to OCT data, a significant group difference was found in mean RNFLt between patients and HC ($p=0.027$) (i.e. 84.24(±17.00)μm vs 92.54(±8.59)μm). A significant difference found in the inter-eye asymmetry of mean RNFLt between patients and HC ($p=0.035$) (i.e. 7.33(±8.48)μm vs 2.54(±2.06)μm).When analysing mfVEP sectors, asignificant group difference was found in mean mfVEP amplitude between patients and HC($p=0.002$)(i.e. signals produced from the 16 paracentral sectors in the upper hemifield).
Conclusion: Abnormality is potentially measurable (via reduced RNFLt and focal analysis of mfVEP amplitude) in patients suspected of having a first episode of ON, but where ffVEP reports normal results.The mfVEP and SD-OCT may together be of value as supplementary tools indiagnosing patients on suspicion of a first episode of ON where ffVEP reports no abnormality.
Disclosure: Dr. F. Schmidt has received a scholar stipend in neurophysiology from Lundbeck. Dr. Pihl-Jensen has received support from Biogen Idec for a currently ongoing observational trial of VisionSearch 1 mfVEP measurements in optic neuritis patients. Dr. Frederiksen has served on scientific advisory boards for and received funding for travel related to these activities and honoraria from Biogen Idec, Merck Serono, Sanofi-Aventis, Teva, Novartis, Genzyme and Almirall. Jette Frederiksen has received speaker honoraria from Biogen Idec, Merck Serono and Teva. She has served as advisor on preclinical development for Takeda.

EPR1099

Frequency, etiology and impact of vestibular symptoms in the emergency department

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Background and aims: We aimed to determine the incidence of all vestibular symptoms in a large interdisciplinary tertiary emergency department (ED) and to describe patient characteristics, presentations and frequency of etiologies.
Methods: In this one-year retrospective study, we manually screened all medical records of 23,608 ED visits over one year and identified a total of 2,596 visits by 2,464 patients. We evaluated all patients older than 16 years with vestibular symptoms as the main or accompanying complaint. We extracted clinical, radiological and laboratory findings as well as etiologies from medical records. Symptoms were classified according to the International Classification of Vestibular Disorders of the Bárány Society.
Results: In 2,596/23,608 visits (11%), patients reported at least one vestibular symptom, and in 1,677/2,596 visits (64.6%) vestibular symptoms were the main reason for the emergency department consultation. Vestibular symptoms were classified as dizziness (43.8%), vertigo (33.9%), postural symptoms (6.5%) or more than one symptom (15.8%). In 324/2,596 visits(12.5%), cerebrovascular events were the etiology of vestibular symptoms, and in 355/2,596 visits(13.7%), no diagnosis could be established. In 23.8% of visits with vestibular symptoms as main complaint, the underlying condition was life threatening.
Conclusion: Eleven percent of ED visits were by patients complaining of vestibular symptoms; in a quarter of visits with vestibular symptoms as main complaint, the etiology was life threatening. Frequency and medical impact of vestibular symptoms in the emergency department were higher than previously reported. Awareness of vestibular symptoms needs to be increased to identify life threatening conditions.
Disclosure: MG was funded by the Swiss Academy of Medical Sciences and the Bangerter-Rhyner Foundation through a Young Talents in Clinical Research grant (YTCR 13/18). Dr. Kalla and Dr. Mantokoudis were supported by the Swiss National Science Foundation (Grant #320030_173081).

EPR1100

Worldwide survey on vestibular testing: high variability of normal and pathological values

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Background and aims: The function of the peripheral vestibular system can be quantified. For the semicircular canals, the video head impulse test (vHIT) and caloric irrigation are used; for the sacculus, cervical vestibular evoked myogenic potentials (cVEMP), and for the utriculus, ocular VEMP (oVEMP) are used. Since there is no agreement on normal and pathological values, we performed a worldwide survey.
Methods: A web-based standardized platform was used to evaluate the "normal range" and "pathological cut-off" values. 38 renowned centers from all continents (except Africa) replied.
Results: "Normal values": vHIT: mean for the VOR gain of left horizontal canal (LHC) 0.91 (range: 0.7-1.01), the RHC 0.92 (0.7-1.05); side-difference 0.23 (0.05-0.1). Caloric irrigation: mean peak slow phase velocity of the caloric induced nystagmus for warm water 18.65°/s (12-30°/s), cold water 18.21°/s (10-25°/s). cVEMP: P13-N23 amplitude mean for the lower limit 28.67μV (16-50μV), upper limit 200μV (50-350μV). oVEMP N10 amplitude lower limit 7μV (6-8μV), N10 upper limit 12.5μV (10-15μV). "Pathological cut-off": vHIT: side difference 0.26 (0.1-0.4), bilateral vestibulopathy <0.61 (0.3-0.8); unilateral vestibulopathy (UVP) 0.68 (0.4-0.8). Caloric irrigation pathological side difference mean 25.93% (17.7-40%) or 12°/sec (5-30°/s); side-difference UVP 26.73% (20-40%) or 29.8°/s (5-100°/s). cVEMP: P13/N23 amplitude mean lower mean cut-off 32.5μV (15-50μV), mean upper cut-off 125μV (50-200μV), asymmetry 36.1μV (20-50μV).
Conclusion: This worldwide survey showed a large variability in terms of normal and pathological cut-off values in the 39 centers included. Therefore, standardization of how to achieve these values and which values one should agree on is highly warranted to guarantee a high quality of vestibular testing.
Disclosure: Nothing to disclose

EPR1101

Retinal thickness and microvascular pattern in early Parkinson's disease.

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Background and aims: Retinal dopaminergic neurons modulates colour vision and contrast sensitivity. Retinal dopaminergic depletion observed in Parkinson's disease (PD), could explain some of the associated visual symptoms. Spectral-domain optical coherence tomography (SD-OCT) studies demonstrated thickness reduction of the inner-retinal-layer in PD patients, notably in the nerve fiber layer (RNFL)1. Few studies have focused on possible correlation between RNLF thickness and retinal microvasculature2. We evaluated changes in retinal thickness and their possible correlates with microvascular pattern in early PD-patients compared to healthy-controls.
Methods: Patients fulfilling UK-Brain-Bank criteria for PD were recruited. Exclusion criteria were concurrent retinal or ocular disease, systemic disease impairing visual system (diabetes, uncontrolled hypertension/hypotension, cardio-vascular diseases) and other neurological diseases. Retinal microvasculature was analysed using coherence tomography angiography (OCT-A) and segmentation analysis of retinal-layers using SD-OCT. Retinal microvasculature was automatically divided into superficial and deep capillary plexus (SCP-DCP).
Results: N=21 eyes from PD patients (63.33±6.78 years) and N=16 eyes from controls (57.25±6.87 years) were evaluated. Considering age difference between-group, statistical inference has been performed using age as covariate. PD patients showed significant lower microvascular density in each macular DCP zones and thinner RNFL compared to control (p=0.05). In PD patients, there was a positive correlation between RNFL thickness and both superficial and deep foveal microvascular density respectively (r=0.67, p=0.006; r=0.65, p=0.008).
Conclusion: Retinal microvascular impairment and thinner RNFL were found in PD patients compared to controls. The correlation found between foveal microvascular density and intraretinal layers thickness in our PD patients could partially explained visual symptoms described since the early stage of disease.
Disclosure: Nothing to disclose

EPR1102

Diagnostic value of key signs in persistent postural-perceptual dizziness

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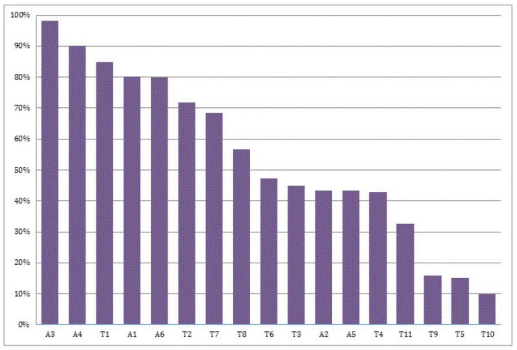
Background and aims: PPPD or persistent postural-perceptual dizziness is the new term which describes a chronic functional vestibular disorder. Brandt et al. (2015) proposed a set of key signs which could be addressed when interviewing patients suffering from psychogenic dizziness. However, their diagnostic value remains untested. The aim of our study was to prospectively assess the sensitivity of each of the aforementioned signs during the first interview of PPPD sufferers from our outpatient vertigo clinic.
Methods: We employed the key signs in 60 patients fulfilling the criteria of PPPD. Each of the key signs represented one question (table). The eligible answers were "yes", "no", "ambiguous"" and "undefined". Diagnostic sensitivity was calculated for each item.

Questions about typical features for a functional dizziness syndrome :
T1. Chronic spontaneous dizziness or unsteadiness lasting for months or longer (85 %)
T2. Dissociation between objective balance tests and subjective imbalance (71,1%)
T3. Fear of falls without a history of falls (45%)
T4. Improvement during bodily activity or mental distraction (42,9%)
T5. Improvement after alcohol consumption (15,2%)
T6. Inappropriate excessive anxiety or fear of impending doom (47,2%)
T7. Dizziness combined with non-vestibular or non-balance symptoms (68,3%)
T8. Situational or social events as triggers of dizziness and avoidance behavior (56,7%)
T9. Rotational vertigo without concurrent spontaneous nystagmus (15,8%)
T10. Unusual or bizarre postural and gait patterns (10%)
T11. Chronic unsteadiness and dizziness following transportation in vehicles (32,7%)

Questions about atypical features for a functional typical syndrome :
A1. Frequent episodic vertigo / dizziness attacks with symptom-free intervals (80,4%)
A2. Nausea and emesis (43,3%)
A3. Rotational vertigo with directional pulsion or falls (98,3%)
A4. Dizziness / vertigo with concomitant auditory symptoms (90%)
A5. Head rotation or head tilt as specific triggers (43,3%)
A6. Spontaneous suspicion of patients that psychological (not physical) stress is causative (80%)

Table: Key signs for PPPD modified after Brandt et al. J Neurol 2015;262:1977-1980. Sensitivities are given in parentheses.

Results: 60 patients completed the study (mean age 53 years). Our data indicated a significant variation in the sensitivity of the key questions with the majority of them displaying a rather low sensitivity (see table and graph). Regarding questions considered typical for PPPD, items T1 and T2 showed the highest sensitivity values (0.85 and 0.71 respectively). Nonetheless, 9 out of 17 items displayed sensitivities <0.5.



Graph: Ranked sensitivities of items for typical and atypical key signs.

Conclusion: We showed that certain questions show a satisfactory sensitivity regarding the diagnosis of PPPD. However, questions that are traditionally considered essential indicators of functional dizziness (such as improvement after alcohol consumption) proved to have very low sensitivity. Clearly, future studies, including organic vestibular disorders, are necessary for shedding light also on the specificity of these key signs, allowing clinicians to prioritize their questions when interviewing PPPD patients.
Disclosure: Nothing to disclose

EPR1103

A novel diagnostic index test to detect stroke as a cause of acute vertigo, dizziness and imbalance with high sensitivity and specificity

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Background and aims: Identifying stroke as a cause of acute vertigo and dizziness is still a challenge. The EMVERT-trial aimed to develop a sensitive and specific diagnostic index test to identify patients with a high risk to have stroke as an underlying cause.
Methods: 335 patients with acute vertigo or dizziness of unclear aetiology were included and underwent standardized clinical and apparative VOG testing, scoring of symptom characteristics and vascular risk factors and a MRI as a reference test for stroke. Data were used to compose a diagnostic index test to predict the risk of stroke. Predictors were analyzed using logistic regression for model selection and validation.
Results: MRI indicated cerebral ischemia in 44 patients. Stroke patients were significantly older (67.1 vs. 57.3 years) compared to non-stroke patients. Median ABCD2 score was 4 in stroke patients and 3 in those without ($p<0.0001$). Median TriAGe+ score was 8 in the stroke subgroup and 6 in the non-stroke subgroup ($p<0.001$). ROC-curves indicated a AUC=0.65 for the ABCD2 and 0.79 for the TriAGe+ score, to correctly indicate stroke. Variable feature selection resulted in a model consisting of age, skew deviation, head impulse test (HIT), history of vertigo, additional central symptoms, and vertigo-specific triggers. The combination of these features to a diagnostic index test resulted in AUC=0.87.
Conclusion: The combination of patient age, patient history, symptom characteristics (triggers, central symptoms) and clinical tests (HIT, test of skew) is feasible to indicate stroke in patients with acute imbalance with a high sensitivity and specificity.
Disclosure: The study was supported by the German Federal Ministry of Education and Research (BMBF) in the context of the foundation of the German Center for Vertigo and Balance Disorders (DSGZ) (grant number 01 EO 0901).

Neurorehabilitation

EPR1104

Neurorehabilitation with electronic games controlled by body movement in elderly patients with amnestic Mild Cognitive Impairment (aMCI)

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Background and aims: Practicing lifelong activities such as study, work, and leisure promote increased cognitive reserve, a brain resilience that makes the individual more tolerant to the pathological decline of cognition. Keeping the practice of these activities late in life can increase this reserve and reduce the risk of Alzheimer's.
The Aim was to verify the effects of neuroorrehabilitation with the use of Microsoft Kinect Sensor in the cognition of elderly patients of the MCI grouped in three levels of education: elementary, middle and higher.
Methods: 89 elderly women with aMCI completed the period of cognitive intervention. Participants were divided, according to educational level, in Experimental Group and Control Group, 44 and 45 participants, respectively. Twenty-four sessions were performed over three months. During this period there were assessments of cognitive performance with neuropsychological tests before and after the intervention sessions. The CG participated in assessments of cognitive performance and encounters with researchers. It was administered to WMS III.
Results: Cognitive intervention improved the performance of older women with elementary education in all WMS III memory measures. While it improved the performance of the high school seniors in immediate and delayed auditory memory, immediate memory and general memory. And maintaining performance in the group of older women with higher education.
Conclusion: The findings suggest that the potential for memory effect of older women with elementary education can be equated with the benefit of higher education. We can conclude that the cognitive training promoted the consolidation of learning in the elderly with low educational level.
Disclosure: Nothing to disclose

EPR1105

Pilot study on BEATPARK, a new wearable device for gait auto-rehabilitation in Parkinson's disease delivering adapted musical stimulation

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Background and aims: Music enhances motivation for physical activity and rhythmic auditory cueing (RAC) improves gait in PD. Music with a tempo synchronized to the patient's gait cadence may be perfecty suited for enhancing gait in PD. The aim of our study is to evaluate safety, tolerance and efficacy of a new device called BeatPark, delivering individualized musical stimulation for gait auto-rehabilitation.
Methods: 45 patients with PD (aged 65±9; H&Y=2.4±0.6) underwent a one-month rehabilitation program (30min/day, 5 days a week) involving walking outside while listening to a music delivered by BeatPark . This device associates sensors detecting gait cadence and a smartphone application modifying the tempo of the music in order to synchronize it to patients gait and increasing it progressively to +10% of the patient's spontaneously. Evaluation was based on questionnaires and a six-minute walk test before and after the rehabilitation program.
Results: Using BeatPark was safe, as the number of falls per week reduced from 0.26±0.85 (before) to 0.14±0.51 (after rehabilitation), ($p<0.005$); tolerance was good without increased fatigue and with significant reduction of pain. Speed was improved from 1.28±0.20 m/s before to 1.32±0.17 after ($p=0.007$), and associated with a significant increase of both cadence (118.0±11.9 vs 121.1±10.1, $p=0.02$) and stride length (1.29±0.13 vs 1.31±0.15, $p=0.04$)
Conclusion: Tolerance and safety of BeatPark are very encouraging. Results on efficacy are promising but a large randomized control trial is needed to confirm these preliminary findings.
Disclosure: FP7 European grant

EPR1106

Coma recovery scale-revised with and without the emotional stimulation of the caregivers

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Background and aims: The Coma Recovery Scale-Revised (CRS-R) (Giacino et al. 2006) is the gold standard of responsiveness assessment in patients with disorders of consciousness (DoC); its advantages are the international validation of the scale, the diagnostic validity, the outcome prediction ability and the standardization of the proposed stimuli. Conversely, its limitations might be considered the marginal role of the caregivers in the evaluation of patients' responsiveness, the poor emotional salience of the proposed stimuli and the scarce motivational efficacy of standardized stimulations.
The principal aim of our study is to search for the possible role of the caregiver if involved in the responsiveness assessment, to improve the arousal, the interaction with the environment and to promote the functional communication recovery.
Methods: 15 patients (10 males and 5 females) with a mean age of 37.1±16.1 years (range 15-60 years), diagnosed with DoC, were consecutively enrolled in the study. Responsiveness assessment was performed by means of CRS-R without and with the caregivers.
Statistical Analysis: Comparisons between the CRS-R scores without and with the caregiver were performed using the Wilcoxon signed rank test, setting the alpha level of significance at 5%.
Results: The mean CRS-R was 8.3±5.0 without the caregiver and 9.2±5.8 with the caregiver, highlighting a statistically significant difference (p=0.001).
Conclusion: Our preliminary findings seem to suggest that the involvement of the caregivers in CRS-R assessment may reveal higher responsiveness and might reduce the misdiagnosis rate in DoC patients.
Disclosure: Nothing to disclose

EPR1107

Automatic identification of motor deficits in differents neurological diseases with a customized comparison algorithm applied to computational movement analysis: AKIRA study.

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Background and aims: Motion Capture Systems (MCS) are currently used in stroke rehabilitation, but its use in stroke diagnosis is still undeveloped. Our aim is to test a customized MCS' algorithm that automatically identifies a motor deficit in neurological diseases.
Methods: Using Kinect camera (Microsoft) and customized software Akira (system friend Inc.) we registered 10 exercises divided into 3 workouts: the first one included trunk stability and walk, the second one included right upper limb exercises and the third one includes left upper limb exercises. We designed a case-control study, in which compared the performance of the exercises between stroke patients (cases) and healthy controls. The controls performance was registered and obtained normality movements values. Then, with a customized comparison algorithm (developed with MATLAB), we automatically compared the cases movement with controls and obtained a complete report of movement trajectories and their deviation.

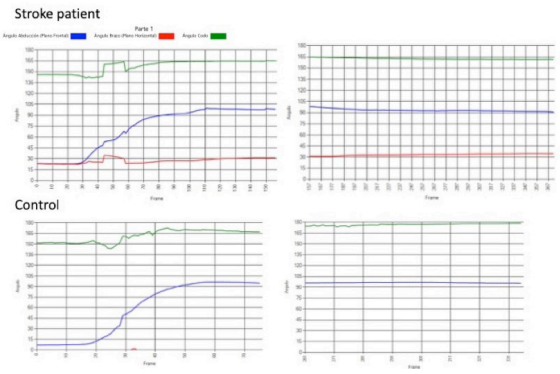

Figure 1. Example of the movement trajectory for one of the upper limb exercise. The graph shows the shoulder angle in abduction during 5 seconds. The top image corresponds to a patient and the bottom to a control.

Results: We analyzed 30 healthy controls, 14 stroke patients (median NIHSS 2, IQR 0-12), 12 sclerosis multiple patients and 3 cerebellar ataxia patients. All patients had alterations in trunk stability (first workout), but within stroke patients, we also found that right hemisphere damage patients tend to imbalance forward, while left hemisphere damage patients tend to imbalance to the left. In the upper limb evaluation, all patients had right or left alteration according to brain damage, except cerebellar ataxia patients that did not show alteration in arms and 2 stroke patients with right hemisphere damage that showed alteration in both arms.

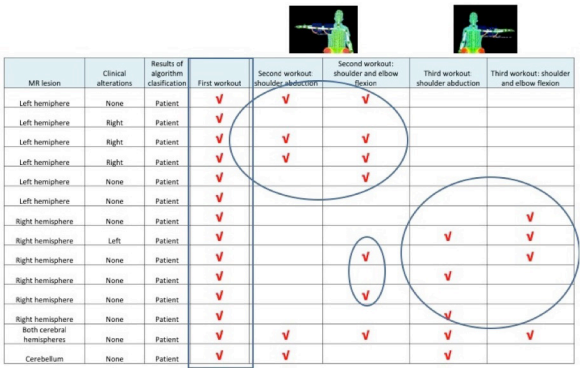

Figure 2. Results of the classification and motor deficits automatically identified by our algorithm.

Conclusion: Our system was useful automatically detecting movement alterations with precision.
Disclosure: System Friend Inc support the software and hardware used in this study.

EPR1108

Translingual stimulation in patients with ataxia after the resection of large and giant vestibular schwannomas

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Background and aims: The non-invasive neuromodulation of cranial nerves is a new method of rehabilitation, based on translingual stimulation (TS) using a device - a portable neuromodulating stimulator – PoNS (Fig. 1). Through electrical stimulation of the anterior surface of the tongue, the afferent nerve fibers of the trigeminal (V) and facial (VII) nerves are activated, producing a modulating effect on the nuclei of the vestibular analyzer and the ascending activating formation of the brainstem.

Fig 1 PoNS

Methods: We used the TS for correction of ataxia, in patients after vestibular schwannomas (large and giant size) surgery. The study was conducted for two years (2016-2017) and included 70 patients (18-80 years old). Ataxia score obtained on scales in standing and walking positions. The functional status of patients was assessed on the Karnovsky scale during the first and tenth sessions. The TS was applied ten times (once a day). Subjects were selected in two groups: Group 1- n=60, when TS applied in less than three months after surgery (4-34 days), Group 2- n=10, with more than three months after surgery.
Results: Patients, who received TS earlier, in the first month after surgery, had significantly better improvement of ataxia (walking and standing), than patients who underwent TS in later period after surgery.
Conclusion: Our results suggest, that TS should be included in the rehabilitation program of ataxia patients in the first month after vestibular schwannomas resection.
Disclosure: Nothing to disclose

EPR1109

Brain computer interface for post-stroke rehabilitation of upper-limb function: results of randomized control trial

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Background and aims: Brain-computer interface (BCI) based on the kinesthetic imagination of movement which controls hand exoskeleton using electroencephalography (EEG) patterns classification have been suggested as a promising method for the rehabilitation of upper limb (UL) of poststroke patients. The purpose of the study was the investigate an efficacy of BCI - hand exoskeleton rehabilitation for stroke survivors with UL paralysis who benefit from 10 BCI training sessions each lasting up to 40 min.

Methods: The study comprised 145 stroke patients (median time since stroke is 8.0 [4.0;14.0] months; median age 59.0 [54.0;65.5]. Patients were divided into two groups: 1) BCI group (n=103) performed motor imagery of opening their hands; 2) control group (n=42) where exoskeleton-driven hand openings were independent of EEG activity. Within each group, the patients were stratified depending on the severity of paresis into two subgroups: 1a - Fugl-Meyer Motor Assessment (FMMA) 14.0 points [10.0;9.0]; Action Research Arm Test (ARAT) 1.0 points [0.0;2.0]; 2b - FMMA 40.0[36.0;37.0]; ARAT 29.0 [19.0;40.0].

Results: After two weeks of training FMMA in two subgroups (1a,1b) were significantly higher in BCI group than in control group ($p<0.001$) reflecting the clinically meaningful change in paretic muscles activity in subgroup with severe paresis (1a) and improvement of highly differentiated movements in 2b subgroup. Following ARAT scale, the significant improvement was observed only in the 2b subgroup ($p<0.001$).

Conclusion: These results suggest that adding BCI control to exoskeleton-assisted physical therapy can improve post-stroke rehabilitation outcomes and could be promising adjuvant therapy in the neurorehabilitation.

Disclosure: Nothing to disclose

EPR1110

Using Kinect based training to improve cognitive function and brain activation in frail and prefrail older adults: A randomized controlled trial

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Background and aims: Cognitive impairment is prevalent among prefrail and frail older adults. Previous studies have suggested that combined exercise and exergaming positively influence cognition in healthy older adults. However, few studies have investigated the effects of exergaming on cognition and brain activation in frail and prefrail older adults. This study compared the effects of Kinect-based exergaming on cognitive function and brain activation in prefrail and frail older adults.

Methods: 46 community-dwelling prefrail and frail older adults were randomly assigned to the Kinect-exergaming (Kinect) group or combined exercise (CE) group for 36 sessions over 12 weeks. Participants were assessed for cognitive function and brain activation before intervention and after the 12 weeks of training. Outcome measures for cognitive function included global cognition, executive function, verbal/episodic memory, attention, and working memory. Prefrontal cortex activation during the global cognition test was documented using functional near-infrared spectroscopy (NIRS).

Results: Both groups showed improved global cognition, executive function, and attention. The group×time interaction effects further demonstrated that Kinect training more significantly improved global cognition than did CE training. Moreover, only the Kinect group showed significant improvements in verbal and working memory after the intervention. The hemodynamics data from NIRS revealed decreased activation in prefrontal areas during the posttrial cognitive assessment in both groups.

Conclusion: In frail and prefrail adults, Kinect-exergaming and combined exercise could improve their cognitive functions, most likely by increasing neural efficiency. Moreover, Kinect may be superior to combined exercise, particularly in improving global cognition.

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Neurorehabilitation; Critical Care

EPR1111

Erythrocyte-rich clots are associated with cardioembolic aetiology, reduced number of manoeuvres, and improved clinical outcome in acute ischemic stroke patients

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Background and aims: Composition of clots retrieved after endovascular thrombectomy (EVT) may influence clinical outcome of patients with an embolic stroke. This study sought to study the impact of thrombus composition on stroke aetiology, EVT-linked procedural and recanalization variables, and clinical outcomes.
Methods: Clots retrieved prospectively from eighty-five acute ischemic stroke patients treated with EVT following an occlusion of the middle cerebral artery, internal carotid artery/carotid-T, or anterior cerebral arteries were studied. Histopathological composition of the clots were compared with clinical, imaging and EVT-linked procedural/outcome data.
Results: The main findings were that a higher percentage of red-blood cells in the thrombus was associated with (i) cardioembolic aetiology, (ii) favourable recanalization, (iii) shorter procedural time and (iv) improved clinical outcome.
Conclusion: Our results suggest that thrombi with predominantly higher RBC percentage may be linked to cardioembolic origin, better recanalization procedural parameters and clinical outcome in acute ischemic stroke with confirmed large vessel occlusion. Putative link between cardioembolic and cryptogenic stroke warrants further investigation.
Disclosure: Nothing to disclose

EPR1112

Brain death determination: Clinical quality and risk management according to German standards

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Background and aims: The diagnosis of brain death (i.e. final, irreversible cessation of the total function of the cerebrum, the brain stem, and the cerebellum) is an indispensable diagnostic instrument in intensive care medicine, independently of the matter of tissue or organ donation. In 2015 the German Medical Association (Bundesärztekammer) has updated its 4th guideline for the precondition and procedure to diagnose brain death. As a new requirement clinical quality and risk management in diagnostic procedures for brain death were implemented in the current guideline.
Methods: We analyzed all cases of brain death diagnostics (independent of the outcome) performed in the past four years at Charité University Hospital with a newly developed tool for clinical quality and risk management in brain death diagnostics. Using this tool, potential deviations across the diagnostic procedures are to be categorized as either minor, moderate or severe. Validation procedure was performed retrospectively on a yearly basis.
Results: A validation procedure was developed to retrospectively (on a yearly basis) analyze all individual cases (139) in which diagnostics were conducted. In 121 cases the criteria of brain death were fulfilled, in 18 criteria were not fulfilled. All cases were diagnosed in compliance with the German guidelines without any significant errors in diagnosing brain death. Nevertheless, audits revealed minor errors of documentation particularly in the transition period after the new regulations were introduced in 2015. The present contribution will aim at summarizing results of this analysis.
Conclusion: The implementation of standardized clinical quality and risk management helps to constantly improve diagnostics of brain death.
Disclosure: Nothing to disclose

EPR1113

The use of a dedicated neurological triage system improves service and process times as well as resource utilization in an Interdisciplinary Emergency Department in Germany

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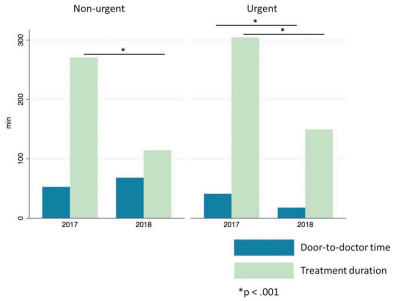
Background and aims: Patients with neurological symptoms contribute to increasing rates of emergency department (ED) utilization in recent years. Existing triage systems represent neurological symptoms rather crudely, neglecting subtler but relevant aspects like temporal evolution or associated symptoms. A designated neurological triage system could, positively impact on patient safety by identifying patients with urgent need for medical attention, and fulfil an important gate-keeper function for adequate utilization of ED and hospital resources.
Methods: ED process times and resource utilization of urgent and non-urgent neurological patients during one month were compared before (2017) and after (2018) the introduction of the Heidelberg Neurological Triage System (HEINTS) in our Interdisciplinary ED.
Results: During the triage period, 300 patients were evaluated by a neurologist, 185 (61.7%) with an urgent condition (cat. 1 or 2). During the control phase of the year prior, 181 (61.4%) of 295 patients were retrospectively evaluated as urgent. For urgent cases, door-to-doctor-time (DDT) decreased from 41.0 min (2017) to 17.7 min (2018), p=.000, and treatment duration decreased from 304.3 min (2017) to 149.4 min (2018), p=.000. Treatment duration for non-urgent patients was also shorter after introduction of HEINTS triage (270.6 min vs. 114.2 min, p=.000), while DDT did not change (52.7 min vs. 68.2 min, p=.081). ED resource utilization (imaging, labwork, consultations) significantly decreased with neurological triage (p=.000).



ED process times according to urgency before (2017) and after (2018) the introduction of a neurological triage system

Conclusion: A dedicated triage system for neurological patients reduces DDT, treatment duration and ED resource utilization, thereby improving ED diagnostic and treatment processes.
Disclosure: Nothing to disclose

EPR1114

Comparison of the neurophysiological and neuroimaging data provides more accurate disorder of consciousness diagnostics.

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Background and aims: The aim of our study was to compare the accuracy of UWS and MCS states differentiation based on TMS-EEG-derived perturbational complexity index (PCI; Casali, 2014) and the index of thresholded connectome intactness (ITCI), which is calculated from resting state fMRI data and reflects the degree of preservation of the strongest functional connections within an individual connectome (Sinitsyn, 2018).
Methods: We included 40 DOC patients: 21 UWS (16 non-traumatic, mCRS-R score 5.7±1.2), 19 MCS (8 non-traumatic, mCRS-R score 15±3.5). 35 patients underwent TMS-EEG with PCI, and for 38 - rs-fMRI was performed with ITCI.
Results: In 18/20 UWS patients PCI was below threshold value PCI*=0.31 while in 10/15 MCS patients it was within the range of 0.31-0.45. ITCI differentiated MCS and UWS at group level (p=0.04, mean ITCI was 0.13 and 0.09, respectively). CRS-R score correlated with PCI (ρ=0.59, p=0.0002), while with ITCI was non-significant (ρ=0,28, p=0.08). PCI provided more accurate UWS and MCS separation (AUROC=0.86) than ITCI (AUROC=0.69). PCI values didn't have significant correlation with ITCI (ρ=0.18, p=0.3). All patients with low values of PCI/ITCI (<0.26/<0.1, respectively) were in UWS, while all but one patient with higher values (>0.31 and >0.1, respectively), were in MCS.
Conclusion: There was no significant correlation between TMS-EEG- and rs-fMRI-derived indices, which can be explained by the methodological differences of these modalities. However they can be used in combination for detecting hidden signs of consciousness.
Disclosure: The study was supported by RSF grant 16-15-00274

EPR1115

Clinical effectiveness of transcranial direct current stimulation and virtual reality on chronic individuals post-stroke with severe hemiparesis

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Background and aims: The absence of voluntary movements after stroke may limit effective neural reorganization that supports functional improvement, and poses a major challenge for rehabilitation. Only a few interventions (motor imagery, mirror therapy, virtual reality) can trigger cortical neural networks of arm movements, which, in turn, can be facilitated by applying transcranial direct current stimulation (tDCS). This study presents the effectiveness of a combined intervention based on virtual reality-based reaching exercises with concurrent tDCS and conventional physical therapy, in comparison to conventional physical therapy alone.
Methods: 30 chronic individuals with severe hemiparesis post-stroke were randomly assigned either to an experimental or a control group, and underwent 24 one-hour sessions, 3-5 times a week. Participants in the experimental group combined 20 minutes of VR and tDCS (Anode: C3/C4; Cathode: Fp2/Fp1; I=2 mA), with 40 minutes of conventional physical therapy. Participants in the control group completed 60 minutes of conventional physical therapy. Assessment included the Fugl-Meyer Motor Assessment-Upper Extremity and the Wolf-Motor Function Test before and after the intervention.
Results: Significant improvements were detected after the experimental intervention not only in the Fugl-Meyer Motor Assessment (5.1±3.9), but also in time (-105.9±139.3 s) and ability subscales (2.2±2.6) of the Wolf-Motor Function Test in comparison to the control group, who presented limited improvement (0.2±1.0, -22.6±43.1 s, 0.7±0.9, respectively).
Conclusion: Improvements in the experimental group exceeded the minimally clinically importance in global arm function, speed and ability, in spite of the chronicity and severity of the hemiparesis, which support the effectiveness of the intervention.
Disclosure: This study was funded by Ministerio de Economía y Competitividad of Spain (Grant BES-2014-068218) and by Universitat Politècnica de València (Grant PAID-06-18).

EPR1116

Long-term prognostic factors in stroke patients for living at home up to 7.5 years after initial inpatient rehablititation

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Background and aims: Prognostic factors in stroke patients after initial inpatient rehabilitation for future long term living at home are unclear. CERISE follow up study (De Wit et al. 2012) showed that higher Barthel-Index (BI) 6 months after stroke greatly impacts five-year mortality.
Aim of this study was to monitor living situation up to 7.5 years, and to derive prognostic factors for future living at home.
Methods: 204 stroke patients discharged from inpatient rehab phase B or C (German model of phases; Schupp 1995) were included. Biomedical data, BI for ADL, EBI for cognition, EQ5D for HRQoL, risk of falls index, and Charlson Index (ChI) for comorbidity, were registered. By telephone interviews we monitored after 2.5, 5, and 7.5 years, if the patients are still living at home. Prognostic factors were derived by binar logistic regression analyses.
Results: At 2.5 years after, 152 (75%) stroke patients lived at home, at 5 years 125 (61%), and at 7.5 years 101 (50%). 2.5 years after, five variables had prognostic value: higher score on EQ5D at discharge, higher gains in HRQoL and in ADL functions during rehab, higher BMI (= less malnutrition), and less comorbidity (ChI). At 5 and 7.5 years, three variables remained: lower age, lower risk of falls, and less comorbidity. The significant ($p<0.001$) prognostic model explored 41% of variance.
Conclusion: Up to 2.5 years, rehab outcome seemed to impact future living at home. After 5 and 7.5 years, biomedical facts tends to be more relevant.
Disclosure: Nothing to disclose

EPR1117

The effect of neurorehabilitation on gait in patients with multiple sclerosis

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Background and aims: Gait disorders are common in patients with Multiple Sclerosis (MS) and tend to accelerate with disease progression. Comprehensive rehabilitation intervention is the best option to improve impaired ambulation. Commonly, the duration of inpatient program does not exceed 21 days, determined by cost approval of medical insurance. Aim of the study was to observe whether a prolongation of inpatient neurorehabilitation can lead to a significant increase of gait abilities.
Methods: A retrospective study was conducted using data of 307 MS-Patients treated in the period January 2015 until December 2016 at the Neurorehabilitation Center Valens, Switzerland. Investigated parameters were: walking speed and distance at entry/discharge, using standard walking tests (10MWT, 20MWT, 2MWT, 6MWT, TDistance) and Extended Barthel Index (EBI) to evaluate an improvement in health-related quality of life (HRQL).
Results: Speed and distance improved significantly in patients with prolonged inpatient rehabilitation (4/5 weeks) in comparison to a standard duration (3 weeks). Velocity increased from 18% in the 3rd week to 33% in the 4th week ($p=0.0001$). Walking distance increased from 25% in the 3rd week to 29% after 4 weeks of hospitalization ($p=0.005$), ranged 37% in the 5th week of prolonged inpatient rehabilitation ($p=0.01$). EBI showed a trend for HRQL-improvement by rising the mobility-subscore from 34.70% in the 3rd week to 39.68% in the 4th week and to 48.0% in the 5th week of inpatient rehabilitation.
Conclusion: Prolonging the duration of inpatient rehabilitation beyond 3 weeks to 4 or 5 weeks further increases gains in mobility and independence.
Disclosure: Nothing to disclose

Neurotraumatology

EPR1118

A prospective, randomized, blinded, and placebo-controlled study of Cerebrolysin effect on long-term functional and histological outcomes in rats with traumatic brain injury

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Background and aims: Our previous study identified an optimal dose of Cerebrolysin as 2.5ml/kg for treatment of mild traumatic brain injury (TBI) when administered 4h after injury. The present study was designed to investigate the effects of Cerebrolysin at this dose on functional and histological outcomes in rats subjected to moderate TBI.
Methods: In this prospective, randomized, blinded, and placebo-controlled preclinical study, male adult Wistar rats, subjected to TBI induced by impact acceleration, were randomly treated with either placebo (saline, n=13) or Cerebrolysin at the dose of 2.5ml/kg (n=13), intra-peritoneally administered daily for 10 days, starting at 4h after TBI. Animals were subjected to cognitive and sensorimotor functional tests at multiple time points and sacrificed at 90 days after TBI for histological analyses.
Results: Compared to the placebo, Cerebrolysin significantly increased neurogenesis, reduced amyloid precursor protein accumulation, astrogliosis and axonal damage and reduced neuronal cell loss in the hippocampus ($p<0.05$). Sensory motor function was significantly improved in the Cerebrolysin group compared to controls from 1 day to 3 months after injury ($p<0.05$). Cerebrolysin significantly improved long-term (up to 3 months) cognitive functional recovery measured by the Morris Water Maze, Odor Recognition, Social Interaction, and Novel Object Recognition tests. There were significant correlations between multiple histological and functional outcomes 90 days after TBI, as detected by Pearson partial correlation analyses.
Conclusion: Our data demonstrate that Cerebrolysin significantly improves functional outcome after moderate TBI in rat, and that functional outcomes are significantly correlated with histological indices of plasticity.
Disclosure: EVER Neuro Pharma GmbH supported this research via a Research Contract grant.

EPR1119

Electrocardiographic abnormalities in patients with severe traumatic brain injury

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Background and aims: Electrocardiographic (ECG) abnormalities are often present in cerebrovascular disease and are considered as a result of autonomic dysregulation with excessive catecholamine release. The significance in patients with traumatic brain injury (TBI) and whether these represent secondary effects of the brain injury is unclear. Therefore, we aimed to investigate the incidence of ECG abnormalities and their association with brain injury severity in patients with severe TBI.
Methods: We analyzed patients aged ≥16 years with severe TBI (Glasgow Coma Scale (GCS) score <8) and intracranial pressure (ICP)-monitoring who were admitted to the intensive care unit (ICU) of the University Medical Center Groningen (UMCG) in the period of 2002 till 2013. Initial ECG recordings from the emergency department (ED) until 24 hours after ICU admission were independently scored according to predefined criteria by two expert-cardiologists. Brain injury severity assessed with head computed tomography (CT) at the ED was categorized according to Marshall-criteria.
Results: Pre-eliminary results: we included 265 patients with median age of 36 years (interquartile range (IQR) 21-55) and an admission GCS score of 6 (IQR 5-7). The incidence of ECG abnormalities was 80%, including 36% arrhythmias. S-T segment changes (41%) are mostly seen in patients with mass lesions (Marshall grade 5-6). Arrhythmias (0-60%) are associated with the severity of more diffuse brain injury (Marshall grade 1-4).

Computed tomography and electrocardiographic abnormalities in patients with severe traumatic brain injury (2002-2013)*

Computed tomography			ECG	Abnormal ECG	Arrhythmia	Abnormal interval			S-T segment abnormality	T-wave abnormality
						PR	QRS	QT		
Marshall		no. %	no. %	no. %	no. %	no. %	no. %	no. %	no. %	no. %
Diffuse injury	I	2 1	1 50	0 0	0 0	0 0	0 0	0 0	0 0	0 0
	II	112 42	67 60	51 76	22 33	2 3	3 4	8 12	14 21	21 31
	III	61 23	37 61	30 81	17 46	3 8	1 3	7 19	14 38	9 24
	IV	17 6	10 59	8 80	6 60	0 0	1 10	3 30	2 20	2 20
Mass lesion	V	42 16	19 45	16 84	5 26	2 11	0 0	6 32	7 37	5 26
	VI	31 12	20 65	18 90	5 25	1 5	1 5	3 15	9 45	6 30
Total		265 100	154 58	123 80	55 36	8 5	6 4	27 18	46 30	43 28

*Corrected for pre-existent cardiac suffering in 7 patients (3 patients familiar with atrial fibrillation and 4 patients had a myocardial infarction).

Computed tomography and electrocardiographic abnormalities in patients with severe traumatic brain injury (2002-2013)

Conclusion: Our study shows a high incidence of ECG abnormalities, mostly arrhythmias, in patients with severe TBI. Furthermore, type (diffuse injury versus mass lesions) and the severity of diffuse brain injury are associated with variety of ECG abnormalities.
Disclosure: Nothing to disclose

EPR1120

Long-term follow-up after traumatic brain injury: what matters for good quality of life? A cross-sectional analysis up to 10 years after the brain injury: CROCFLAME

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Background and aims: Traumatic Brain Injury (TBI) is the leading cause of disability in young adults and more prevalent than stroke. How patients cope with the long-term consequences and why one third of patients present with decline, suggesting a neurodegenerative polypathology, are the crucial questions in the field. Thus, we assessed health-related quality of life (HRQoL) in chronic TBI patients to elucidate outcome predictors.
Methods: 135 chronic TBI patients reported HRQoL using the QOLIBRI (Quality of Life after Brain Injury) questionnaire with a maximum score of 100. A score <60 indicates an increased risk for psychiatric disorders. HRQoL was correlated with parameters as TBI severity, sex differences, decompressive craniectomy (DC), and neurorehabilitation using regression models.
Results: DC was associated with better HRQoL with the largest effect in initially mild injured ($p=0.001$, adj. $R2=0.45$). 40% of non-craniectomized and 24% of craniectomized patients were at risk for psychiatric sequels. Shorter neurorehabilitation correlated positive with better HRQoL ($p<0.001$; adj. $R2=0.1$). Neurorehabilitation improved functional outcome (immobile at admission/discharge: 81%/33%; mobile at admission/discharge: 16%/67%). Women (n=33) reported lower HRQoL than men (n=102) ($p=0.13$)—albeit not significant—and were at higher risk for psychiatric sequelae (49% versus 31%).
Conclusion: DC is a predictor for good HRQoL up to 10 years following TBI, especially in patients prone to secondary deterioration and reduces the risk for psychiatric sequels by 16%. Hence, the relevance of DC after TBI needs to be re-evaluated as not the first-line recommendation. If posttraumatic psychiatric disorders are a risk for decline after TBI needs to be elucidated.
Disclosure: Nothing to disclose

EPR1121

Vasopressin V1a receptors mediate post-trauma brain edema by regulating cerebral aquaporin 1

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Background and aims: Brain edema formation and subsequent intracranial hypertension are well known to result in secondary brain damage and, hence, unfavorable outcome following traumatic brain injury (TBI). Half of post-trauma brain edema evolves secondarily and is thus amenable to treatment. Aquaporins (AQP) are ubiquitously expressed, highly selective water channels that mediate the formation of post-trauma brain edema, but in contrast to systemic water regulation in the kidney their cerebral regulation is poorly understood. Thus, we investigated whether vasopressin receptors regulate cerebral aquaporins, thereby mediating post-trauma brain edema.
Methods: Cerebral AQP1 and AQP4 mRNA and protein levels were quantified in wild-type (WT) and V1a receptor knock-out (V1a-/-) mice at baseline, 15 min, 1, 3, 6, 12 or 24 hours following experimental TBI by controlled cortical impact (8m/s, 150 ms, 1 mm).
Results: In non-traumatized mice, we found AQP1 and AQP4 expression in cortical neurons and astrocytes, respectively. Experimental TBI increased AQP1 mRNA at 24 hours ($p=0.031$) and AQP1 protein at 15 min and 24 hours ($p<0.05$) post-injury in WT, but not in V1a-/- mice. AQP4 was not regulated by V1a receptors following experimental TBI.
Conclusion: Vasopressin V1a receptors regulate cerebral AQP1 following experimental TBI. This regulation occurs within 15 minutes as well as 24 hours post-trauma brain injury, the latter representing the time point of maximum brain swelling following experimental TBI. Thus, we suggest V1a receptors and AQP1 in cortical neurons as potential new target protein for translational research to prevent neuronal swelling following TBI.
Disclosure: Nothing to disclose

EPR1122

Age-related outcome and health-related quality of life after mild TBI

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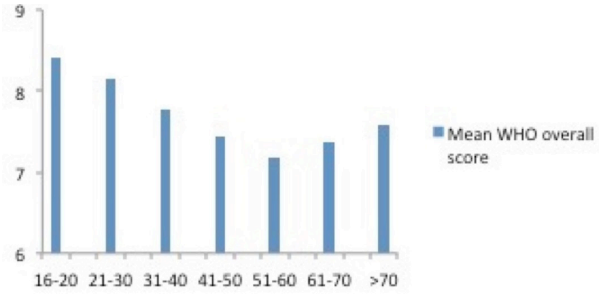
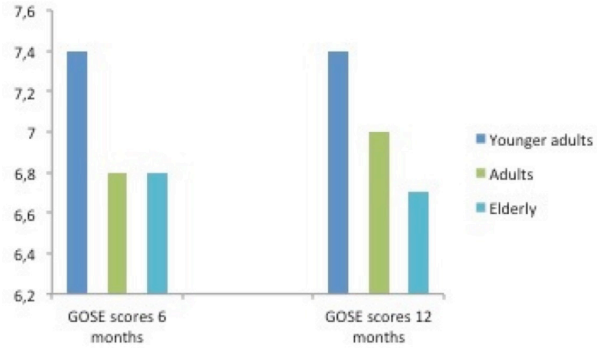
Background and aims: The risk of sustaining mild traumatic brain injury (mTBI) increases with age. Currently one in 4 patients admitted to the Emergency Department (ED) is aged 60 years or older. Most outcome studies focus on patients of working age and information on long-term HRQol and outcome is missing. The aim is to determine age-related predictive factors for outcome.
Methods: Long-term follow-up study of mTBI patients admitted to the ED of three Dutch level-1 hospitals between 2013-2015. Data were collected on posttraumatic complaints, functional outcome, coping and emotional distress 6 months post-injury. HRQoL was determined 12 months postinjury. Three age-groups were created: young adults (16-40), adults (41-60) and elderly (≥61 years).
Results: In total 1,151 patients were included with 292 (25%) aged 60 years or olders (mean age 49.8 (±18.2), range 16-91 years. Six months post-injury, 43% of patients showed incomplete recovery (young adults 35%, adults 49%, elderly 43%, p=0.06). At one year HROoL was high with 75% rating level 4-5 (good–very good). Young adults had significantly more post-traumatic complaints (85%) compared to older patients. Pre-injury complaints, coping style, emotional distress and frailty were main predictors of long-term HRQL and outcome (Nagelkerke R2 46% and 32%).



Health related quality of life



Functional outcome over time

Conclusion: This study demonstrates that one year post-injury most patients show relatively high HRQL despite incomplete recovery, even elderly patients. Injury related factors and personality characteristics are main predictors of long-term HRQL and outcome. Identification of long-term HRQL could provide more information in an ageing population of MTBI patients.
Disclosure: Grant Dutch Brain Foundation

Peripheral nerve disorders

EPR1123

Vestibular impairment in Charcot-Marie-Tooth disease

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Background and aims: Imbalance is a frequent complaint of patients with Charcot-Marie-Tooth disease (CMT). While it is considered to be mainly due to somatosensory impairment, vestibular failure might also contribute.
Aim: To evaluate peripheral vestibular function and examine the relationship between the severity of (a) the CMT disease, (b) the vestibular impairment and (c) postural balance impairment in a mixed group of CMT patients.
Methods: Vestibular function was evaluated in 32 (14 F/18M) CMT patients and 26 (17F/9M) healthy controls by measuring the vestibulo-ocular reflex with the video head impulse test (vHIT) of semicircular canal (SCC) function. Postural stability was evaluated with a comprehensive test battery comprising: (a) modified Clinical Test of Sensory Integration and Balance, (b) Berg Balance Scale; (c) Dynamic Gait Index; (d) Fall Efficiency Scale; (e) International Cooperative Ataxia Rating Scale; and (f) Dizziness Handicap Inventory.
Results: Of the 32 CMT patients, 14 had vestibular impairment, ranging from mild - affecting just a single semisircular canal, to severe - affecting all 6 SCCs. Vestibulo-ocular reflex gain was low from all 6 SCCs in 1 patient, from 4SCCs in 1 patient, from 3 SCCs in 2 patients, from 2 SCCs in 6 patients and from only 1 SCC in 4 patients. Postural stability tests were significantly impaired in CMT patients. ICARS posture and gait score is moderately correlated with vHIT gain.
Conclusion: Peripheral vestibular impairment is common in CMT patients. Since vHIT is correlated with posture and gait, vestibular rehabilitation might have an impact on CMT patients' imbalance.
Disclosure: Nothing to disclose

EPR1124

A very mild phenotype of Charcot-Marie-Tooth disease type 4H caused by two novel mutations in FGD4

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Background and aims: Mutations in the FGD4 gene cause an autosomal recessive demyelinating Charcot-Marie-Tooth disease also referred to as CMT4H. Previously reported patients presented an infancy or early childhood-onset and slow progression. To date, the majority of FGD4variants have been identified in homozygous with loss-of-function allele and all mutations were situated at earlier positions in comparison to the patients reported here.
Methods: Two patients with CMT4H were thoroughly studied clinically and genetically. Genetic testing was performed using a panel of genes and FGD4mRNA expression was analysed through reverse transcription and quantitative PCR.
Results: Two novel variants in FGD4(c.514delG and c.2211dupA) were identified in two mildly affected Spanish siblings with a late adolescence onset. Index patient (II:2) is a 17-year-old male and his sister (II:1) still remains asymptomatic at 20 years. On examination, foot deformity (Fig. 1A-B) without weakness or sensory involvement was observed. Muscle MRI of the lower extremities showed no fatty replacement (Fig. 1C-D). Further analysis of FGD4 expression in peripheral blood suggested that neither the mutations affected splicing process, nor did they affect mRNA dosage of FGD4compared to a healthy control (Fig. 2). Therefore, two truncated proteins for each allele are predicted: p.Ala172Glnfs*28 (c.514delG) and p. Ala738Serfs*5 (c.2211dupA).The last one would contain all functional domains (Fig. 3).

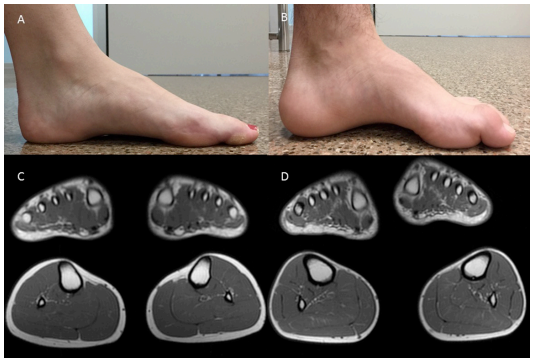


Fig. 1 Clinical pictures and muscle MRI (T1 weighted images shown). A Mild pes cavus of patient II:1. B Moderate pes cavus with hammer toes of patient II:2. C Muscle MRI of patient II:1 showing no fatty replacement at feet and calf level. D Muscle MRI of patient II:2 showing no significant abnormalities at either feet or calf level.

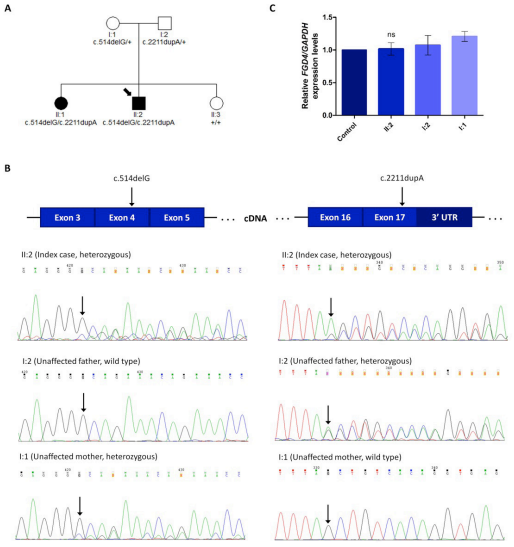
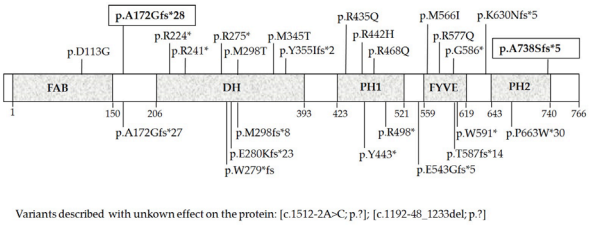


Fig. 2 Expression of FGD4 mutations in peripheral blood cells. A Family pedigree and FGD4 genotypes. B Sequencing of RT-PCR products (cDNA) obtained in the experiment. Both mutations were present at cDNA level. C qPCR analysis of FGD4 mRNA from peripheral blood tissue in the progenitors (I:1; I:2), index case (II:2), and healthy control sample.



Variants described with unkown effect on the protein: [c.1512-2A>C; p.?]; [c.1192-48_1233del; p.?]

Fig. 3 Distribution of the pathological mutations reported in the FGD4 protein. Mutations identified in our patients are noted in bold and framed. Five functional domains are represented for FGD4. FAB (F-actin binding), DH (Dbl homology), PH (Pleckstrin homology), FYVE (Fab 1, YOTB, V ac 1, and EEA1 zinc finger domain).

Conclusion: Conservation of all functional domains in the p.Ala738Serfs*5 (c.2211dupA) predicted protein could explain both the milder phenotype and the later onset in our patients. These results expand the clinical and mutational spectrum of FGD4-related peripheral neuropathies.

Disclosure: This work was supported by the Instituto de Salud Carlos III (ISCIII) [grant number PI16/00403], co-funded with FEDER funds, and by the Generalitat Valenciana [grant number PROMETEO/2018/135]. ASM contract is supported by Fundació Per Amor a l'Art. HAE is financially supported by the Health Research Institute Hospital La Fe [grant number 2017/0351].

EPR1125

Mutational profile in patients with IgM paraproteinemic neuropathy and anti-myelin-associated glycoprotein neuropathy (MAG) antibody

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Background and aims: Neuropathy with antibodies to myelin-associated-glycoprotein (MAG) is the most common IgM paraproteinemic neuropathy, characterized by sensory ataxia, upper limbs tremor, disability. Although the IgM paraprotein is commonly a monoclonal gammopathy of undetermined significance (MGUS), it may underscore lymphoproliferative disorders, mainly Waldenstrom's Macroglobulinemia (WM). Recently, the discovery of the mutational profile of the MYD88 and CXCR4 genes have radically changed the prognostic evaluation of IgM monoclonal gammopathies Namely, MYD88L265P is the most common mutation in WM and IgM-MGUS, and somatic mutations in the C-terminal domain of CXCR4 is associated with more aggressive WM disease. Finally, MYD88/CXCR4 status in WM seems predictive of response to ibrutinib, the first-in-class inhibitor of Bruton's tyrosine.
Methods: We assessed the mutational profile of MYD88 and CXCR4 genes in 16 patients (5 women, mean age 68±10 years) with anti-MAG antibody neuropathy. Eight had IgM MGUS, 6 WM, 2 chronic lymphocytic leukemia (CLL). Molecular analysis was performed on DNA extracted from bone marrow mononuclear cells MYD88L265P and CXCR4 S338X mutations were searched with highly sensitive allele-specific-PCR assays. Sanger sequencing was required for mutations of the CXCR4 C-terminal domain in S338X negative samples.
Results: In the first 16 patients, 13 had the MYD88 L265P mutation, namely all the 6 WM patients, 6/8 MGUS patients and 1/2 CLL. No demographic or clinical variables were different between MYD88 L265P and unmutated cases, nor between untreated and relapsed patients.
Conclusion: The results helped identify a mutational target for a potential new therapy for anti-MAG antibody neuropathy.
Disclosure: Nothing to disclose

EPR1126

Patisiran, an RNAi therapeutic agent in hereditary transthyretin amyloid polyneuropathy: First experience in the real life

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[1]Neurology, Henri Mondor Hospital - East Paris University, Créteil, France, [2]Pharmacy, Henri Mondor Hospital - East Paris University, Créteil, France, [3]VERDI, Inserm, CIC[1430] , Henri Mondor Hospital - East Paris University, Créteil, France, [4]Cardiology, Henri Mondor Hospital - East Paris University, Créteil, France, [5]Neurophysiology, Henri Mondor Hospital - East Paris University, Créteil, France, [6]Neuro, Henri Mondor Hospital - East Paris University, Créteil, France

Background and aims: Patisiran, a transthyretin silencing RNA, is a new effective therapeutic in hereditary transthyretin amyloid polyneuropathy (hATTR-PN) evaluated in the phase 3 Apollo trial.
We report our first experience on the safety and efficacy of patisiran in hATTR-PN.
Methods: After premedication, patisiran 0.3mg/kg was administered intravenously every 3 weeks. An assessment was performed at baseline and every 6 months, included the Neuropathy Impairment Score (NIS), Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN), modified body mass index (mBMI), and serum TTR level. Adverse events were recorded.
Results: 20 hATTR-PN patients [16M, 13 ATTR-Val30Met, mean age 66yo (range: 45-86)] received patisiran. 4 were enrolled in the Apollo open-label extension study, since April 2016, 16 others in the early access program since May 2018. Disease course averaged 6.6 years (range: 1.9-13.9). The mean NIS was 64 (range: 12-128). 19 patients received prior TTR stabilizer. At last evaluation, the mean serum TTR level has decreased by 76% from baseline (16 cases). The NIS was unchanged in all cases evaluated at 6 months (N1=6) and at 12 months (N2=2). The delta-NIS change was less than 5 at 24 months (N3=2). mBMI was unchanged. All patients but one had an improved Norfolk QOL-DN score (mean change: -12.5). Safety was generally good. Local erythema or flush occurred in 3 cases. 2 patients presented a serious adverse event attributable to the premedication (dexamethasone) including a hyperglycaemia and a cardiac failure episode.
Conclusion: Patisiran appears an effective and well-tolerated treatment to stabilise hATTR-PN. Longer follow-up will be presented.
Disclosure: Dr Planté-Bordeneuve received support for meeting, travelling fees and consulting from Alnylam, Pfizer and Akcea.

EPR1127

Baclofen, Naltrexone and Sorbitol all contribute to PXT3003-induced myelination and improve energy metabolism and degradation pathways altered in CMT1A DRG co-cultures

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Background and aims: Charcot-Marie-Tooth type 1A (CMT1A) disease is due to the duplication of the gene encoding the PMP22 protein and is characterized by a dysmyelination of peripheral nerves leading to a progressive muscle weakness. Although CMT1A is the most common inherited neuropathy, there is currently no approved treatment. We previously demonstrated the ability of a novel therapy (PXT3003) combining three low-dose repositioned drugs to be effective in CMT1A preclinical models. The aim of this work was to demonstrate the ability of PXT3003 to synergistically induce myelination of CMT1A neurons and characterize PXT3003 mechanism of action.

Methods: We developed an in vitro model of sensory neurons and Schwann cells co-culture derived from CMT1A transgenic rats that mimics the pathophysiological process of in vivo myelination. We quantified the impact of PXT3003 on total myelin length, protein degradation pathways, Endoplasmic Reticulum (ER) stress and metabolic alterations.

Results: We confirmed myelination impairment of CMT1A neurons and tested 27 combinations of PXT3003. Six combinations induced myelination synergistically. The most active PXT3003 combination reduced ER stress, and corrected degradation pathways (ER stress, autophagy and proteasome activity) as well as some energy metabolism alterations (ATP and mitochondria).

Conclusion: We validated a sophisticated co-culture system mimicking the pathophysiological myelination process in CMT1A. We confirmed PXT3003 synergistic activity on myelination induction, by potentially modulating the function of protein clearance pathways and energetic supply. These findings highlight the value of combinational drug repurposing at low doses to act synergistically on pleiotropic pathways and represent an important novel approach for rapid drug development and safety improvement.

Disclosure: All authors are employes of Pharnext. NC, RH, SN and DC are cited in patents held by Pharnext.

EPR1128

Impact of baseline neuropathy stage in patients with hereditary transthyretin-mediated (hATTR) amyloidosis with or without patisiran treatment

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Background and aims: Hereditary transthyretin-mediated (hATTR) amyloidosis is a rare, rapidly progressive disease with heterogeneous clinical manifestations leading to severe morbidity. In the phase 3 APOLLO study, patisiran demonstrated improvement in neuropathy compared to placebo in patients with hATTR amyloidosis with polyneuropathy and was generally well-tolerated. This analysis evaluates changes in neuropathy in patisiran and placebo groups stratified by disease stage at baseline.

Methods: Post-hoc analyses from the APOLLO study were used to evaluate the impact of disease stage at baseline on neuropathy progression by calculating the percent change in mNIS+7 from baseline to 18 months. A higher mNIS+7 score indicates worsening of neuropathy. Baseline disease stage was defined by Familial Amyloid Polyneuropathy (FAP) Stage and Polyneuropathy Disability (PND) Score, two highly related staging systems used in this disease.

Results: Placebo patients in the earliest stages of disease (FAP Stage 1; PND Score I/II) experienced the greatest rate of deterioration in neuropathy over 18 months (mean mNIS+7% change 68.9% and 58.8%/68.5%, respectively; Table 1). Patisiran-treated patients improved relative to baseline in neuropathy impairment over 18 months across all baseline disease stages (mean mNIS+7% change ranging from -2.4% to -6.1% for all FAP Stages and PND Scores; Table 1).

Table 1. Percent Change from Baseline in mNIS+7 at Month 18 by Treatment and Baseline PND and FAP Scores

Treatment Group	Baseline Neuropathy Stage		Mean mNIS+7 % change (SD) from baseline to 18 months
Placebo	PND Score	I (n=15)	58.8 (56.3)
		II (n=14)	68.5 (82.6)
		IIIA (n=16)	42.3 (32.2)
		IIIB/IV (n=6)	16.5 (9.5)
	FAP Stage	1 (n=25)	68.9 (73.0)
		2/3 (n=26)	34.4 (28.1)
Patisiran	PND Score	I (n=35)	-5.2 (43.6)
		II (n=37)	-3.0 (25.7)
		IIIA (n=39)	-4.2 (18.7)
		IIIB/IV (n=26)	-4.1 (15.0)
	FAP Stage	1 (n=64)	-6.1 (35.3)
		2/3 (n=73)	-2.4 (19.9)

Table 1. Percent Change from Baseline in mNIS+7 at Month 18 by Treatment and Baseline PND and FAP Scores

Conclusion: Disease progression was more rapid in early stages of hATTR amyloidosis with polyneuropathy than in more advanced stages. Compared to untreated patients, those on patisiran demonstrated improvements in neuropathy. These data underscore the importance of early diagnosis and intervention in treating neuropathy impairment in hATTR amyloidosis.

Disclosure: This study was funded by Alnylam Pharmaceuticals.

EPR1129

Morphological evidence for mitochondrial damage in an animal model of Guillain-Barré syndrome

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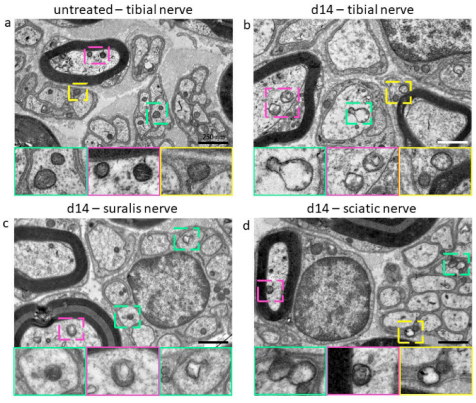
Background and aims: Little is known about mitochondrial damage subsequent to endoneural inflammation in Guillain-Barré syndrome (GBS). Experimental autoimmune neuritis (EAN) is an animal model that replicates clinical and morphological features of GBS.
Methods: Lewis rats were immunized with P0 myelin protein and adjuvants. Animals were sacrificed at two timepoints (14d,28d) and sural, tibial, and sciatic nerves were examined by light and electron microscopy. Mitochondrial morphology was studied in myelinated, unmyelinated axons, and Schwann cells.
Results: Animals developed clinical symptoms with a maximum at d14 and recovery at d21. Histological examination revealed no changes in axon count, but significant decrease in g-ratio in all nerves at d14 and d28. There was a significant increase in mitochondrial diameter at d14 in myelinated and unmyelinated axon as well as in Schwann Cells. Morphological changes in mitochondria correlated with formation of onion bulbs and axonal sprouts. During recovery (d28), mitochondrial diameters shrank back to original values.



Mitochondria diameter increases at disease peak (14d). Electron microscopy images of tibial, suralis and sciatic nerve from control and treated rats (n=4). Mitochondria in unmyelinated axons (blue), myelinated axons (pink), Schwann cell (yellow). Scale bar=250nm. (a) Control tibial and tibial (b), suralis (c) and sciatic nerve (d) from treated rats

Conclusion: Endoneural inflammation and demyelination in EAN is associated with profound but reversible changes in mitochondrial morphology. Our observations support the notion that mitochondrial damage contributes to temporal nerve damage in EAN.
Disclosure: Nothing to disclose

EPR1130

Chronic inflammatory demyelinating polyneuropathy (CIDP) associated with sarcoidosis or connective tissue disease: Is nerve's camouflage the sinew of war?

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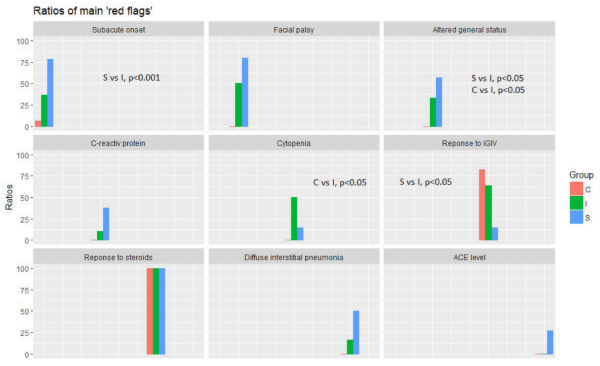
Background and aims: CIDPs are heterogeneous pathologies. Diagnosis can be challenging because of atypical presentations and differential diagnoses to exclude. Neurosarcoidosis (NS) and connective tissue diseases (CTD) are rarely associated with CIDP. We analysed the presentations of CIDP associated with these diseases and highlight the helpful "red flags".
Methods: We performed a retrospective study by analysing patients with NS (group S) and CTD (group C) fulfilling EFNS-PNS CIDP diagnosis criteria and compared them with patients with idiopathic CIDP (group I). Zajicek criteria were used for NS diagnosis and ACR criteria for CTD.
Results: A total of 44 patients were recruited (median age 60 yo, 23 women): 17 in group I, 16 in group S and 11 in group C. According to Zajicek criteria we found 9 cases of definite NS (granuloma within peripheral nerve tissue), 6 probable and 1 possible. We found 7 Gougerot-Sjogren syndrome (GSS), 1 systemic lupus erythematous (SLE), 2 SLE with GGS and 2 mixed connective tissue diseases. CIDP diagnosis was definite in 57.1% in group S and 54.5% in group C. Compared to group I, we found significantly ($p<0.05$) more altered general status in both groups; subacute onset (78.6% vs 5.9%) and unresponsiveness to treatment by IVIg (14.3% vs 82.4%) only in group S. CSF and histological analyses showed no differences expect for the presence of granulomas.



Principal red flags and statistical significance across groups

Conclusion: Our results confirmed and enhance some of the known red flags according CIDP diagnosis. It is, to our knowledge, the first study comparing idiopathic CIDP to CIDP associated or caused by NS or CTD.
Disclosure: Nothing to disclose

Sleep disorders 1

EPR1131

Killer cell immunoglobulin-like receptor genes and sleep disorders in a Portuguese population

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Background and aims: HLA class II genotyping has been a useful tool in the diagnosis of Sleep Disorders (SD). Associations for other HLA loci, namely HLA class I, remain inconclusive. The HLA class I molecules are ligands for the Killer immunoglobulin-like receptors (KIR) of Natural Killer cells and could thus have a role in immune regulation. Our aim was to investigate whether KIR gene polymorphisms are associated with SD susceptibility and presentation in a Portuguese cohort and to evaluate their putative vale as a differential diagnosis tool.
Methods: 73 patients (28 Narcolepsy Type1; 12 Narcolepsy Type 2 and 33 with hypersomnia), complaining of periods of excessive daytime somnolence from the Sleep Outpatient Clinic of HSA/CHP were assessed by clinical, night PSG and MSLT. KIR genes and their HLA-Cw ligand epitopes (C1 and C2) were genotyped by PCR-SSP methodology. A Control Population (CP) comprising 121 healthy individuals from the same geographic origin was used.
Results: Lower frequencies of KIR3DS1 gene (33% vs 44%; p=0.002; OR=0.173) were found in SD patients compared to CP. The difference was particularly relevant in Narcolepsy Type 2 patients (p=0.0014; OR=0.125).
Conclusion: To the best of our knowledge, this is the first study to examine the association between KIR genes and sleep disorders. NK cells are described to have regulatory functions in Central Nervous System, through the elimination of auto-reactive immune cells. This can explain the protective effect of KIR3DS1 gene in immune-mediated sleep disorders, and provides further support for the proposed role of immune system dysfunction in SD development.
Disclosure: Nothing to disclose

EPR1132

Gender differences in clinical, laboratory, and polysomnographic features of Restless Legs Syndrome

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Background and aims: Restless Legs Syndrome (RLS) is a common neurological disorder with a clear female predominance. This study aims to evaluate gender differences in clinical, laboratory, and polysomnographic features in RLS patients.
Methods: For this retrospective analysis, 42 women and 42 men from the Innsbruck RLS database matched by age and therapy were included. Demographic data as well as different severity scales (IRLS, RLS-6, and CGI) were evaluated. Laboratory parameters included several indicators of serum iron status. In all patients, polysomnography was performed according to the AASM guidelines and periodic leg movements during sleep (PLMS) were scored according to the AASM criteria.
Results: IRLS and RLS-6 revealed more severe symptoms in women [IRLS median (range): 17.5 (0-35) vs. 13.5 (0-32), p=0.028; RLS-6 median (range): 18 (0-39) vs. 12 (1-42), p=0.014]. Women had lower serum ferritin levels than men [median (range) in µg/l: 74 (9-346) vs. 167 (15-389), p<0.001]. 22 women and 8 men (53.7% vs. 22.2%, p=0.003) had ferritin values below 75 µg/l. PLMS indices were significantly lower in women than in men [median (range) in number/h: 11.4 (0-62.5) vs. 40 (0-154), p=0.004, and 12.6 (0-58.5) vs. 40 (0.5-208), p=0.002, for night I and night II respectively].
Conclusion: RLS severity as measured by validated scales was worse in women, while PLMS indices were higher in men. These results suggest a possible gender difference in phenotypical presentation of RLS, manifesting with predominantly sensory symptoms in women and predominantly motor symptoms in men.
Disclosure: This work was supported by the Austrian Science Fund (KLI 236).

EPR1133

Real-world treatment of pediatric narcolepsy with pitolisant

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Background and aims: Narcolepsy is a chronic autoimmune brain disorder. Key symptoms are excessive daytime sleepiness (EDS) and cataplexy. Recently, an impaired histaminergic neurotransmission in children with narcolepsy (NT1) has been described. First symptoms of narcolepsy often occur in childhood. Treatment options for children are very limited. Pitolisant has been approved for the treatment of narcolepsy with and without cataplexy in adults.
We aimed at assessing effects and tolerability of pitolisant in narcoleptic children/adolescents in a real-world setting.
Methods: Single-center, observational investigation with consecutive pediatric narcolepsy patients treated with pitolisant. Assessment included demographic and clinical characteristics and questionnaires.
Results: 9 children (5 girls), aged between 8 and 17 years (8-12 years: n=4; 13-17 years: n=5); all suffering from NT1 were treated with pitolisant. Treatment was initiated after failure of prior methylphenidate treatment (development of tolerance (n=5); side effects (n=6)). 6 children were treated with pitolisant as monotherapy; in three children, co-medication included sodium oxybate (n=1), venlafaxine (n=1) and citalopram (n=1). Mean pitolisant dosage for children was 15.75mg/d and 28.8mg/d for adolescents, respectively. Treatment was effective for EDS: ESS-CHAD score decreased from 15.8 (SD 2.1) to 13.2 (1.5), and weekly cataplexy frequency improved from 5.2 at baseline to 3.5 after 3 months. Pitolisant treatment was well tolerated. Side effects were minor, usually short-term and included nausea (n=2), headache (n=2) and insomnia (n=1).
Conclusion: This analysis of real-world clinical data suggests that in pediatric NT1, pitolisant treatment is effective for EDS and cataplexy and is generally well-tolerated.
Disclosure: A Triller and A Hof zum Berge report no conflicts of interest. U Kallweit reports receiving research grants from Bioprojet Pharma, the European Narcolepsy Network, Jazz Pharmaceuticals, and UCB Pharma; and serving as a consultant or advisory board member for AOP Orphan Pharmaceuticals, Bioprojet Pharma, Harmony Biosciences, Jazz Pharmaceuticals, and UCB Pharma.

EPR1134

Morning-evening differences in the functional brain connectivity in insomnia patients

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Background and aims: Hyperarousal is considered the main mechanism in insomnia and might be mediated by the changes in the brain functional connectivity (FC) (in its morning-evening differences).
We studied FC changes in insomnia patients (IP) and its morning-to-evening differences.
Methods: We included 15 IP (8 males, mean age 38±12yrs, DSMV criteria) who have not got sleeping pills/other medications with the potential effect on functional brain activity. Control group included 15 age-/sex-matched healthy subjects. Resting-state FC magnetic resonance imaging (rsfcMRI) was used to investigate FC in the morning (after awakening) and evening (after routine workday, no daytime nap allowed). The correlation between the brain network connection (NC) of the anterior cingulate (AC) cortex (CX), the posterior cingulate (PC) CX were compared.
Results: IP showed enhanced NCs in the morning vs evening in the vermis, left (L) supracalcarine CX with AC-CX, and weaker brain FC in the right (R) caudate, L-frontal-orbital CX with PC-CX. In the morning, IP demonstrated weaker NCs in the R/L-inferior-temporal gyri, R/L-superior-parietal lobules (SPL), R/L-intraparietal sulci, subcallosal CX, L-frontal-eye-fields, L-lateral-occipital (LO) CX, L-cerebelum Crus 1 (CC1), L-temporal-fusiform (TF) gyrus with AC-CX; weaker NCs in the R/L-supramarginal gyri, R/L-temporo-occipital gyri (TOG) and CX, L-LO-CX, L-TF-CX with PC-CX. In the evening, IP had weaker NCs in the subcallosal CX, R/L-SPL, R/L-intraparietal sulcus, R-inferior temporal gyrus, R/L-TOG, R-LO-CX, L-CC1 with AC-CX; weaker NCs in the R-temporal pole with PCCX.

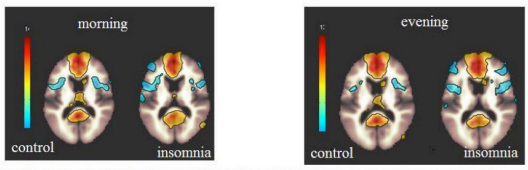

Fig. Changes in the functional connectivity of the anterior cingulate cortex in the morning and evening.

Conclusion: Compared to the controls, IP showed changes in brain FC both in the morning and evening, which might be related to the pathophysiological mechanism of insomnia.
Disclosure: The work was supported by the grant of the Russian Scientific Foundation, project # 17-75-10099.

EPR1135

Brain glucose metabolism in chronic insomnia

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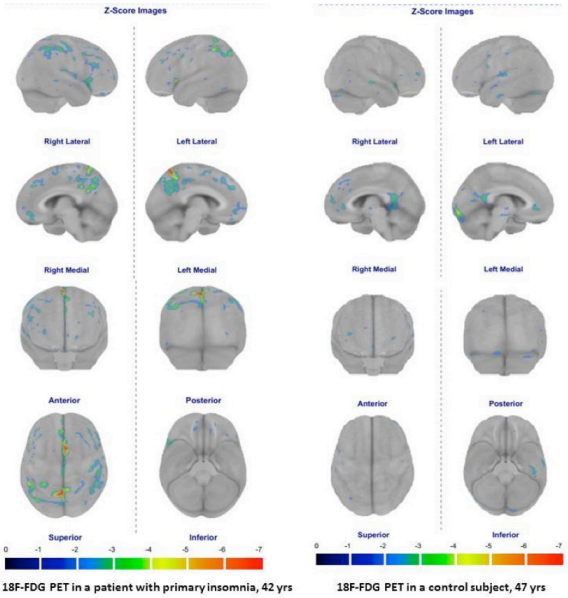
Background and aims: Insomnia is assumed to be related to the alteration in brain region activation which might be mediated by the changes in metabolism both in sleep and wakefulness. We assessed the relative regional cerebral glucose metabolic rate at wakefulness in patients with primary insomnia (PI) and control group.

Methods: 18-FDG was performed in 10 patients with PI (8 males, mean age 40±9 years, DSM V criteria, no sleeping pills or other medications with the potential effect on brain activity) and 7 control good sleepers (4 males, mean age 33±6 years). All subjects underwent 18fluorodeoxyglucose positron emission tomography (18F-FDG PET) in wakefulness. Brain PET/CT scanning was performed 30 min. after administration of 250 MBq 18F-FDG. The PET images were statistically analyzed by 3D-SSP method (Z-score) using software package Cortex ID.

Results: PI patients demonstrated hypometabolism in the right inferior parietal cortex [-1.59 (-4.6;-0.02) vs. -0.86 (-1.52;0.58), p=0.04] and left prefrontal medial cortex compared to controls [-1.48 (-3.75;1.21) vs. -0.46 (-1.34;0.97), p=0.04]. The rate of hypometabolism in these regions was higher in PI group (prefrontal medial: n=2 vs. n=0, McNemar p=0.008; parietal inferior: n=4 vs. n=0, p=0.031). At the same time the number of regions with hypermetabolism [2.5 (1;4) vs. 1 (0;4), p=0.08] did not differ between PI and control groups.



18F-FDG PET/CT in a patient with primary insomnia and in a good sleeper

Conclusion: Insomnia is associated with the regional cerebral glucose metabolism disturbance in wakefulness, in particularly, hypometabolism in the regions implicated in the somatosensory and executive functions.

Disclosure: The study was supported by the grant of the Russian Scientific Foundation, project #17-75-10099.

Sunday, June 30 2019
Ageing and dementia 3

EPR2001

Concordance among neuropsychological profile, functional and pathological biomarkers in Primary Progressive Aphasia: a single centre experience

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Background and aims: Diagnostic classification of Primary Progressive Aphasia (PPA) identifies three variants: Progressive Non-Fluent Aphasia (PNFA), Semantic Dementia (SD) and Logopenic Aphasia (LPA). PNFA and SD are considered variants of Frontotemporal Dementia (FTD) whereas LPA is considered as an atypical presentation of Alzheimer's Disease (AD). There is no absolute association between each PPA variant and a single pathological entity. We aimed to investigate the role of neuropsychological assessment (NPS), 18F-Fluorodeoxy-glucose-PET (FDG-PET), CSF and Amyloid-PET (A-PET) in the diagnosis of PPA variants.
Methods: We included 10 PNFA, 11 SD, and six LPA subjects. All patients underwent NPS with language evaluation, FDG-PET and A-PET or CSF biomarkers measurement.
Results: FDG-PET and NPS had a low concordance as one third of PNFA/SD subjects presented AD hypometabolism pattern. Only 1 LPA subject had FTD FDG-PET pattern (Fig.1). 5 PNFA subjects (50%), 3 SD subjects (27%) and 4 LPA subjects (67%) presented AD pathology according to CSF or A-PET (Fig.2). APOE-ε4 was more frequent in PNFA/SD with AD pathology than in PNFA/SD without AD pathology. We performed a descriptive analysis of discordant cases and found that all PNFA/SD subjects with AD FDG-PET pattern had CSF AD profile, not confirmed by A-PET. Two LPA subjects did not show Aβ1-42 reduction but tau/Ab ratio was augmented.

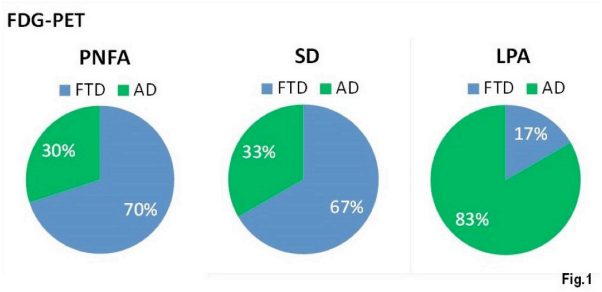

Fig.1

70% of PNFA subjects showed FTD FDG- PET pattern and 30% showed AD FDG-PET pattern. 67% of SD subjects had FTD FDG-PET and 33% had AD FDG-PET pattern. Only one LPA subject had FTD FDG-PET pattern

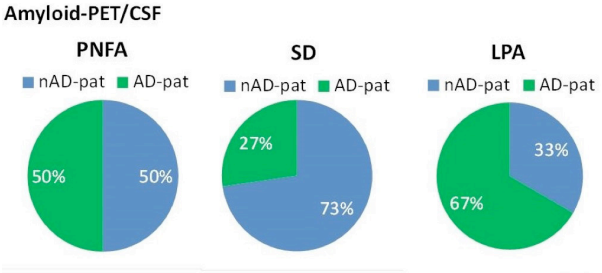

Fig.2

50% PNFA, 27% of SD subjects and 67% of LPA subjects presented AD pathology according to CSF biomarkers or A-PET (AD-pat). 50% of PNFA, 73% of SD and 33% of LPA subjects did not present AD pathology (nAD-pat)

Conclusion: Amyloid-PET could be especially useful in discordant cases of PPA to exclude AD pathology. In contrast, if Amyloid-PET is positive but CSF is negative, an underlying AD pathology might be in doubt. CSF biomarkers ratios could be useful tools in clinical practice.
Disclosure: Nothing to disclose

EPR2002

Frequent alteration of the amyloid pathway in prodromal Lewy body dementia.

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Background and aims: To analyze the "core" CSF biomarkers of Alzheimer's disease in patients with prodromal Lewy body disease (LBD) to known if the amyloid or tau pathways may be altered in this illness.
Methods: Between 2008 and 2017, we included mild cognitive impairment (MCI) patients, following Petersen's 2006 criteria, from three hospitals in the Alicante province. A physical and neurological examination, neuropsychological testing, blood tests, brain MRI and lumbar puncture were performed at inclusion. A cerebral DAT-SCAN were done when LBD were suspected. The clinical progression to LBD was assessed according to McKeith criteria 2005.
Results: 430 patients were included. 29 have been clinically stable as MCI almost 5 years and 26 developed LBD. In 16 LBD patients (61%), Aβ 1-42 protein levels were under the normality accepted in our laboratory (700 pg/dl). The Aβ 1-42 protein levels in CSF were lower LBD patients (616±197 pg/dl versus stable MCI 976±262 pg/dl; $p<0.0001$). Both groups were very homogeneous excluding the age (LBD: 74±6.7 years versus stable MCI: 70±7.0 years; $p<0.01$) that should not explain the differences found. There were not differences in tau protein levels.
Conclusion: We emphasize the frequent alteration of the amyloid pathway in prodromal LBD, almost in our population, and the current concept that different metabolic pathways may be altered in the same clinically defined dementia.
Disclosure: Nothing to disclose

EPR2003

Predictors of progression of cognitive impairment in patients with Parkinson's disease in Tomsk region, Russia

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Background and aims: Mild cognitive impairment (MCI) in Parkinson's disease (PD) is common and may be associated with accelerated progression to dementia, which significantly affects the quality of life, prognosis and mortality [Natalie C. Palavra, 2013]. The aim was to report the predictors of progression of either normal cognitive function or MCI to dementia in PwPD.
Methods: 819 PwPD are registered in movement disorders electronic database in Siberian region. Clinical assessments were carried out using UPDRS, H&Y Scale. 446 nondemented PwPD (women:men=233:213, mean age 66.2±8.3, PD mean duration 7.6±5.6, mean H&Y stage 2.86±2.64, mean UPDRS III 33.2±16.3) were investigated using Montreal Cognitive Assessment, including investigation of 5 areas: attention/working memory, executive, verbal, and visual memory, language, and visuospatial; Beck depression inventory II; Hospital Anxiety and Depression Scale; Apathy Scale; PD Sleep Scale; Epworth Sleepiness Scale; PD Questionnaire-39. Patients were classified as having normal cognitive function and MCI at baseline; normal cognitive function, MCI and dementia followed in yearly intervals for 6 consecutive years from 2013 to 2018.
Results: About 12% of incident MCI cases had progressed to dementia in PwPD by every year. According to multivariate analysis cognitive impairment in PwPD was predicted by older PD debut ($p<0.001$), presence of freezing ($p<0.001$), more excessive UPDRS motor score ($p<0.001$), more score depression ($p<0.005$), anxiety ($p<0.005$), daytime sleepiness ($p<0.005$), worse global cognitive score ($p<0.001$).
Conclusion: Monitoring for CI is important in patients with risk factors to recognize and treat it.
Disclosure: Nothing to disclose

EPR2004

Sensitivity of the free and cued selective reminding test (FCSRT) in Alzheimer's disease (AD) and specificity versus other causes of cognitive impairment

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Background and aims: The FCSRT is sensitive to detect memory impairment deriving from derangement of hippocampal-based memory networks in the earliest stages of AD. Its accuracy has been mainly tested against healthy controls or non-converter mild cognitive impairment (MCI) patients but seldom versus other diseases.

Methods: We retrospectively selected 436 consecutive subjects evaluated at our outpatient memory clinic for MCI or mild (MMSE>20) dementia between 2013 and 2017, and followed-up for at least one year (mean: 24.9±14.6 months). We considered the final diagnosis, according to current criteria, and unblinded to results of FCSRT. Main demographic and clinical characteristics of the 12 subgroups are shown in table 1. The scores of the seven FCSRT main indexes were compared with the Italian normative values. We computed sensitivity of indexes in AD dementia (ADD) and prodromal AD (Table 2) as well as specificity versus ten other subgroups (Table 3).

Table 1. Demographic and clinical characteristics of patient subgroups

	Age (y)	Gender M/F	Education (y) M±SD	MMSE score M±SD
AD (n 108)	75.93±6.89	42/66	9.49±4.23	25.11±2.37
pAD (n 66)	76.73±5.62	28/38	9.83±4.23	26.91±2.37
DEP (n 69)	72.48±8.18	19/50	9.62±4.68	27.97±2.23
DLB (n 13)	77.80±4.73	7/6	10.54±3.43	24.23±3.04
FTD (n 36)	75.20±7.26	15/21	8.28±4.00	26.06±2.46
unclass MCI (n 29)	78.25±6.11	13/16	8.41±5.10	27.00±1.74
VCI (n 23)	79.02±5.44	11/12	10.52±4.25	27.78±2.43
Miscellaneus (n 19)	70.36±10.85	12/7	10.00±4.22	26.74±2.84
PSP (n 7)	78.02±6.75	5/2	7.29±3.41	26.57±2.06
Psychiatric (n 13)	69.43±11.33	5/8	10.08±3.79	26.62±1.94
SNAP (n 11)	77.06±3.82	6/5	8.82±3.86	27.73±2.00
SCI (n 41)	72.38±10.65	22/19	11.56±4.21	29.10±1.14

ADD= Alzheimer disease dementia; pAD= prodromal Alzheimer's disease; DEP= cognitive presentation of depression; DLB= Dementia with Lewy Bodies; FTD=Frontotemporal Dementia; unclass MCI= undiagnosed MCI; VCI= Vascular Cognitive Impairment; Miscellaneus= various etiologies; PSP= Progressive Supranuclear Palsy; Psychiatric= other psychiatric disorders; SNAP= Suspected non-Alzheimer pathology; SCI= Subjective Cognitive Impairment.

Table 1

Table 2. Sensitivity in ADD and pAD

	ADD (n 108)	pAD (n 66)
IFR	.945	.805
ITR	.850	.725
DFR	.945	.835
DTR	.880	.755
RP	.435	.395
ISC	.795	.680
IW	.205	.091

Sensitivity of the 7 indexes in ADD and pAD
IFR = immediate free recall;
ITR= immediate total recall;
DFR= delayed free recall;
DTR= delayed total recall;
RP= recognition phase;
ISC= index of sensitivity of cueing;
IW= intrusion words

Table 2

Table 3. Specificity

	DEP (n 69)	DLB (n 13)	FTD (n 36)	unclass MCI (n 29)	VCI (n 23)	Miscellaneus (n 19)	PSP (n=7)	Psychiatric (n 13)	SNAP (n=11)	SCI (n=41)
IFR	.635	.540	.360	.275	.520	.525	.430	.540	.010	.855
ITR	.795	.770	.555	.480	.695	.630	.570	.690	.180	.950
DFR	.650	.460	.390	.310	.565	.580	.430	.540	.180	.880
DTR	.725	.770	.555	.380	.610	.630	.715	.460	.270	.900
RP	.900	.925	.775	.690	.740	.840	1.000	.925	.725	.975
ISC	.800	.925	.555	.515	.650	.735	.570	.615	.180	.950
IW	.940	.925	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.975

Specificity of the 7 indexes in ADD and pAD are shown as 1-sensitivity in the other 10 conditions.
Legend: IFR = immediate free recall; ITR= immediate totale recall; DFR= delayed free recall; DTR= delayed total recall; RP= recognition phase; ISC= index of sensitivity of cueing; IW= intrusion words

Table 3

Results: Immediate and delayed free recall were very sensitive in detecting AD, however specificity of these two indexes was good only to discriminate against Subjective Cognitive Impairment (SCI). The index of sensitivity of cueing showed specificity ≥80% versus cognitive presentation of depression and SCI while the recognition phase and the word intrusion index were generally very specific versus most of other conditions but presented a very low sensitivity in AD.

Conclusion: The relatively low specificity of FCSRT in AD versus other cognitive disorders could be explained by its exquisite sensitivity to failure of hippocampus-centered memory networks, which can however be found at various extent even in non-AD conditions.

Disclosure: Nothing to disclose

EPR2005

Virtual navigation assessment and APOE genotype in early Alzheimer's disease

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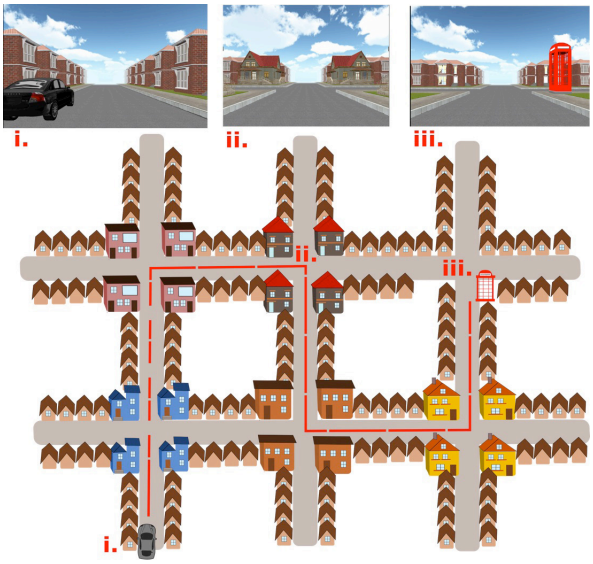
Background and aims: Alzheimer's disease (AD) is associated with gradual decline of cognitive functions including spatial navigation. APOE 4 genotype is the strongest genetic risk factor for sporadic AD. The aim was to characterize spatial navigation impairment in the early clinical stages of AD and to evaluate the effect of APOE 4 genotype.

Methods: Participants with amnestic mild cognitive impairment (aMCI) due to AD (n=19), mild AD dementia (n=18) and cognitively normal adults (CN; n=22) underwent spatial navigation assessment in a virtual realistic-looking "Intersections" test and APOE genotyping. The test consisted of three tasks: i) egocentric "route repetition" – participants were repeatedly passively transported through a virtual city and consecutively repeated the same route, ii) allocentric "route retracing" – similar to route repetition task where participants indicated way back, and iii) allocentric "different approach direction" – participants were passively transported to a specific intersection and afterwards indicated their original position from a different perspective.



Intersections test

Results: The aMCI and dementia groups had less accurate performance in route repetition (p's≤.003), route retrace (p's≤.022) and different approach direction (p's≤.004) tasks than the CN group. The CN group, unlike aMCI and dementia groups, improved their performance in route retrace task indicating a significant learning effect (p's<.02). APOE genotype did not affect performance in the tasks.

Conclusion: Egocentric and allocentric spatial navigation impairment depends more on the severity of AD, than on APOE E4 genotype. The virtual "Intersections" test may be a useful tool for assessment of spatial navigation deficit in early AD.

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EPR2006

Microglia activation and brain glucose metabolism in early onset Alzheimer's disease: a PET study

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Background and aims: Early onset Alzheimer's disease (EOAD) is characterized by young age of onset (<65 years), severe neurodegeneration and rapid disease progression. Previous studies have consistently shown that microglia activation plays a role in AD pathogenesis. We investigated in vivo microglia activation in a group of EOAD patients, addressing its relationship with brain glucose metabolism to verify whether microglia activity can exacerbate neurodegeneration.

Methods: We used [11C]-PK11195-PET, which shows the expression of the Translocator Protein (TSPO) in brain activated microglia, to study twelve EOAD and in nine Healthy Controls (HC). Binding potentials (BPs) were obtained using reference regions selected with an optimized clustering followed by a parametric analysis. Single-subject TSPO overexpression z-score maps were calculated at the voxel-level in comparison to HC. [18F]-FDG PET brain metabolism was assessed by an optimized SPM voxel-wise single-subject method which includes comparison with a large HC database. A correlation analysis in AD-signature regions was used to evaluate the association between hypometabolism and microglia activation.

Results: EOAD patients showed both significant microglia activation and marked brain glucose hypometabolism in typical AD-signature regions, namely the temporo-parietal areas, with additional variable frontal and occipital hypometabolism, as in the AD variants. There was a spatial concordance and a significant correlation between these altered biomarkers in temporal and parietal regions.

Conclusion: EOAD is characterized by a severe microglia activation coupled with brain glucose hypometabolism in AD-signature regions. A possible strong interrelationship between local immune response and neurodegeneration may contribute to the rapid disease progression observed in EOAD.

Disclosure: Nothing to disclose

Cerebrovascular diseases 3

EPR2007

Histopathological analysis of human cerebral thrombi

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Background and aims: Inflammation is emerging as one of the main triggers of thrombosis, and in particular neutrophils have been demonstrated to promote thrombus formation through different mechanisms.
We here aimed to unravel the histopathological composition of cerebral thrombi, with a focus on inflammatory cells and their by-products, to understand the mechanisms of thrombo-inflammation in ischemic stroke, to establish the origin of the thrombus and to discover new possible indirect markers of its composition.
Methods: We performed a systematic histological analysis of cerebral human thrombi retrieved by mechanical thrombectomy in acute stroke patients. We investigated the clot composition, in terms of structural and inflammatory components (red blood cells, fibrin, platelets, von Willebrand Factor, inflammatory cells, neutrophil extracellular traps), by means of specific immunostainings.
Results: Thrombi of 80 patients with large vessel occlusion stroke were collected during mechanical thrombectomy. Cerebral thrombi are heterogeneous in terms of macroscopic appearance and in their structural microscopic composition. Neutrophils are the most represented inflammatory cells, and NETs are represented within all cerebral thrombi, with neutrophils proportions correlating to NETs levels. Percentage of NETs seems to be higher in cardioembolic compared to atherosclerotic clots. Percentage of NETs is lower in patients with parenchymal haemorrhagic transformation (type 1 and 2) of ischemic lesion.
Conclusion: Our pilot study has shown that analysis of thrombus composition might act as a glimpse in stroke pathogenesis and suggests common interacting pathways of thrombosis and inflammation in stroke.
Disclosure: Nothing to disclose

EPR2008

Biomarkers of connective tissue dysplasia in patients with cervical artery dissection

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Background and aims: Cervical artery dissection (CeAD) is the most common cause of ischemic stroke in young adults. According to our previous studies arterial wall dysplastic changes underlies its weakness and predisposes to dissection. Biochemical markers of connective tissue dysplasia (CTD) have not been studied in CeAD patients.
Methods: We examined 82 patients (mean age 38.3±6.5; 49 females, 63%) withCeAD, verified byMRI/MRA and 40healthy volunteers. Matrix metalloproteinases-9 (MMP9), tissue inhibitor of metalloproteinase-1 (TIMP1), hydroxyproline, sulfated glycosaminoglycans were evaluated byELISA (microplate readerVictor2, PerkinElmer (USA). Orosomucoid was evaluated on an automatic biochemical analyzer Konelab30IPrime (Finland).
Results: MMP9 level inCeAD patients was higher than in normal controls (384±69.3ng/ml vs 203.1±60.5ng/ml, $p<0.0005$), that could lead to increased extracellular matrix degradation in the vascular wall.
TIMP1 was also raised in CeADpatients (393.9±63.4ng/ml vs control134.4±30.8ng/ml, $p<0.0005$), apparently in response to increased MMP9 level reflecting the extracellular matrix restructuring.
Sulfated glycosaminoglycans which are the component of the extracellular matrix of the connective tissue (CT) were elevated in CeADpatients (6.2±1.4μg/ml vs 4.5±0.8μg/ml, $p<0.0005$) and could reflect CT damage.
Orozomukoid, the acute phase protein,was increased in CeAD patients (121.6±27.8mg/dl vs 88.8±17.4mg/dl, $p<0.0005$), probably due to local inflammatory in response to vascular wall damage.
The level of hydroxyproline in CeAD patients (604.9±350.9ng/ml vs 1293.6±214.5ng/ml, $p<0.0005$) was reduced, that could limit collagen synthesis.
Conclusion: The changes of CTD biomarkers in CeAD patients assume CT damage, that seem to be cause of vascular wall weakness predisposes to dissection. The high sensitivity and specificity of the studied biomarkers allow to consider them as biological markers of CTD in CeAD patients.
Disclosure: Nothing to disclose

EPR2009

GLIAS-II study: Analyzing the influence of diabetes mellitus in brain damage and repair biomarkers levels in acute stroke:

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Background and aims: To analyze the influence of diabetes mellitus (DM) in brain damage and repair biomarkers levels in acute ischemic stroke (IS).
Methods: Secondary analysis of GLIAS-II study: a multicentre observational prospective study. We analyzed circulating biomarkers related to inflammation (interleukin-6 [IL-6], interleukin-4 [IL-4], interleukin-10 [IL-10], tumor necrosis factor-α [TNF-α], transforming growth factor beta [TGF-B] and C-reactive protein [CRP]); prothrombotic activity (plasminogen activator inhibitor [PAI-1]); endothelial dysfunction (vascular cell adhesion protein [VCAM], intercellular adhesion molecule [ICAM]); blood-brain barrier rupture (matrix metalloproteinase 9 [MMP-9]); cell death (annexin V, Abcam); and repair processes (vascular endothelial growth factor [VEGF], brain-derived neurotrophic factor [BDNF] and anti-NogoA) at 24-48 hours and 72-96 hours.
Results: 213 patients were included. 64 (30%) had a previous history of DM. No significant differences in biomarkers levels between DM and non-DM were found. Higher IL-6 at 24 and 72 hours were associated with poor outcomes (modified Rankin scale ≥3) at 3 months regardless of DM (OR 1 CI 95% 1.001-1.013 and OR 1.01 CI 95% 1.006-1.024) in logistic regression analysis.
Conclusion: Biomarkers levels did not differ in patients diagnosed with DM. Higher levels of biomarkers were found in patients with poor outcome independently of DM.
Disclosure: Nothing to disclose

EPR2010

Multicenter RESTAIC registry: risk and benefits of oral anticoagulant therapy in clinical practice

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Background and aims: After the development of the novel oral anticoagulants for stroke prevention, prospective registries to evaluate the results of their implementation in clinical practice are mainly based on primary prevention. Our aim is to explore the long-term outcomes differences according to the oral anticoagulation (OAC) in secondary cardioembolic stroke prevention.
Methods: A prospective, multicentric, registry including IS patients who were discharged under OAC. Three months follow-up was scheduled at outpatient clinic with annual phone interviews for 3 years. Principal outcomes: stroke recurrences, intracranial hemorrhage, mayor hemorrhage and mortality. Patients were classified and compared into 4 study groups according to OAC at discharge: Vitamin K antagonist (AVK), Factor Xa inhibitor (FXa-I), direct thrombin inhibitor (DTI) and other OAC.
Results: 256 patients were included. Patients under FXa-I were older (age >75: 55.8% vs. 24.8% AVK, 14.5% DTI and 18.6% other OAC P=0.01), had higher frequency of hypertension (48% vs. 33% AVK, 18.8% DTI and 14% other OAC P=0.001), had higher CHA2DS2-VASc (median 6 vs. 5 in all the other groups; P=.007), without differences in HASBLED scores. We found low mortality rates (3 death/year), stroke recurrences (5.6 stroke/year), intracranial hemorrhages (0.6 hemorrhage/year) and major hemorrhages (0.6 hemorrhage/year) for the first year, without differences between OAC. For the second and third year, no intracranial hemorrhages were reported and the incidence rate decline to 0.05 stroke/year.
Conclusion: Stroke secondary prevention with OAC is safe without significant differences in stroke recurrence rates at long-term between anticoagulant treatments.
Disclosure: Nothing to disclose

EPR2011

In-hospital strokes: a recall to every ward

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Background and aims: In-hospital acute stroke is a medical emergency, occurring mainly in patients admitted for non-neurological reasons. The stroke code activation depends on hospital staff awareness and treatment considerations are different than those for community-onset strokes. We aim to describe in-hospital stroke (IHS) code activations of a single hospital center.
Methods: Retrospective analysis of all IHS code activations between 2012 and 2018. Demographic, stroke assessment and treatment data were collected.
Results: We found 77 patients; 44 (57.1%) male, median age 76-years-old. Stroke code was mostly activated by cardiology (22.1%), surgical wards (18.2%) and intensive care units (16.9%). Mimics represented 26% of the activations (syncope 5, iatrogenic 5, epileptic seizure 3, sepsis 2, psychogenic 2, others 3), and cerebrovascular events were: 61% ischemic stroke, 3.9% hemorrhagic stroke, and 9.1% transient ischemic attack (TIA). These events occurred after an invasive procedure (major surgery, endovascular cerebral or coronary procedure) in 42.6%. The events were witnessed by a nurse (33.3%) or a doctor (22.1%) in most cases. The median days since admission to stroke/TIA was 3 days (range 3-38).
Of all activations, 10.3% underwent thrombolysis, 11.6% endovascular treatment and 3.9% both.
In-hospital case-fatality was 27.3% for all patients, slightly higher (33.3%) when mimics are excluded.
Conclusion: Patients with cardiac pathology or requiring invasive procedures are more prone to develop IHS, mostly during the first days of admission. Only one quarter was eligible for acute stroke treatment, mainly thrombectomy. It is of the uttermost importance to have fast in-hospital protocols to avoid missing treatment opportunities.
Disclosure: Nothing to disclose

EPR2012

Spatial relation of blood-brain barrier impairment with the ischaemic lesion and risk of haemorrhagic transformation in ischaemic stroke patients

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Background and aims: Infarcted tissue is frequently spontaneously affected by hemorrhagic transformation (HT) in ischaemic stroke patients. The aim of the study was to assess the relation of HT occurrence to the proportion of the area of an impaired blood-brain barrier (BBB) located within the ischaemic lesion on MRI.
Methods: Prospective monocentric study on patients with supratentorial acute ischaemic lesion without previous stroke and no HT on early imaging (24-72 hours). MRI with gadolinium was performed 7-12 days after stroke. The areas of hyperintensity on DWI, FLAIR hyperintensity and gadolinium leakage (BBB impairment) were detected by an automatic algorithm. Volumes and the extent of overlapping of these areas were compared between HT and non-HT groups.
Results: 72 patients were included (64% men, average age 67 years, median NIHSS 5, 36% received intravenous thrombolysis, 13% mechanical thrombectomy). HT occurred in 25 patients. Patients affected by HT had significantly larger ischaemic lesions on all compared MRI sequences. HT and non-HT groups showed different localization of the area affected by BBB disruption: 63.7% vs. 48% ($p=0.019$) of area of BBB disruption was FLAIR positive, 22.4% vs. 26.5% ($p>0.05$) DWI positive, 66.6% vs. 52.6% ($p=0.029$) FLAIR positive or DWI positive, 44.1% vs. 26% ($p=0.003$) FLAIR positive and DWI negative at the same time, this parameter was the best predictor of HT in ROC analysis (0.726).
Conclusion: Patients with ischaemic stroke affected by HT have a significantly larger proportion of the area of BBB disruption located within the ischaemic lesion.
Disclosure: Nothing to disclose

EPR2013

Brain collateral circuits as outcome determinants following thrombectomy

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Background and aims: To investigate the individual as well as integral impact of proximal and distal cerebral collateral systems on poor outcome (in-hospital death) in patients treated with endovascular thrombectomy (ET) due to middle cerebral artery occlusion stroke.
Methods: We consecutively included stroke patients with acute occlusion of the M1 portion of middle cerebral artery (MCA) who underwent ET. We recorded demographics, National Institutes of Health Stroke Scale (NIHSS) scores, baseline clinical and radiographic characteristics, and in-hospital death. Incomplete Circle of Willis (iCW) was defined as absence of the anterior communicating artery and absence of posterior communicating artery ipsilateral to the affected side on the CT angiography.
Results: In total, 152 patients were studied [median age 73 (interquartile range [IQR] 59-80), median admission NIHSS score 17 (IQR 12-21)]. In-hospital death rate following the intervention was 14.5% (n=22). The survivors were younger [median age 73(58-79) vs 81(69-86)], had lower NIHSS [17(12-20) vs 20(17-26)], and lower rates of anticoagulant medication intake [12.3% vs 36.4%], all $p<0.01$. In a logistic regression analysis adjusted for age, NIHSS, anticoagulation, infarct volume, symptomatic hemorrhage, in-hospital death was significantly associated with iCW [OR 8.3(CI 1.2-56.8)], as well as with combined variable for proximal and distal collateral circuits [OR 3.4(CI 1.1-11.4)], all $p<0,05$, whereas not with poor leptomeningeal collateral system alone.
Conclusion: Insufficient proximal collaterome is a stronger predictor of poor outcome after ET in patients with MCA occlusion rather than the leptomeningeal system.
Disclosure: Nothing to disclose

Cerebrovascular diseases 4

EPR2014

Characteristics of hospitalizations due to recurrent ischaemic stroke in the Silesian Province, Poland, between 2009 and 2015

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Background and aims: The aim of the study was to analyse the hospitalizations related to recurrent ischaemic stroke (RIS) in Silesia - industrial region covering 12% of Polish population.
Methods: Statistical analysis of data contained in stroke questionnaires transferred to the Polish National Health Fund by hospitals in Silesia between 2009 and 2015.
Results: In the analyzed period the number of hospitalizations due to RIS was 16,256 (23.4% of all acute ischaemic strokes). Large-artery atherosclerosis and cardioembolism were significantly more often recognized in RIS than in first-ever ischaemic stroke (FIS) (consecutively, 38.2% vs 36.0%, and 21% vs 18.1%; $p<0.001$); lacunar stroke was less often diagnosed in RIS than FIS (8.8% vs 10.0%; $p<0.001$). The etiology of stroke was undetermined in 30.4% of RIS and 34.1% of FIS subjects. In-hospital mortality in RIS was significantly higher than in FIS (16.2% vs 13.9%; $p<0.001$). The rtPA therapy was applied to 5.3% of FIS and 3.2% of RIS patients. The in-hospital mortality in RIS subjects treated and untreated with rtPA was similar. Also no statistical difference was found between the in-hospital mortality in FIS and RIS patients treated with rtPA. Antiplatelet drugs were administered in 81.7% of RIS and 84.3% of FIS patients, oral anticoagulants – in 26.2% of RIS and 23% of FIS subjects.
Conclusion: This is the first so comprehensive analysis of RIS in Poland. It can help in implementation of appropriate programs to improve the health status of the society.
Disclosure: Nothing to disclose

EPR2015

Endovascular treatment in patients with acute stroke and comorbid cancer: analysis of the Italian registry of endovascular treatment in acute stroke

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Background and aims: Acute stroke patients with comorbid cancer are more preferably addressed to endovascular recanalization treatment (EVT) than thrombolytic therapy, due to the presumed potential risk of hemorrhagic transformation and systemic bleedings. This study aims to evaluate clinical and procedural outcomes of acute stroke patients with comorbid cancer receiving EVT.
Methods: Using the Italian Registry of Endovascular Treatment in Acute Stroke, we retrospectively reviewed patients with ischemic stroke and comorbid cancer (CC), treated with EVT from 2011 to 2017. Outcome measures were TICI score, occurrence of symptomatic intracerebral hemorrhage and 3-month modified Rankin score. We compared CC patients with a control group of acute ischemic stroke patients without cancer (noCC) receiving EVT.
Results: Out of 4642 stroke patients treated with EVT, 255 (5.5%) had a comorbid cancer. Vascular risk factors were not significantly different and admission NIHSS was 18 (IQR 13-21) in both groups. TICI 2b-3 was obtained in 72.9% of CC and 74.4% of noCC patients ($p=0.6$), while post-treatment symptomatic intracerebral hemorrhage rate

was 8.2% in both groups. Three-month mortality was 35.6% in CC and 18.6% in noCC (p <0.001) patients and mRS 0-2 was reached respectively by 34.3% and 46.7% of patients (p<0.001).
Conclusion: Although 3-month mortality was significantly higher in CC than in noCC patients, successful recanalization was comparable in both groups with a same hemorrhagic transformation rate. Further investigation of leading causes of death in CC patients are warranted to clarify prognosis of stroke patients with malignancy.
Disclosure: Prof. Danilo Toni received honoraria as member of Advisory Board and speaker honoraria from Abbott, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer. Unrestricted research grant from Boehringer Ingelheim. Dr Salvatore Mangiafico acts as a consultant for Johnson&Johnson. Dr Andrea Zini received speaker fees and consulting fees from Boehringer-Ingelheim and Medtronic, and serves as advisory board from Boehringer-Ingelheim, Stryker and Daiichi-Sankio.

EPR2016

Validation and comparison of noncontrast CT scores to predict intracerebral hemorrhage expansion

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Background and aims: The BAT, BRAIN and HEP scores have been proposed to predict hematoma expansion (HE) with noncontrast CT (NCCT). We sought to validate these tools and compare their diagnostic performance.
Methods: We retrospectively analyzed two cohorts of patients with primary intracerebral hemorrhage. HE was defined as volume growth >33% or >6mL. Two raters analyzed NCCT scans and calculated the scores, blinded to clinical and imaging data. The inter-rater reliability was assessed with the interclass correlation statistic. Discrimination and calibration were calculated with area under the curve (AUC) and Hosmer-Lemeshow $\chi 2$ statistic respectively. AUC comparison between different scores was explored with DeLong test. We also calculated the sensitivity, specificity, positive and negative predictive values of the dichotomized scores with cutoffs identified with the Youden's index.
Results: A total of 230 subjects were included, of whom 86 (37.4%) experienced HE. The observed AUC for HE were 0.696 for BAT, 0.700 for BRAIN and 0.648 for HEP. None of the scores had a significantly superior AUC compared with the others (all p>0.4). All the scores had good calibration (all p>0.3) and good to excellent inter-rater reliability (interclass correlation >0.8). BAT >3 showed the highest specificity (0.81) whereas BRAIN >6 had the highest sensitivity (0.76).
Conclusion: The BAT, BRAIN and HEP scores can predict HE with acceptable discrimination and require just a baseline NCCT scan. These tools may be used to stratify the risk of HE in clinical practice or randomized controlled trials.
Disclosure: Nothing to disclose

EPR2017

Safety and efficacy of Tenecteplase compared to alteplase in acute ischaemic stroke

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Background and aims: We studied the safety and efficacy of Tenecteplase versus Alteplase in patients with acute stroke who were eligible for intravenous thrombolysis.
Methods: Adults with acute ischemic stroke admitted within 3 hours of symptom onset who were eligible for thrombolysis, were randomly assigned to receive intravenous tenecteplase 0.2 mg/kg (to a maximum of 20 mg) or alteplase 0.9 mg/kg (to a maximum of 90 mg). The primary outcome was good functional outcome defined as modified Rankin Scale (mRS) score 0-1 at the end of 1 and 3 months. The secondary outcome was recanalization of artery involved on days1, 30 and 90.
Results: 126 patients were randomly assigned to the Tenecteplase (n=42) or Alteplase (n=84) groups. The median age was 54.3 years. The median National Institutes of Health Stroke Scale score at baseline was 8.2. The primary outcome was achieved by 78% in the Tenecteplase group and 58%) in the Alteplase group (p=0≤04). The rates of recanalization in the Tenecteplase group was significantly better than the Alteplase group. The symptomatic intracerebral hemorrhage (sICH) rate was 0.9% compared to 1.6% in the Alteplase group.
Conclusion: Tenecteplase is safe and effective. The realization rate was better in the Tenelecteplase group with evern Terminal Internal Carotid and proximal Middle cerebral vessels opening up. The rate of symptomatic intracerebral hemorrhage was less with Tenelecteplase group. Considering the above and also the one third cost of the drug makes Tenelecteplase the drug of choice in acute ischemic stroke.
Disclosure: Nothing to disclose

EPR2018

withdrawn

EPR2019

Thrombus histology: does it really depend just on stroke etiology?

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Background and aims: Analysis of thrombi responsible for large vessel occlusion (LVO) in acute ischemic stroke (AIS) may be a potential diagnostic tool for AIS ethiopathogenic classification, particularly in cryptogenic events. Nonetheless the available results are controversial. Aim of our study was to evaluate a possible correlation between AIS etiology and thrombus composition.
Methods: We analysed prospectively thrombi retrieved from LVO in AIS within 24 hours since the last time patients were seen healthy. Retrieved thrombi were stored in formaldehyde. Physical characteristics and histological composition, in terms of red blood cells (RBC), and fibrin and platelets (FP) percentage were determined. Thrombi composition was correlated with baseline radiological and interventional data and TOAST subtypes.
Results: We included 34 patients among 41 recruited. 25 thrombi with prevalent RBC and 9 with prevalent FP composition were collected. All the thrombi from patients with atherothrombotic stroke presented FB percentage over 70%. Nonetheless, no significant correlation between thrombi histology and AIS etiology was found. While we found a significant correlation between thrombus length (TL) and AIS subtypes, with a mean TL of 0.87mm in cardioembolic events, 1.83mm in atherothrombotic events, 0.55mm in artery dissections and 1.42mm in cryptogenic strokes (f=3.30, p=0.38).
Conclusion: Our results confirm no correlation between thrombus composition and stroke subtypes, suggesting that thrombus composition may also be related to mechanisms occurring in intracerebral arteries. Finally, we suppose that in cardioembolic and dissective strokes, smaller thrombi would detach from more stable thrombi lying in cardiac cavities and from arterial false lumen.
Disclosure: Nothing to disclose

EPR2020

Intracerebral hemorrhages (ICH) and antiplatelet/anticoagulant therapy (AAT): a clinical dilemma. A retrospective cohort study of 190 primary ICHs admitted between 2012 and 2016

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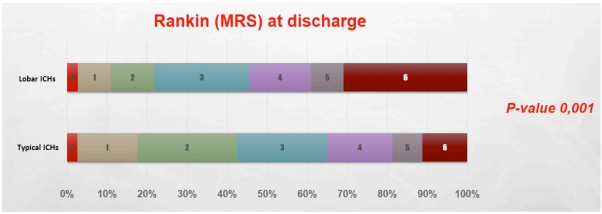
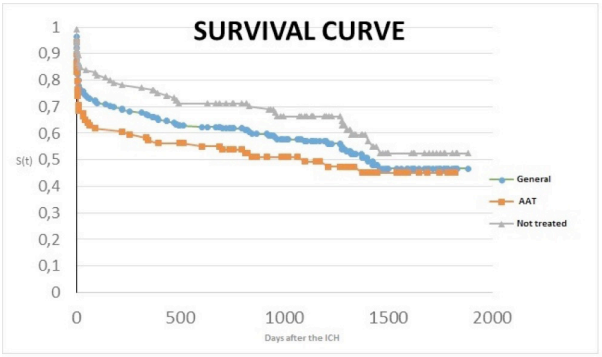
Background and aims: Intracerebral hemorrhages (ICH) account for 6-20% of all strokes. The role of antiplatelet/anticoagulant therapy (AAT) in these patients represents a clinical dilemma. In our study, we investigated differences in stroke severity and prognosis between patients on treatment and not. Furthermore, we analyzed the association of AAT resumption with the risk of developing new vascular events.
Methods: We included only patients admitted to our hospital between 2012 and 2016, diagnosed with primary ICH. The follow-up lasted for at least one year.
We enrolled 196 patients (excluding 6 ICHs, diagnosed as secondary during the follow-up). 106 were lobar; 84 typical. At admission 32% patients were on antiplatelet; 16.9% on oral anticoagulation.
Results: Lobar ICHs showed a worse prognosis compared to typical ICHs, both at discharge and during the follow-up (P-value<0.005). Being on AAT before ICHs increases the risk of death in the first days (P-value:0.007). During the follow-up, no statistical differences in survival appeared between these two groups. A vascular event occurred in 12.9% of patients that did not resume AAT and in 14.9% of patients after restarting AAT.



Degree of disability at discharge of patients who had suffered lobar ICHs, compared to typical ICHs.



Survival curve. Patients on antiplatelet or anticoagulation therapy during the follow-up compared to patients not treated with AAT.

OUTCOME Not treated	TOTAL
ICH	6 (4,1%)
Ischemic stroke	6 (4,1%)
PE	3 (2%)
TIA	2 (1,4%)
SAH	1 (0,7%)
MI	1 (0,7%)
TOT	19 (12,9%)

OUTCOME On treatment	TOTAL
ICH	2 (4,2%)
Ischemic stroke	2 (4,2%)
TIA	3 (6,4%)
SAH	1 (2,1%)
MI	1 (2,1%)
TOT	9 (14,9%)

Vascular events occurred during the follow-up to patients treated with AAT after the ICH and to patients not treated with AAT.

Conclusion: In conclusion, we observed that the type of ICH influences survival. Conversely, AAT seems to increase the risk of death in the acute phase without modifying survival during the follow-up. Resumption of AAT was not related to the risk of developing a further vascular event. Pending the results of ongoing trials on the resumption of AAT after ICH, our data seem to support a lack of major effect on hemorrhagic relapse in patients resuming AAT after ICH.

Disclosure: Nothing to disclose

Child neurology/developmental neurology

EPR2021

Burden test of selected autism-associated genes in a Hungarian cohort

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Background and aims: Autism spectrum disorder (ASD) is heterogeneous both phenotypically and genotypically. Earlier genetic studies indicated that both common and rare variations in autism-associated genes need to be considered. Here we analysed prevalence of rare variants within selected autism-associated genes and their phenotypic associations.
Methods: In a cohort of 174 ASD patients, we used next generation panel sequencing to detect rare variants in 101 autism-linked genes. As the first approach, we focused on identificating syndromic autism cases. As the second approach rare variant burden testing was performed, and we looked for gene enrichment in phenotypically created cluster of patients.
Results: 13 patients were diagnosed with syndromic autism. Intellectual disability, epilepsy, the presence of neurological symptoms were strongly associating with identification of a monogenic disease. However, the number of minor malformation on itself was not. The burden test confirmed the association of five genes with ASD (AUTS2, NHS, VPS13, NSD1, SLC9A9). There was no correlation between the minor malformation burden and rare variant burden, nor between rare variant burden and autism severity. We created four phenotypic clusters based on detailed clinical information, but gene enrichment was not found.
Conclusion: Our study indicates that targeted gene sequencing is useful, when there are certain strong clinical predictors for a monogenic disease, altough unselected panel testing may not provide a reasonable diagnostic yield. Besides this, in the more common, multifactorial cases interpretation of the individual results is very uncertain at this time. However, these rare variants might still have significant impact on the phenotype, on which evidences are growing.
Disclosure: This work was supported from Research and Technology Innovation Fund BIOKLIMA KTIA_AIK_12-1-2013-0017 and Hungarian National Brain Research Program KTIA_NAP_ 2017-1.2.1-NKP-2017-00002.

EPR2022

Deficit of visual memory in delayed recall condition in preschool children with ADHD

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Background and aims: It was shown that children with ADHD have deficit in prefrontal cortex functions including deficit in working memory (Martinussen et al., 2012). In our previous research we have revealed that ADHD children at the age of 8-9 years have deficit in memory in delayed recall condition (Kiselev et al., 2017). The goal of this research was to examine the hypothesis that preschool children with ADHD have the same deficit in memory in delayed recall condition as children at the age of 8-9 years.
Methods: The experimental group included 15 children with ADHD at the age of 5-6 years. The control group included 15 typically developing children. The children from experimental and control group were matched for IQ, gender and age. Children from both groups were assessed with visual memory subtest from Luria's neuropsychological assessment battery. This subtest is designed to assess the ability to perform visual memory for objects in immediate and delayed recall conditions. Two-way ANOVA was used to reveal group differences in reproducing the objects in two conditions.
Results: We have not revealed significant differences between children from experimental and control group in reproducing the objects in immediate condition. However, the interaction of condition type and group was significant ($p \leq 0.05$). ADHD children were less successful in reproducing the objects in delayed recall condition.
Conclusion: In view of the obtained results, it can be assumed that preschool children with ADHD have specific deficit in memory in delayed recall condition.
Disclosure: The research was supported by Act 211 Government of the Russian Federation, agreement no. 02.A03.21.0006.

EPR2023

Neonatal seizures: a retrospective study of semiology, etiology and outcome

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Background and aims: Determining the etiology of neonatal seizures is critical, as it determines the prognosis and guides therapeutic strategies. We aim to characterize neonatal seizures of newborns admitted in our center, regarding demography, etiology and outcome.
Methods: Retrospective descriptive study of hospitalized neonates (≤28 days) presenting with seizures, from 2010-2017. We collected clinical information regarding the perinatal history, seizure classification (Volpe), etiology, treatment and outcome at one-year follow-up.
Results: A total of 97 neonates were included (48 males, mean age 2.7±5.3 days). The most frequent etiologies were hypoxic-ischemic encephalopathy (HIE) (83%), stroke (11%) and infection (4%). Metabolic disorders (MD) (2%) and epileptic syndromes (ES) (2%) were infrequent. Pathological CTG significantly more frequent in HIE (p=0.007). The most prevalent seizure semiology was focal clonic (34%). Electrographic and subtle seizures occurred exclusively in HIE (12%, 10%) and stroke (20%, 10%). Conventional EEG was abnormal in 87% HIE, 73% infections and in all remaingin etiologies. Seizure onset was earlier in ES (1 day) compared to HIE (1.2±2.3 days). MRI was abnormal in 79% HIE, and in all stroke and infections. Mortality was higher in MD and infections (14%). HIE, stroke and ES seizures required at least one antiepileptic drug at discharge (27%, 45%, 100%). HIE, stroke and ES had poorer outcome with severe motor and cognitive sequelae (18%, 60%, 100%).
Conclusion: Acute symptomatic seizures were more frequent and HIE the main etiology. HIE, stroke and ES required more antiepileptics and had worst outcome. Conventional and amplitude-integrated EEG are crucial in monitoring neonates of high seizure risk.
Disclosure: Nothing to disclose

EPR2024

Pediatric muscle biopsy: a 10-year retrospective study

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Background and aims: Despite some debate in literature, most studies advocate muscle biopsy (MB) as an important diagnostic test in the investigation of a child with suspected neuromuscular disorder. The aim of this study was to investigate the results of MB performed in children, with a focus on histopathologic study (HP) and its correlation with clinical diagnosis.
Methods: We retrospectively reviewed results of pediatric MB performed at our tertiary center during the 2008 to 2018 study period.
Results: 57 biopsies from 54 children (58% male) were included. Mean age of patients at biopsy was 6.4±5.0 years. The main indications for MB were hyperlactacidemia associated with an abnormal neurological examination or delayed psychomotor development (42.1%), muscle weakness (19.3%) and neonatal hypotonia (12.3%). HP was normal in 26.3% of cases and suggestive of a specific diagnosis in 38.7%. Major pathologic diagnoses were mitochondrial myopathy (19.3%), muscular dystrophy (10.5%), metabolic myopathy (5.3%), congenital myopathy (1.8%) and macrophagic myofasciitis (1.8%). Non-specific myopathic abnormalities were found in 3.5% of biopsies, neurogenic atrophy in 1.8% and mild non-myopathic changes in 28.1%. MB results were concordant with the primary clinical diagnosis in 31.6% of cases. A change in clinical diagnosis following MB occurred in 15.8% of cases. Genetic testing was performed in 52 children, being positive in 44% of them.
Conclusion: In our sample, MB allowed to confirm or exclude disease with muscle involvement in most cases (65%). Despite the disadvantages associated with an invasive technique, MB has proved to be a useful diagnostic tool in our sample.
Disclosure: Nothing to disclose

EPR2025

Attention deficit hyperactivity disorders (ADHD) in women with Turner syndrome

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Background and aims: Girls with Turner syndrome (TS) often demonstrate behavioral problems related to anxiety, hyperactivity, impulsivity and inattention. We hypothesize that patients with TS have higher prevalence of attention deficit hyperactivity disorders (ADHD) when compared to general population based on our clinical observation.
Methods: A retrospective chart review of diagnosis codes of TS or Gonadal Dysgenesis between 2005 and 2015. 94 patients (Age 5 - 50 years) were evaluated based on documented karyotype as well as the presence of short stature, ovarian failure, hearing or visual impairment, and hypothyroidism. Diagnoses were determined by ICD 10 code, neuro-psychology evaluation, self-reported history or medications associated with psychiatric conditions. Patients with hearing loss were excluded.
Results: 94 patients had a diagnosis Codes of Turner Syndrome or Gonadal Dysgenesis; of those 82 patients met the inclusion criteria. Of the 82 patients 29 were positive for Neuropsychiatric Disorder (35%). ADHD was most prevalent condition with 11 patients (13%) having a documented ADHD diagnosis. Of those with ADHD 91% had ovarian failure.
Conclusion: Patients with Turner Syndrome have higher prevalence for ADHD when compare to general population. Prevalence of ADHD in general population is about 5% with higher prevalence in males. In our study we find a prevalence of 13% in women with TS. ADHD screening, early diagnosis and management should be an essential part of managing women with TS. It is also important to screen for other comorbidities of TS such as hearing loss and thyroid disorders which may affect attention span.
Disclosure: Nothing to disclose

Cognitive neurology/neuropsychology 1

EPR2026

Longitudinal cortical changes associated with apathy in Parkinson's disease

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Background and aims: To follow clinical/cognitive and cortical thickness (CT) changes in Parkinson's disease (PD) patients with stable apathy (PD-sAp), without apathy (PD-noAp), and patients who developed apathy (PD-cAp) during 3 year follow up.
Methods: We selected 96 patients with known apathy outcome at the initial exam or during 3 years of follow-up and 46 matched controls. We identified 37 PD-sAp, 33 PD-noAp, 26 PD-cAp patients. Patients and controls underwent clinical/neuropsychological evaluations and 3D T1-weighted MRI scans at baseline. Patients performed evaluations also once a year for 3 years. CT at baseline and over time was investigated within and between groups.
Results: At baseline, the PD-sAp and PD-cAp groups showed worse memory abilities relative to PD-noAp. Over time, apathy worsened significantly every year in all patients except of PD-sAp group. At baseline, PD-sAp patients showed cortical atrophy of bilateral fronto-temporo-parietal areas relative to controls and of left anterior cingulate and superior temporal gyri compared to the other patient groups. PD-sAp did not accumulate further cortical damage overtime. A greater progression of cortical thinning of the right superior temporal, inferior frontal and parietal regions was observed in PD-cAp relative to PD-noAp patients.
Conclusion: In this study we suggested that PD-sAp and PD-cAp are characterized by similar cognitive profile already in the early phase of the disease and by a similar pattern of cortical alterations overtime, involving the right superior temporal, inferior frontal and parietal regions.
Disclosure: Ministry of Education and Science Republic of Serbia (Grant #175090).

EPR2027

Sentence Anagram Test and syntactic-processing brain network in primary progressive aphasia

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Background and aims: To test the ability of the Sentence Anagram Test (SAT) to distinguish between the non-fluent/agrammatic (nfv-) and phonological/logopenic (lv-) variants of primary progressive aphasia (PPA), and to determine the relationship between SAT variables and brain integrity in PPA patients.
Methods: 13 nfvPPA and 8 lvPPA patients were evaluated with the 44-item-version of SAT and a MRI scan. Performance were recorded and compared between patient groups. A ROC curve analysis assessed the ability of SAT in discriminating nfvPPA and lvPPA syndromes. The correlation between anatomical changes and SAT variables with highest discriminatory power were assessed. A brief version of SAT based on 22 items was also tested for classification ability.
Results: Compared to lvPPA, nfvPPA patients had worse scores in both canonical and non-canonical sentences. SAT non-canonical sentence and total scores well discriminated nfvPPA from lvPPA patients, achieving the highest diagnostic accuracy (area under the curve [AUC]: 0.93 and 0.91, respectively). These variables were positively correlated with the grey matter volume of the left inferior frontal gyrus and with the integrity of the corpus callosum. The SAT 22-item-version total and non-canonical sentences scores reached diagnostic accuracy comparable to the full version (AUC: 0.94 and 0.92, respectively).
Conclusion: SAT, in particular the non-canonical syntax measure, is an effective clinical tool to distinguish between nfvPPA and lvPPA patients. The patient performances were correlated with the integrity of crucial brain regions implicated in syntactic-processing. The 22-item-brief version of SAT is suitable for clinical practice and research.
Disclosure: Supported by Italian Ministry of Health (GR-2010-2303035;GR-2011-02351217).

EPR2028

Cognitive prognosis in cardiac arrest: place of brain MRI?

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Background and aims: Cardiac arrest leads to brain damage due to hypoxia-ischemia, causing death (short-term) and cognitive impairment (long-term). Brain MRI predicts a poor vital prognosis but its cognitive value remains underestimated. We investigated the value of MRI performed in acute phase of an out-of-hospital cardiac arrest (OHCA), to predict neuropsychological disorders after 3 months.

Methods: Brain MRI was prospectively performed the month following an OHCA. An extensive and standardized neuropsychological assessment was realized after 3 months. We considered two groups: "deficient" (D) in case of memory and/or dysexecutive and/or attention disorders versus "preserved" (P). Standardized brain MRI and volumetric Voxel-Based Morphometry (VBM) analysis were performed for each group compared to 21 healthy controls (S).

Results: 25 patients were included, 11 D and 14 P. Number of vascular lesions was identical between the two groups ($p=.41$). Group D had a significantly decreased right thalamic volume compared to groups P and S ($p<.001$ uncorrected; $k=60$). Correlations with decrease in visual spatial working memory ($r=.46$) and increase in behavioural dysexecutive disorders ($r=-.86$) and apathy ($r=-.50$) were found ($p<.05$). These results suggest that vascular lesions do not explain cognitive impairment after OHCA, while a volume effect (right thalamus in our study) seems to be associated with cognitive deficits. This could result from early atrophy secondary to OHCA or shows pre-existing OHCA atrophy.

Conclusion: Our study suggests the interest of VBM analysis in predicting post OHCA cognitive impairment. A complementary functional connectivity study would evaluate the hypothesis of a disconnection of the thalamus.

Disclosure: Nothing to disclose

EPR2029

Recollection impairment in patients with a bilateral mediodorsal thalamic stroke

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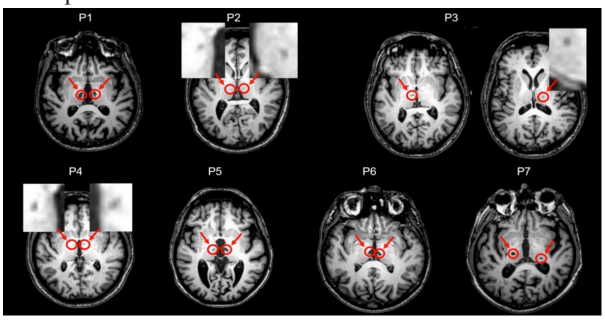
Background and aims: Models of recognition memory have postulated the anatomical and functional independence of recollection and familiarity processes, and have hypothesized that the mediodorsal nucleus of the thalamus (MD) plays a direct role in familiarity and an indirect role in recollection (Aggleton et al., 2011). Recent studies including unilateral lesions unconfirmed MD involvement in familiarity whereas bilateral MD lesion effect remain unknown. The present study aimed to better understand the role of MD in recognition impairment after bilateral stroke.

Methods: We recruited 7 subjects with a bilateral thalamic infarction. They were matched for age and education level to 10 controls. Subjects underwent a neuropsychological assessment – including verbal and visual memory, executive functions, language and behaviour – as well as 3 experimental recognition tasks assessing familiarity and recollection processes (PDP: Process Dissociation Procedure task, ROC: Receiving Operating Characteristics, RKG: Remember-Know-Guess). Participants received a high resolution MRI scan. Lesions were manually segmented, automatically localized and quantified using a specific digitalized atlas of the thalamus as well as a method we previously developed.

Results: The lesions location of the patients P1, P2, P3, P5 and P6 reached the MD. These patients performed worse than controls in recollection measured by the ROC task. Their performance was also lower in executive functions.



T1 axial sections of the patients' native brains. The red circles indicate infarcts. P2, P3 and P4's lesions are hardly visible on the picture. We therefore provide a zoom.

Conclusion: This study shows that MD bilateral damage impacts recollection but not familiarity as well as executive functions. This suggests that 1/ models of familiarity, which assign a critical role to the MD, should be reappraised and that 2/ MD executive role has to be further explored.

Disclosure: Nothing to disclose

EPR2030

Brain connectivity between left hemisphere regions during driving performance

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Background and aims: Many studies have reported on effective connectivity during various cognitive tasks, brain connectivity during tasks requiring complex cognitive processing, such as driving, is yet to be researched in detail. This study aims to use functional magnetic resonance imaging (fMRI) to observe effective connectivity between brain areas activated in the left hemispheres during driving using dynamic causal modeling (DCM).
Methods: 15 adult males without any history of mental or neurological diseases and with a mean driving experience of 2.5±1.6 years (mean age: 26.0±1.4 years old) were selected as the subjects. In experiment, subjects drove with an MR-compatible driving simulator consisting of a driving wheel and accelerator and brake pedals, which created an environment similar to actual driving environments. And the subjects maintain the speed at 80km/h in driving.
Results: In the left hemisphere, the inferior parietal lobule (IPL), superior temporal gyrus (STG), and inferior frontal gyrus (IFG) were the three areas with the highest z-scores.
Conclusion: This study investigated effective connectivity between brain areas activated during driving for left hemisphere. The inhibitory control movement pathway, which are synesthesia processing pathways required for driving, were prominent in the left hemisphere. Inhibitory control is a multi-domain executive function critical for flexible responsivity to changing task demands, and thereby an essential component of adaptive behavioral regulation. Pathways regulating movement through such inhibitory control was prominent during driving, as expected.
Disclosure: This work was supported by a Mid-career Researcher Program Grant through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (MOE) (No. 2017R1A2B2004629).

Epilepsy 3

EPR2031

Sleep-related movement disorders, parasomnias and physiological sleep variants in adult patients with focal epilepsy: a videopolysomnographic study in 100 patients

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Background and aims: Sleep and epilepsy are two bidirectionally interconnected phenomena. Objective of the present study is to evaluate the frequency of sleep disorders and physiological sleep variants in patients with focal epilepsy, by means of nocturnal video-polysomnography.
Methods: We performed a retrospective observational study in the Neurological Clinic of the University of Catania. All patients with diagnosis of focal epilepsy who underwent a nocturnal video-polysomnography in the 2007-2015 period were enrolled. Exclusion criteria were: epileptic encephalopathy and obstructive sleep apnea syndrome. The following sleep disorders were considered: periodic sleep movements in sleep (PLMs), REM sleep behaviour disorder (RBD), REM sleep without atonia (RSWA), disorders of arousal (DoA) in NREM sleep, sleep-related bruxism, alternating leg muscle activation (ALMA), excessive fragmentary myoclonus (EFM), propriospinal myoclonus at sleep onset and neck myoclonus.
Results: 100 patients were enrolled [mean age 30.3±14.7 years, 40 (40%) males]. In 73% of patients a sleep disorder was recorded, 31% showed more than one sleep disorder. The most frequent sleep disorder recorded was DoA in 26 patients followed by neck myoclonus in 22 patients, PLM in 20, bruxism in 20 and ALMA in 17. A positive association was found between the presence of sleep disorders and male sex. DoA positively correlated with a lower age as well as bruxism while PLM significantly increased with age as well as EFM; ALMA was associated with male sex and SHE.
Conclusion: The results of our study show a high frequency of sleep disorders and physiological variants in patients with focal epilepsy.
Disclosure: Nothing to disclose

EPR2032

Does treatment with modified Atkins diet for drug resistant epilepsy affect thyroid function?

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Background and aims: Despite increasing use of modified Atkins diet (MAD) in adult patients with drug resistant epilepsy, the effects on endocrine function are largely unknown. The aim of this study was to investigate whether use of MAD for 3 months influenced thyroid function.
Methods: 53 adults with difficult-to-treat epilepsy (mean age 37.9 years, 33 women) were included. They used MAD for 12 weeks. Adherence to the diet was ensured by measuring daily urine and blood ketosis at 12 weeks. The patients were enrolled from March 2011 to March 2017.
Thyroid function was assessed by measuring T3, rT3, fT4 and TSH at baseline and after 12 weeks on the diet. Blood samples were drawn between 8 and 10 a.m. after an overnight fast.
Results: All patients had normal thyroid function at baseline. After 12 weeks on the diet, there was a significant reduction in T3 and increase in fT4 with a non-significant tendency to increased TSH. There was no difference between women and men. Further, no relation could be found between thyroid hormone levels and seizure frequency, levels of ketosis or the use of enzyme-inducing vs. non-inducing antiepileptic drugs.
Conclusion: MAD significantly reduced thyroid hormone levels with a reduction in T3 and increase in fT4. In addition, a tendency to increased TSH was observed. This might imply reduced conversion from fT4 to T3 and not increased degradation from T3 to rT3. Thyroid hormone levels should be monitored regularly when using MAD in adults with pharmacoresistant epilepsy.
Disclosure: Nothing to disclose

EPR2033

Neurofilament 1 as a possible biomarker of limbic encephalitis

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Background and aims: Limbic encephalitis (LE) is an important cause of temporal lobe epilepsy (TLE). Many patients with TLE have clinical or MRI features of LE yet no typical autoantibodies. We therefore investigated whether biomarkers of cell death can help to differentiate LE from other seizure disorders.
Methods: We compared frozen serum and CSF samples from patients with definite LE (n=11) and various autoantibodies to patients with idiopathic generalized epilepsy (IGE; n=7) or psychogenic non-epileptic seizures (PNES; n=7). Tau, NFL, GFAP and UCHL1 were measured with a highly sensitive single-molecule array. Data were examined by Kruskall-Wallis and Dunn post testing as well as ROC analysis. Data are presented as mean and 95% confidence intervals.
Results: NFL was particularly elevated in serum and CSF of LE patients. An ROC analysis comparing serum NFL in LE to IGE showed an AUC of 0.92. At a cutoff value of 11.97 pg/ml, the sensitivity was 81.8% (48.2-97.7%) and the specificity was 85.7% (42.1-99.6%). In CSF, the ROC had an AUC of 0.90. A cutoff value of 351.4 pg/ml achieved a sensitivity of 90.9% (58.7-99.7%) and a specificity of 85.7% (42.1-99.6%).
Conclusion: Our data show that increased rates of cell death can be detected in LE. NFL appears to be a particularly suitable marker. Studies with more patients and long-term clinical follow-up in patients with non-inflammatory TLE, as well as possible and probable LE with no definite patterns of autoantibodies are in the planning stage.
Disclosure: Nothing to disclose

EPR2034

Biomarkers of neuronal cell death after generalized and focal to bilateral tonic-clonic seizures

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Background and aims: Whether self limited seizures lead to cell death in humans has been a matter of debate for decades. We utilized ultra high sensitivity measurements of four biomarkers of glial and/or neuronal cell death.
Methods: We included consented adults (>18 years) in our epilepsy monitoring unit. Blood samples were drawn at baseline and immediately after a generalized or focal to bilateral tonic-clonic seizure as well as after 2, 6 and 24 hours. Among other laboratory parameters, we measured tau, GFAP, NFL and UCHL1 in frozen samples with a single molecule array. Data were analyzed with the Friedman test and Dunn's post-hoc test for repeated, non parametric data. P-levels <0.05 were regarded as significant.
Results: Data of 20 patients with 20 seizures were included. All four markers showed subtle but significant peaks after the seizures and normalized within the next hours ($p<0.05$). A rise >100% of baseline was detected in 30% for tau, 25% for UCHL-1 and 15% for GFAP, while NFL levels did not rise above 100%. Overall, evidence for cell death was found in 50% of all cases.
Conclusion: Our data support the assumption that some degree of neuronal cell death occurs not only in status epilepticus but also in self limited, generalized or focal to bilateral tonic clonic seizures. Ultra high sensitive measurements of cell death biomarkers may provide a novel window to investigate the complex interactions between inflammation and cell death in seizures and epilepsy.
Disclosure: Nothing to disclose

EPR2035

EEG spectral power analysis in idiopathic generalised epilepsy

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Background and aims: A single inter-ictal electroencephalogram (EEG) has a sensitivity of around 50% for epilepsy and relies on the detection of abnormal discharges, which are not objectively defined. Examining objective differences in the background rhythm of the EEG, using methods such as Spectral Power Analysis, is of potential value to improve the diagnostic capability of EEG. Furthermore, there is currently no biomarker of drug resistance in epilepsy, which affects 20-30% of patients. Despite this, there is limited research exploring objective EEG measures in drug-resistant epilepsy.

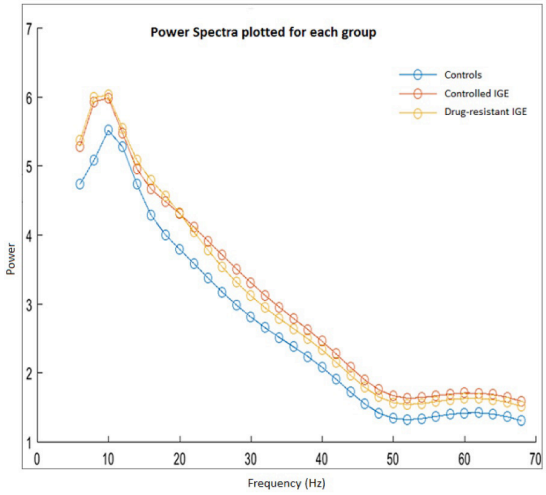
Aim is to To compare EEG spectral power in Idiopathic Generalised Epilepsy (IGE) to controls. To compare EEG spectral power in controlled IGE to drug-resistant IGE.

Methods: Participants: 16 drug resistant IGE,16 controlled IGE, 16 age and sex matched controls.

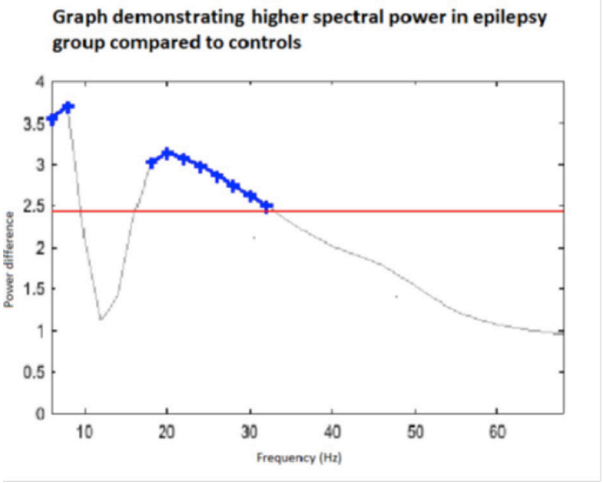
Data acquisition & EEG analysis: A 3-minute, 63 channel, eyes-closed, resting state EEG was recorded. Data was pre-processed using EEGLAB software. Using SPM, time frequency analysis was carried out on 1-second epochs using a Morlet transform with 5 wavelet cycles. Data was time-averaged and converted to an image representing spectral power.

Statistical analysis: ANOVA testing was conducted on 1D spectra images at 6-70Hz frequency. This was controlled for all frequencies tested using FWE <0.05.

Results: EEG power was significantly higher in IGE compared to controls at 6Hz-8Hz and 18-32Hz. There was no difference between controlled and drug resistant IGE.



Power spectra plotted for each group



Graph shows significantly higher power at 6Hz-8Hz and 18-32Hz in the IGE group compared to controls. The grey curved line represents the difference in spectral power between IGE group and controls. The horizontal red line is the threshold for significance. The blue crosses represent statistically significant differences in data points.

Conclusion: People with IGE have greater background EEG power than controls. This finding could be further built upon as a method to improve the diagnostic capability of EEG.

Disclosure: Nothing to disclose

EPR2036

Neurodegenerative markers and structural brain atrophy in adult PKU patients

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Background and aims: Adult PKU patients might have an increased risk of neurodegenerative disorders given the co-presence of risk of phenylalanine aggregation, metabolic abnormalities and oxidative damage. The aim of the study was to evaluate neurodegenerative markers and cortical thickness in adult PKU patients.
Methods: Inclusion criteria: classical PKU (Phe levels >1200 μmol/l) patients older than 30 years and age-matched controls (Ctrl, n=30). Assessment: neurological evaluation, neuropsychological testing, 3T structural and functional MRI (analysed on single-subject, by voxel-based morphometry-VBM and using cortical thickness technique), sensory and motor evoked potentials, blood and urine analyses. Cerebrospinal fluid (CSF) concentrations of neurodegenerative markers were also evaluated in a subset of patients who underwent lumbar puncture.
Results: A total of 21 early treated PKU patients (mean age 38.5 + 5.7 y, range 30-46 y) with different dietary treatment regimens entered the study. Motor, autonomic and cognitive abnormalities were more common in adult PKU patients compared with age-matched controls. This early features and the Parkinson's disease (PD) prodromal risk correlated with blod Phe levels. CSF analyses in 12 patients showed no Alzheimer specific alteration (Tau/Abeta42 ratio). VBM and cortical thickness analyses showed grey matter atrophy in putamen, bilateral frontal and temporal structures which correlated with Phe blood levels.
Conclusion: The findings suggested a possible relationship between poor metabolic control and neurodegenerative markers in adult PKU patients. Larger studies are pivotal in order to understand the role of life-long metabolic control, genetic variability and environmental factors as modulators of brain damage in adult PKU patients.
Disclosure: Nothing to disclose

EPR2037

Calorie intake during status epilepticus and outcome: a prospective study

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Background and aims: Recommendations regarding nutrition during status epilepticus (SE) are lacking and it is unclear whether restriction of calorie intake would result in beneficial effects or potential harm. We thus aimed to investigate associations between daily calorie intake and outcome in adult SE patients deriving from an 5-year cohort with a systematic and prospective collection of nutritional data.
Methods: From 2012 to 2016, all consecutive ICU patients with SE were prospectively monitored regarding nutrition support provided according to the guidelines. Relative risks(RR) of no return to baseline were estimated by Poisson regression with robust error variance, and adjusted for potential confounders.
Results: Of 203 patients, 86 (42%) had return to baseline. Metabolic characteristics of patients with and without return to baseline did not differ. Patients without return to baseline received more calories and proteins per SE day, and increasing nutritional support was associated with ventilator-associated pneumonia (RR=1.19, 95% confidence interval[CI] 1.09-1.28). Multivariable regression analysis revealed significant increases in relative risks for no return to baseline with every percent of days with nutrition (RR=1.41, 95%CI 1.11-1.78), with every 100kcal (RR=1.1, 95%CI 1.01-1.1) and gram of protein intake (RR=1.01, 95%CI 1.01-1.013) per SE day, independent of potential confounders (including fatal etiology, duration and severity of SE, Charlson comorbidity index, and treatment with anesthetics).
Conclusion: Our results indicate that increased calorie intake during SE is independently associated with unfavorable outcome. These findings require further validation and investigations into potential mediators, such as induction of ketogenesis, (associated) immunomodulating effects and/or reduction of ICU-associated complications, such as infections.
Disclosure: Nothing to disclose

Headache and pain 2

EPR2038

Effect of rTMS and amitriptyline versus rTMS alone in chronic migraine: a randomized controlled trial

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Background and aims: Chronic migraine (CM) is often refractory to treatment. We report the efficacy and safety of high rate repetitive magnetic stimulation (rTMS) and amitriptyline compared to rTMS alone in chronic migraine (CM).
Methods: Patients with CM diagnosed using International Classification of Headache Disorder 3 were included after a 15 days wash out period. Children, elderly (>65years), pregnant women, and patients with intracranial lesion, seizures and major psychiatric illness were excluded. Their demographic and migraine characteristics were noted. Group I received 3 sessions of 10Hz rTMS on left motor area, and group II received rTMS with additional 25 to 50mg amitriptyline at bed time. Primary outcome was reduction in headache frequency and secondary outcome reduction of severity, number of abortive drugs and side effects at one month.
Results: 35 patients were in group I and 36 in group II, and base line characters were similar between the two groups. At 1 month, both the groups had reduction in headache frequency; the proportion of patients converted to episodic migraine was insignificantly higher in group II compared to group I (37% vs 61%; P=0.05). The VAS score reduced in group II (6.9+1.9 vs 5.6+1.7; P=0.004), but number analgesic intake was similar in both the groups (9.8+9.7 vs 8.4+7.7; P=0.5). None of the patient had to withdraw due to side effects.
Conclusion: In chronic migraine, combination of high rate rTMS and amitriptyline is better than only rTMS.
Disclosure: Nothing to disclose

EPR2039

Medication-overuse headache: characterization of the abuse pattern in a tertiary headache centre

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Background and aims: Medication-overuse headache (MOH) is a secondary headache and an aggravating factor of previous headaches. We aimed to characterize the pattern of medication abuse of a sample of patients followed in a Headache outpatient clinic of a tertiary centre and relate it with their outcome.
Methods: A retrospective analysis of the hospital registry of one consultant of the Headache outpatient clinic was done (2013-2018), fulfilling MOH criteria. Clinical and demographic data were collected (namely socioeconomic status, previous headache diagnosis, age onset, period of abuse, current medication consumption, frequency and duration of attacks, comorbidities, total follow-up time) and related to the outcome (interruption or abuse maintenance).
Results: 84 patients were identified (47.1 years old±13.9), 70 women. Most patients had headaches since adult age (65.5%), with a previous migraine diagnosis (75.1%), and the majority had abuse criteria for >2 years (58.3%). 40 patients (50%) maintained abuse during follow-up; the most abused drugs were NSAIDs (50%) and other simple analgesics (40%). The outcome and type of medication were unrelated to socioeconomic status. The number of symptomatic medication and a high frequency of attacks (≥15/month) were associated with maintenance of abuse during follow-up. Use of NSAIDs, triptans and opioids were more likely to be associated with bad outcome than simple analgesics.
Conclusion: As previously described, most patients evolved from adult-onset migraine to MOH. Contrary to previous data, NSAIDs, in addition to opioids and triptans, were also associated with worse prognosis.
Disclosure: Nothing to disclose

EPR2040

Efficacy of Erenumab in chronic migraine patients with and without allodynia

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Background and aims: Allodynia is associated with migraine chronification and may have negative implications for prognosis and treatment responsiveness. Erenumab, a human anti-calcitonin gene-related peptide receptor antibody, is approved in the United States and European Union for migraine prevention; however, the impact of allodynia on erenumab efficacy is unknown. We assessed the efficacy of erenumab in chronic migraine (CM) patients with and without allodynia.

Methods: Posthoc analysis of a pivotal double-blind, randomised, 3-month study of erenumab (70 mg or 140 mg monthly) in CM patients (NCT02066415) was performed for subgroups with the extremes of allodynia at baseline: no allodynia (Allodynia Symptom Checklist [ASC]12-sum score <3) versus moderate-severe allodynia (ASC-12 ≥6). Efficacy was measured as change from baseline in monthly migraine days (MMD). Due to sample size considerations, results were pooled for the 2 erenumab dose groups.

Results: Of 648 randomised patients with baseline ASC-12 allodynia scores, 386 (59.6%) had no allodynia and 153 (23.6%) had moderate-severe allodynia. Mean (standard deviation) baseline MMD were 17.6 (4.8) and 18.9 (4.3), respectively. Compared to placebo, erenumab had greater MMD reductions and higher proportions of patients achieving ≥50% MMD reductions at month 3 in both allodynia subgroups (Table 1).

Table 1. Outcome measures

	No allodynia			Moderate-severe allodynia		
	Erenumab	Placebo	Difference or odds ratio (95% CI); p-value	Erenumab	Placebo	Difference or odds ratio (95% CI); p-value
Least square mean change (95% CI) in MMD from baseline at Month 3	−6.6 (−7.4 to −5.8)	−4.0 (−4.9 to −3.1)	−2.5 (−3.7 to −1.4); p<0.001	−7.3 (−8.6 to −6.1)	−4.1 (−5.7 to −2.5)	−3.3 (−5.3 to −1.3); p=0.001
>=50% reduction in MMD from baseline at Month 3, (%)	41.5%	23.2%	2.34 (1.49 to 3.68); p<0.001	44.0%	23.0%	2.69 (1.27 to 5.70); p=0.008

CI, confidence interval; MMD, monthly migraine days

Outcome measures

Conclusion: Erenumab demonstrated efficacy in CM patients both without allodynia and with moderate-severe allodynia. These results suggest that allodynia does not negatively predict treatment response to erenumab.

Disclosure: This study was supported by Amgen Inc., Thousand Oaks, California, USA. Erenumab is co-developed by Novartis and Amgen. Abstract also submitted to AAN 2019

EPR2041

Analysis of the health care situation of migraine patients in Germany (PANORAMA study)

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Background and aims: Physicians have a range of therapeutic options in migraine therapy. Acute and preventive migraine medications, as well as non-pharmacological treatments are often used in combination. Up to now, there is no data available about the therapeutic algorithms used in daily practice, the number of treatment options migraine patients have already tried and which patients might be in high medical need for new treatment options in Germany. Here we report the final results of the data collection PANORAMA.

Methods: The data collection 'PANORAMA' was carried out with 119 headache and neurology centres over 10 months. The first part comprises an interview in order to generate an individual centre profile. In the second part, the centre conducts a thorough database research to characterize the migraine patients currently in medical treatment. The third part is an expert interview, to define the significance of migraine therapy in the centre.

Results: 13.8% of patients being treated per calendar quarter at the 119 centres are suffering from migraine and about 88% of these migraine patients were referred from another practice. On average 43% of the migraine patients at each site currently receive prophylactic treatment, while 68% are taking triptanes. The majority of patients (60%) have at least 4 migraine days per month and 13% have a chronic condition.

Conclusion: The PANORAMA study provides a comprehensive overview on the current treatment paradigm for migraine treatment and elucidates the lack of a common treatment algorithm in Germany. The analysis further reveals a disproportionately long patient-journey.

Disclosure: Employee of Novartis Pharma GmbH Germany

EPR2042

Vessel-wall enhancement: a useful tool in distinguishing primary and secondary thunderclap headache?

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Background and aims: Clinicians facing patients with thunderclap headache (TC) have to distinguish between primary and secondary life-threatening headaches. Blood exams, TC head scan and, if this is negative, lumbar puncture are necessary. If an un-ruptured intracranial aneurism is discovered, they have to determinate if it was responsible for symptoms, possibly predicting its risk of rupture, in order to guide therapeutic decisions.
Methods: We report two clinical cases of patients, who underwent MRI with vessel wall study because of a thunderclap headache leading to the discovery of an aneurysm. The first one was migraineous, had no wall enhancement of the saccular 10mm aneurysm of anterior communicating artery and no signs of vessel inflammation or damage macroscopically seen during aneurysmal clipping. The second patient, not suffering from primary headaches, presented wall enhancement in the 7mm aneurysm of right carotid syphon and was treated with embolization and stenting.
Results: In 3-4% of adults, an aneurysm may be incidentally discovered. 11% of patients with aneurysm have a thunderclap headache as clinical presentation. Thunderclap headache also exists as a rare primary headache disorder, in patients with no evidence of an underlying cause, especially in migraineous patients. Aneurysmal size, location and symptoms, significantly predict the risk of rupture. Vessel-Wall MRI study has an impressive sensitivity (95%) and negative predictor factor (96.2%) for aneurysmal stability.
Conclusion: We would like to put in light how Vessel-Wall aneurysmal enhancement did correlate with the pathological characteristics of the aneurysm and how it could have been useful in patients' therapeutic decision-making.
Disclosure: Nothing to disclose

EPR2043

Neural correlates of visuospatial processing in migraine patients: does the pain network interfere?

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Background and aims: Previous clinical studies demonstrated impaired visuospatial abilities in migraine patients. Aim of this study was to explore functional magnetic resonance imaging (fMRI) correlates of visuospatial processing in migraine patients and their relation with visuospatial performance and patients' clinical characteristics.
Methods: An fMRI visuospatial task, including an angle and a colour discrimination paradigm, was administrated to 17 headache-free migraine patients and 16 controls. fMRI activity during the visuospatial condition was correlated with subjects' performance, clinical and neuropsychological variables.
Results: The response accuracy and reaction times did not differ between migraineurs and controls. All study subjects activated frontal, parietal, occipital and cerebellar regions during both the angle and colour task. The comparison angle vs colour task revealed an increased activity of the right insula, middle frontal gyrus, bilateral orbitofrontal cortex and middle cingulate cortex and decreased activity of the bilateral posterior cingulate cortex (PCC) in migraine patients compared to controls ($p<0.05$, FWE corrected). In migraineurs, a better performance in the angle task was associated with higher activation of the right insula ($r=0.84$, $p<0.001$, uncorrected) and orbitofrontal cortex ($r=0.83$, $p<0.001$, uncorrected). Decreased activity of the PCC correlated with shorter disease duration ($r=0.92$, $p<0.05$, FWE corrected).
Conclusion: Migraine patients experienced abnormal activation of visuospatial processing brain areas that are commonly involved also in nociception. The increased activity of the insula and frontal lobes and the decreased recruitment of the PCC might represent an adaptive response, strengthen by the recurrent activation of these regions during migraine attacks.
Disclosure: Nothing to disclose

Motor neurone diseases 2

EPR2044

Modelling and investigation of spinal muscular atrophy pathology with human 3D organoids

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Background and aims: Spinal muscular atrophy (SMA) is a motor neuron disorder and the leading cause of genetic death during childhood. SMA is caused by mutations in the Survival Motor Neuron (SMN) gene coding for the SMN protein, which is crucial for RNA processing. A broader understanding of SMN biology in reliable models is paramount for the optimization of available treatments and the development of complementary therapeutic approaches. Here, we successfully modelled SMA pathology in 3D human central nervous system (CNS) organoids. Brain and spinal cord-like organoids could closely recapitulate the endogenous developmental program, presenting interdependent neuronal regions and reproducing the integrated connection of the CNS.
Methods: Brain organoids were obtained from induced pluripotent stem cell (iPSCs), which were differentiated with a free-floating 3D culture method. We performed immunohistochemical and qPCR analyses to confirm their differentiation state and electrophysiological studies to verify their activity. Using a modified protocol to promote neural caudalization and ventralization, we also derived spinal cord-like organoids.
Results: We generated iPSCs from SMA patients and healthy controls' fibroblasts and developed CNS organoids giving rise to an early cerebral cortex-like formation containing progenitor cells and more mature neural subtypes. Preliminary results demonstrated that SMA organoids exhibited alteration in the CNS development and in the electrophysiological activity.
Conclusion: Spinal cord organoids offer an unprecedented powerful tool to elucidate early motorneuron pathology and identify potential causes of motorneuron death. CNS organoids represent an innovative in vitro system, which can be used as a platform for studying neurological disease pathogenic mechanisms and to test potential therapeutic strategies.
Disclosure: Nothing to disclose

EPR2045

The interactome of human TDP-43 in a cellular model of amyotrophic lateral sclerosis

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Background and aims: The C-terminal mutation M337V of TDP-43 causes ALS. Its C-terminal region is important for protein-protein interactions why studying its interactome likely gives insights into ALS pathogenesis.
Methods: (BAC)-transgenic mouse embryonic stem cells expressing GFP-tagged human TDP-43wt/- or TDP-43M337V/- were differentiated to motor neurons (±NaAs-Stress treatment). Anti-GFP co-immunoprecipitation of human TDP-43 was performed and interactors detected by mass spectrometry. Stress granules were analysed by confocal microscopy and extracellular vesicles by size-exclusion-chromatography and nanoparticle tracking.
Results: Human wildtype TDP-43 interacts with proteins involved in transcription, translation, poly(A)-RNA-binding. On stress treatment there is a clear shift towards components of the endoplasmic reticulum, endosomal and exocytosis pathways. In the TDP-43M337V/- interactome a striking reduction of those protein interactions was observed. There was an acquired interaction with proteins of the ubiquitin-proteasome and lysosome involved in ALS-associated pathways. Importantly, binding of TDP-43wt/- to Poly(A)-binding protein, a protein involved in translation and stress granule formation, was shown to be disrupted in the presence of the C-terminal pathogenic mutation and linked to reduced Poly(A)-binding protein positive stress granule formation in TDP-43M337V/- motor neurons. Gene ontology enrichment analysis further suggested that TDP-43M337V/- displays dysfunctionality of binding to extracellular secretion proteins such as rab-GTPases. This led to the identification of reduced extracellular vesicle secretion in the TDP-43M337V/- and human M337V iPSCs-derived motor neurons.

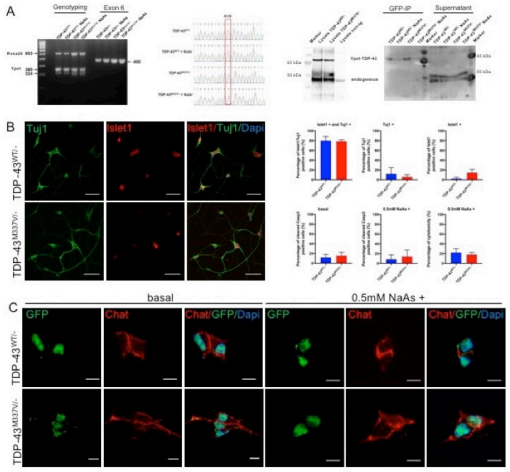

Figure 1 Characteristics of motor neuron cultures expressing human GFP-tagged wildtype and M337V mutant TDP-43

A Mouse embryonic stem cell derived motor neurons are heterozygous for Ypet-tagged human TDP-43 inserted at the Rosa26 locus with the point mutation A>G in exon 6 for human TDP-43$^{M337V/-}$. Low expression levels of human TDP-43 result in only 40% protein expression at 72kDa compared to endogenous mouse TDP-43 levels at 45kDa. GFP-immunoprecipitation (IP) specifically enriches Ypet-tagged human TDP-43 with endogenous TDP-43 left behind in the remaining sample (Supernatant). **B** 80% of all cells express neuronal (Tuj1) and motor neuronal (Islet1) specific markers (scale bar 50µm). Apoptosis assessed by cleaved Caspase3 staining and cytotoxicity by MTS assay are not altered between genotypes after 0.5mM NaAs treatment for 60 min. **C** Cell cultures express mature motor neuronal markers (Chat) and Ypet-tagged human TDP-43 (GFP) is observed in the nucleus -/+ 0.5mM NaAs treatment (scale bar 10µm).

Figure 1

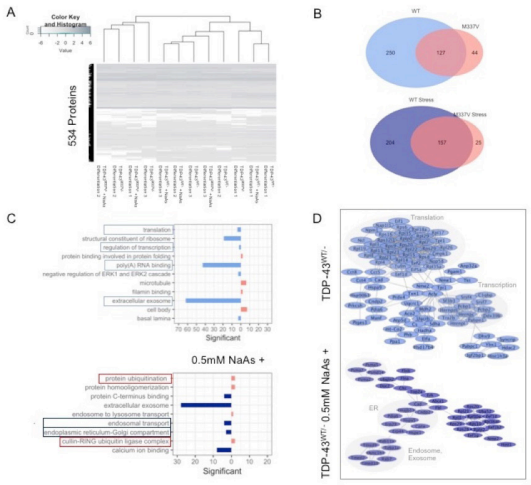

Figure 2 The interactome of human TDP-43 by mass spectrometry

A Hierarchical cluster of all human TDP-43 GFP affinity-enriched samples. Ion abundancies of the 534 proteins identified by LC-MS/MS over all samples cluster TDP-43$^{M337V/-}$ samples with a majority of low or missing ion abundancies to the left. **B** Many Proteins were only present in the TDP-43$^{WT/-}$ interactome (blue) and absent in the TDP-43$^{M337V/-}$ interactome (red) showing a reduction of proteins that bind to TDP-43$^{M337V/-}$. **C** Gene ontology enrichment analysis demonstrates that the proteins bound to TDP-43$^{WT/-}$ are significantly enriched for terms such as transcription, translation and Poly(A)RNA binding (blue) while TDP-43$^{M337V/-}$ proteins are significant enriched for terms such as protein folding (red) and protein ubiquitination after 0.5mM NaAs treatment. **D** Protein-protein interaction networks of the wildtype TDP-43 interactome show a stress response with a shift from translation and transcription (light blue) towards the endoplasmic reticulum (ER) and endosomal-extracellular secretion (dark blue) upon NaAs stress treatment.

Figure 2

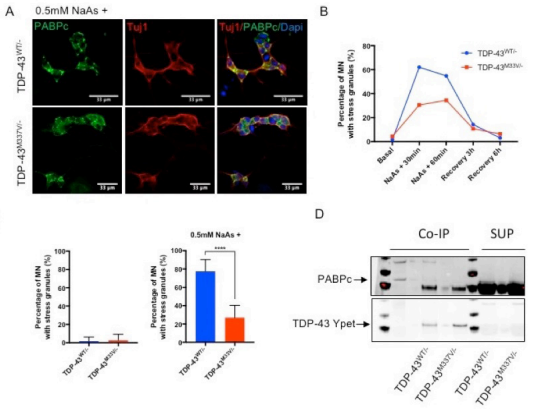

Figure 3 Impaired Poly(A)-binding protein binding to human TDP-43$^{M337V/-}$ is linked to a reduced stress granule formation

A Human TDP-43$^{WT/-}$ and TDP-43$^{M337V/-}$ neurons (Tuj1) are stained for Poly(A)-binding protein (PABPc) after 60 min of 0.5mM NaAs treatment to assess the formation of stress granules. **B** The percentage of neurons with PABPc positive stress granules is reduced in human TDP-43$^{M337V/-}$ motor neurons over different times of treatment and recovery. **C** TDP-43$^{M337V/-}$ motor neurons with stress granules are significantly reduced after 60 min of NaAs treatment compared to TDP-43$^{WT/-}$ (n=3 differentiations, p=0.0001). **D** Co-immunoprecipitation confirms that PABPc does not bind to human TDP-43$^{M337V/-}$.

Figure 4

Conclusion: TDP-43M337V/- shows a significant loss of binding to established TDP-43wt/- interactors resulting in the identification of characteristic phenotypes that suggest activation of cellular processes involved in the pathogenesis of ALS that can now be targeted for potential treatments.
Disclosure: Nothing to disclose

EPR2046

An indirect comparison of time to treatment effect in spinal muscular atrophy type 1 (SMA1)

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Background and aims: Spinal muscular atrophy type 1 (SMA1) is a rare, rapidly progressing, debilitating, genetic neuromuscular disease. This study compared recent clinical trial data demonstrating the relationship between treatment timing, time to treatment effect, and clinical outcomes in patients with SMA1.
Methods: A post-hoc indirect treatment comparison was conducted to measure differences in time-to-effect between AVXS-101 (CL-101, NCT02122952, cohort 2) and nusinersen (ENDEAR, NCT02193074) and between AVXS-101 and risdiplam (FIREFISH, NCT02913482) according to Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores.
Results: When compared with nusinersen, AVXS-101 led to more rapid increases in mean CHOP-INTEND scores from baseline, particularly in the first few months after dosing (9.8- and 14.9-point increases at 1- and 2-months post-AVXS-101, versus ≤5-point increase at 2-months post-nusinersen). Greater survival benefits and lower rates of permanent ventilatory support were also observed in AVXS-101-treated patients relative to nusinersen-treated patients. Similarly, when indirectly compared with risdiplam, AVXS-101 demonstrated significantly greater increases in median CHOP-INTEND scores (14.0 points at 2-months post-AVXS-101 versus 5.5 points at ~2-months post-risdiplam). Additionally, treatment differences were maintained through 8 months with additional improvements at all time points.
Conclusion: Although treated patients in these 3 cohorts are not entirely matched for age and disease severity, useful comparisons can still be made. Based on CHOP-INTEND improvements, a single AVXS-101 dose appears to have more rapid effects than multiple doses of either nusinersen or risdiplam. These clinical findings suggest that timely restoration of effective SMN protein production may be essential for maximizing outcomes in SMA1 patients.
Disclosure: This study is funded by AveXis, Inc. (USA)

EPR2047

Generation of C9-ALS patient specific iPSC-derived motor neurons for pathogenetic studies and evaluation of Morpholino oligomers efficacy

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Background and aims: GGGGCC repeat expansions in C9ORF72 gene are the most common genetic cause of amyotrophic lateral sclerosis (ALS). Pathogenic mechanisms involve loss of function of the C9Orf72 protein, gain of function from accumulation of RNA foci and sequestration of RNA binding proteins (RBPs), and toxicity caused by dipeptide-repeats proteins (DPRs) produced by repeat-associated non-ATG (RAN) translation. Patient-specific induced pluripotent stem cells (iPSC)-derived lines can provide fundamental insights to better understand C9-ALS pathogenesis. Antisense oligonucleotides (ASOs) are designed to bind complementary mRNA and interfere with specific biological processes. We aimed to characterize the pathological phenotype of the C9-ALS iPSC-derived lines and evaluate the therapeutic effect of ASOs administration.
Methods: Fibroblasts from C9-ALS patients and controls were reprogrammed into iPSCs and differentiated towards motor neurons (MNs). We characterized the pathological phenotype of the C9-ALS lines compared to controls, evaluating survival, RAN products expression, presence of TDP-43 inclusions, dysregulation of RBPs interacting with RNA foci and R-loops formation. Finally, we transfected ALS-MNs with two different ASOs with Morpholino chemistry, one binding to the expansion motif and the other one binding to the promoter and silencing the whole gene.
Results: C9-ALS iPSC-derived MNs showed pathological accumulation and mislocalization of the protein involved in nuclear trafficking RanGAP, the RBP Pur-a and TDP-43, other than R-loops increase and DNA-damage response activation. Moreover, Morpholino could rescue the pathological phenotype.
Conclusion: Our results suggest that patient specific iPSC-derived MNs are a valuable tool to deepen the knowledge of C9ORF72 pathogenic mechanisms, and to validate new promising therapeutic strategies such as Morpholino-mediated approach.
Disclosure: Nothing to disclose

EPR2048

SUNFISH part 1: safety, tolerability, PK/PD, and exploratory efficacy data in patients with Type 2 or 3 spinal muscular atrophy (SMA)

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Background and aims: SMA is caused by reduced levels of survival of motor neuron (SMN) protein from deletions and/or mutations of the SMN1 gene. SMN2 produces only low levels of functional SMN protein. Risdiplam (RG7916/RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing towards increasing SMN protein levels.

Methods: SUNFISH (NCT02908685) is an ongoing, multicentre, double-blind, placebo-controlled, operationally seamless study (randomised 2:1, risdiplam:placebo) in patients aged 2–25 years, with Type 2 or 3 SMA.

Part 1 (N=51) assesses safety, tolerability and PK/PD of different risdiplam dose levels (plus exploratory outcomes). Pivotal Part 2 (N=180) is assessing the safety and efficacy of the risdiplam dose level that was selected based on results from Part 1.

Results: SUNFISH Part 1 included patients of broad age range and clinical characteristics (functional level, scoliosis and contractures). To date (data-cut, 06/07/18), a sustained, >2-fold increase in median SMN protein versus baseline was seen after 1 year of risdiplam. Adverse events were mostly mild, resolved despite ongoing treatment and reflected the underlying disease. No drug-related safety findings have led to withdrawal. Despite not being designed to detect efficacy, patients on risdiplam showed improvement over 12 months in MFM versus natural history. Safety, tolerability, PK/PD and novel exploratory efficacy data, including motor outcome measures will be presented from patients in Part 1 treated for ≥1 year.

Conclusion: To date, no drug-related safety findings have led to withdrawal. Risdiplam has led to sustained increases in SMN protein. Part 2 is ongoing worldwide.

Disclosure: Study sponsored by F. Hoffmann-La Roche AG, Basel, Switzerland. Writing and editorial assistance was provided by MediTech Media, UK, in accordance with Good Publication Practice (GPP3) guidelines.

EPR2049

AVXS-101 gene replacement therapy (GRT) for spinal muscular atrophy type 1 (SMA1): pivotal studies clinical update (STR1VE-EU and STR1VE)

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Background and aims: SMA1, a rapidly progressing disease caused by functional loss of the survival motor neuron 1 gene (SMN1), typically results in death/permanent ventilation by 2 years of age. The investigational GRT onasemnogene abeparvovec (AVXS-101) is a one-time intravenous therapy that treats the genetic root cause of SMA and is designed for immediate, sustained SMN protein expression in neurons. In a phase 1 study, treatment with AVXS-101 demonstrated exceptional improvements in survival, bulbar and motor function. We report preliminary data from STR1VE-EU (2017-000266-29/NCT03461289) and STR1VE (NCT03306277), pivotal phase 3 studies evaluating efficacy and safety of a one-time AVXS-101 infusion.

Methods: STR1VE-EU and STR1VE are multicentre, open-label, single-arm studies in SMA1 patients aged <6 months (bi-allelic SMN1 mutations, 1–2 SMN2 copies [1–2xSMN2]) run in EU and US, respectively. Outcomes include independent sitting ≥10 seconds (STR1VE-EU) or ≥30 seconds (STR1VE) at 18 months and survival (no death/permanent ventilation) at 14 months.
Results: As of 27 September 2018, 5 SMA1 patients (2xSMN2; 3 male, 2 female) are enrolled in STR1VE-EU. Mean age (range) at enrolment was 3.2 (2.2–5.6) months. Mean (range) baseline CHOP-INTEND score was 22 (19–28). With a mean (range) of 15 (3–30) days in the study, 4 treatment-emergent, non-serious adverse events were reported in 3 patients: gastroenteritis (resolved) and hypertransaminasaemia (n=3; one case [increased aspartate aminotransferase] resolved). Updated post-baseline data, available at the time of the congress, from STR1VE-EU will be presented side-by-side with the available post-baseline data from STR1VE (enrolment complete, n=22).
Conclusion: STR1VE-EU and STR1VE are ongoing.
Disclosure: This study is funded by AveXis, Inc. (USA)

EPR2050

Current evidence for treatment with nusinersen for spinal muscular atrophy: a systematic review

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Background and aims: Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by mutation in the survival of motor neuron (SMN) 1 gene resulting in decreased expression of SMN protein causing degeneration of motor neurons. The SMN2 gene also encodes for SMN protein but differs by 11 nucleotides from SMN1 resulting in production of a non-functional protein. The SMA phenotype is related to the copy number of the SMN2 gene. Nusinersen, an antisense oligonucleotide drug, can be injected intrathecally to enhance expression of SMN protein.
Methods: We systemically reviewed the evidence of efficacy concerning improvements in motor function, achieving motor milestones and survival of nusinersen in SMA patients versus standard medical care. A MEDLINE and CENTRAL search was performed on the 21st of December 2018.
Results: Four studies were included of which two multicenter phase III randomized controlled trials, one phase I and one phase II open-label clinical. There are significant and meaningful changes in motor scales (CHOP-INTEND, HINE-2, HFMSE) in SMA type 1 and 2. There is a significant increase in survival and event-free survival in SMA type 1.
Conclusion: Treatment with nusinersen in SMA type 1 and 2 results in significant and meaningful improvement in motor function (level A, high in SMA type 1, moderate in SMA type 2), but does not restore age-appropriate function. Improvement is better if started earlier in disease course and results in prolonged event-free survival and survival in patients with SMA type 1 (level A, moderate). There is need for additional research in SMA types 3 and 4.
Disclosure: Nothing to disclose

Movement disorders 4

EPR2051

Quality of life in patients with advanced Parkinson's disease after long-term subthalamic deep brain stimulation

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Background and aims: STN-DBS serves a rescue therapy in advanced Parkinson's disease with severe motor fluctuations and dyskinesias. However, initial improvement tend to wane over time. We aimed to assess predictors of better outcome in quality of life (QOL) after STN-DBS in long-term follow-up.
Methods: Of the 69 PD-patients who underwent STN-DBS between 2003 and 2011, in 34 follow-up data for more than 5 years were available (age at surgery 53.1±6.7 years, disease duration 11.7±3.3 years, Hoehn&Yahr 3.4±0.5). Motor and functional outcome (UPDRS), QOL (PDQ-39 questionnaire), activities of daily living (Schwab&England scale), and medication regimen (L-dopa equivalent daily dose) were analyzed preoperatively and annually after STN-DBS until the eighth year.
Results: We observed significant amelioration in OFF-symptoms and L-dopa therapy complications following STN-DBS. At 8-year follow-up, UPDRS-3 OFF-score remained improved by 28.9±16.7 points (50%), UPDRS-2 OFF-score by 7.2±8.6 (26%), UPDRS-4 by 6.4±3.2 (66%), and OFF-Schwab&England score by 22%. In ON-state, motility was relatively stable, although, marked deterioration in daily life activities was noticed (-6.7, UPDRS-2, $p<0.001$). QOL was not improved significantly anymore to the 8th year. LEDD was decreased by 31% with overall slight deterioration (L-dopa by 42%, $p<0.0001$); two patients had L-dopa still withdrawn. Interestingly, that in early years extent of PDQ-39 improvement correlated positively with preoperative Hoehn&Yahr stage and severity of QOL-impairment. After 5-year follow-up, PDQ-39 improved better in patients with longer disease duration, earlier PD-onset, and more pronounced motor complications ($p<0.05$).
Conclusion: Age of PD-onset, disease duration, and severity of treatment complications might be related to long-term QOL improvement in STN-DBS.
Disclosure: Nothing to disclose

EPR2052

Epidemiology of Parkinson's disease in Israel: annual rates and time trends over 14 years

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Background and aims: To estimate annual incidence and prevalence rates of Parkinson's disease (PD) in Israel; based on a validated large-scale population-based cohort of PD patients for the years 1999-2012; to assess time trends and age-sex specific rates.
Methods: The PD cohort was assessed using a well-established anti-parkinsonian drugs (APD) tracer algorithm, based on purchases of any APD available in Israel, all PDs were members of a large Health Maintenance Organization (serves 25% of Israeli citizens). Overall and specific prevalence and incidence rates of PD with 95% confidence intervals (95%CI), and time trends were estimated based on Poisson distribution
Results: The PD cohort included 9,462 prevalent cases and 7,643 incident cases (mean age at first treatment 70.7±11.5 years). The annual prevalence rate (per 100,000 population) significantly increased from 170 in 2000 to 286 in 2011 (by 68%), 5% per year and was slightly higher among men. The annual incidence rate remained stable of 33:100,00 (RRmen=1.003, 95%CI: 0.976–1.031; RRwomen=0.98; 95%CI: 0.95–1.01), and was significantly higher in men compared to women (RR=1.20, 95%CI: 1.05–1.38). PD annual rates increases with aging: The incidence
rates for ages 65+yrs and 75+yrs were 2.5% and 5.4% respectively , and the prevalence rates for ages 65+yrs and 75+yrs were 2.1% and 3.5%, respectively.
Conclusion: Stable incidence rates of PD with increased prevalence rates over time, reflect increase in longevity, perhaps owing to improved care. These findings also demonstrate the growing burden expected of PD morbidity in Israel, and should influence future health-plans.
Disclosure: Nothing to disclose

EPR2053

Functional responses to joystick movements during Parkinson's disease progression: a longitudinal fMRI study

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Background and aims: Functional imaging has shown decreased activation in basal ganglia-thalamo-cortical motor loops for Parkinson's disease (PD) patients versus healthy controls (HC), along with changes in cerebello-thalamo-cortical motor loops. However, few studies have tested the longitudinal progression of PD functional activity.
Methods: At baseline, 48 PD and 16 HC underwent structural and functional magnetic resonance imaging in conjunction with a joystick task. 42 PD were re-scanned after 18-months and 34 after 36months. T-tests were used to compare functional motor responses between PD and HC, and linear mixed effects models to examine differences within PD. Correlations of motor-activity with bradykinesia, rigidity and tremor symptom severity were also tested. All contrasts used whole-brain analyses, thresholded at $Z>3.1$ and cluster-wise $P<0.05$.
Results: Baseline activation was significantly greater in PD than HC across contralateral parietal and occipital regions, ipsilateral precentral gyrus, and thalamus. Longitudinally, cerebellar activity increased from baseline to both later visits. From baseline to 36 months there was also increased activity in contralateral motor, parietal and temporal areas, whilst frontal activity decreased. Bradykinesia and rigidity showed both overlapping and independent positive correlations with functional activity in the cerebellum, whilst tremor showed a negative correlation in the occipital pole.
Conclusion: Functional activity initially increased in the ipsilateral cerebellar-loop and later in the contralateral basal ganglia and bilateral cerebellar loops, suggesting that functional changes in these circuits progress at different disease stages. Similar to clinical findings, functional activity related to bradykinesia and rigidity overlapped, whilst that related to tremor was separable.
Disclosure: The Transeuro study received funding from an FP7 EU Consortium. An NIHR award of Biomedical Research Centre to the University of Cambridge/ Addenbrooke's Hospital and Imperial College London supported part of this study. Travel of Lund patients with staff has been funded by local grants in addition to TransEuro (Swedish Parkinson Academy, Regional Academic Learning Grants, and Multipark).

EPR2054

Medical conditions before progressive supranuclear palsy (PSP) diagnosis in real world settings identified in electronic medical records from general practitioners, internists and neurologists in germany

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Background and aims: The occurrence of medical conditions linked to PSP before diagnosis in real world settings in Europe has not been systematically examined. This study determined the onset and prevalence of 19 medical conditions before PSP diagnosis in outpatient settings in Germany.
Methods: Included were patients with first diagnosis of PSP [ICD-10 G23.1], diagnosed 2010-2017, aged ≥40 years, both sexes, within electronic medical records databases sourced by Disease Analyzer (IQVIA) from general practitioners/internists ("primary care") and neurologists practices, having at least 365 days of observation before diagnosis. The onset of a medical condition was determined by its first record prior to the PSP diagnosis. The median time of observation before PSP diagnosis was 5.7 years in the primary care database and 3.3 years in the neurologist database.
Results: The sample consisted of 89 patients from primary care and 81 from neurologists. The mean ages at diagnoses were in the early 70ies, with slight male predominance. The prevalence of common (>10%) diagnoses typically related to PSP occurring 3 years prior were: in the primary care database, Parkinson's disease (PD), autonomic, motor, falls, cognition, depression, and vision (56%, 46%, 41%, 31%, 22%, 21%, 14%, respectively); in the neurologist database Parkinson's disease, other neurodegenerative, depression, motor, cognition, and autonomic (55%, 22%, 20%, 15%, 13%, 10%, respectively).
Conclusion: Diagnoses of PD, autonomic and motor problems, depression, and falls are common years before the PSP diagnosis and might be clinical clues to both primary care physicians and neurologists for earlier detection of patients.
Disclosure: This work was funded by AbbVie Inc. AbbVie participated in the study design, research, data management, analysis and interpretation of data, writing, reviewing, and approving the publication. Dr. Hoeglinger has served as a consultant to AbbVie, and has received speaker fees from AbbVie. Drs. Oleske, Zamudio, and Holman are employees of AbbVie.

EPR2055

Survival in Parkinson's disease: the Trondheim Cohort

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Background and aims: We aim to report follow-up data on three key irreversible milestones: dementia (MoCA score below 26), postural instability (Hoehn and Yahr 3) and death in The Trondheim PD cohort.
Improved understanding of Parkinson's disease (PD) prognosis would allow better information, improved health service planning and improved clinical trial design.
Methods: The cohort consists of 1276 PD patients followed longitudinally for more than 20 years. Clinical, cognitive (MoCA score) and genetic testing were performed. By the end of December 2018, 505 patients have died.
Results: Of the patients, 84% had developed MoCA scores below 26 within the first 15 years of the disease, while 16% had normal MoCA scores.
Kaplan-Meier survival estimates, based on age at disease onset (AAO) categories, show statistically significant difference in the median survival time in AAO 20-39, 40-59, 60-69, 70-79 and 80 plus, respectively 32, 20, 14, 11 and 7 years.
Kaplan-Meier survival estimates, based on MoCA scores at 5 year, 10 year and 15 year, show a statistically significant difference in the median survival time in patients with MoCA scores below 26 compared to those with normal MoCA scores, respectively 5 versus 14 years, 6 versus 13 years and 5 versus 12 years.
Conclusion: Early onset PD patients had the longest median survival time. However, when MoCA score drops below 26, there is a statistically significant shortening in median survival time compared to those with normal MoCA scores, confirming that cognitive function is a good indicator for survival in Parkinson's Disease.
Disclosure: Nothing to disclose

EPR2056

Movement disorder in Wilson disease (WD): correlation with MRI and biomarkers of cell damage

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Background and aims: Neurologic WD (NWD) is commonly associated with movement disorder (MD), but there is paucity of study in WD correlating type and severity of movement disorder with MRI and biomarkers of cell damage. To report frequency of different movement disorder in WD and their relationship with MRI and cell damage
Methods: NWD Patients were included, clinical details, presence of movement disorder, MRI findings were noted. Dystonia severity was noted on Burke-Fahn-Marsden (BFM) score and others on 0-4 scale. Serum cytokine, oxidative stress, XIAP and caspase-3 were measured
Results: 97/110 (88.18%) had MD; dystonia in 77.3%, oromandibular dystonia in 61.8%, tremor in 43.6%, chorea in 19.1%, athetosis in 11.8% and myoclonus in 9.1%. MRI was abnormal in 99%, included caudate in 64.6%, putamen in 69.5%, globus pallidus (GP) in 70.7%, thalamus in 73.2%, brainstem in 59.8% and cerebellar in 14.6% patients. Dystonia correlated with thalamic lesion ($P<0.01$), GP ($P<0.05$), putamen ($P<0.05$), caudate ($P<0.05$) and brainstem ($P<0.05$); myoclonus with cortical involvement ($P<0.05$); tremor with cerebellar ($P<0.01$); oromandibular dystonia with thalamus ($P<0.05$), GP ($P<0.05$) and brain stem ($P<0.05$). Active caspase-3 (0.55±0.11 vs 0.38±0.06ng/ml), TNFα (76.05±29.01 vs 36.05±21.01pg/ml), IL8 (590.19±89.19 vs 193.43±71.01pg/ml) levels were increased whereas XIAP (84.66±10.39 vs 95.76±10.11ng/ml) levels were decreased compared to controls. BFM score correlated with XIAP ($P<0.01$) and caspase-3 ($p<0.05$).
Conclusion: Movement disorder occurs in about 88% patients, and dystonia is most common disabling. BFM score is related to increased expression of caspase-3 and decreased XIAP
Disclosure: Nothing to disclose

EPR2057

"Dual Frequency" deep brain stimulation programming paradigm for gait and balance impairment in Parkinson's disease

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Background and aims: High-frequency deep brain stimulation (HFS) is more effective for appendicular than axial symptoms. Low-frequency stimulation (LFS) may reduce gait/balance impairment, but results in worsening appendicular symptoms. A programming paradigm (PP) was created with a combination of LFS and HFS using the interleaving function.

Methods: The novel PP (interlink-interleave, IL-IL) consists of two overlapping LFS programs on each lead, with the overlapping area focused around the optimal contact. This area receives HFS aimed at controlling appendicular symptoms. The non-overlapping areas receives LFS potentially reducing gait/balance impairment. A randomized, cross-over trial comparing optimized conventional-HFS and IL-IL is currently underway. The primary outcome measure is the CGI-S. Secondary outcome measures include patient preferred setting, MDS-UPDRS-I-IV, PDQ-39, FOG-Q, and FES. Data from each period will be combined and analyzed. Patients will also be separated into two groups based on preferred setting and appropriate analysis will be applied.

Results: Twenty-five patients have been recruited, 12 completed, and 2 dropped out. Seven preferred IL-IL and 5 conventional-HFS. Combined data demonstrated no significant difference in any outcome measure between settings. Those who preferred IL-IL had improvements in PDQ-39 (p=0.01), FOG-Q (p=0.01), FES (p=0.047), and CGI-S (p=0.03) when on IL-IL. Those who preferred conventional-HFS had no difference in any outcome measure between settings.

Conclusion: Preliminary results (n=14) demonstrate no difference in appendicular symptoms between settings suggesting IL-IL did not provide inferior appendicular symptom control. In those who preferred IL-IL there was improvement in gait and quality-of-life without impact on appendicular symptoms. Final analysis (n=25) will be presented.

Disclosure: Nothing to disclose

Movement disorders 5

EPR2058

Long-term safety and efficacy of apomorphine infusion in Parkinson's disease (PD) patients with persistent motor fluctuations: results of the open-label phase of the TOLEDO study

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Background and aims: The randomised, double-blind phase (DBP) of the TOLEDO study (NCT02006121) confirmed the efficacy of apomorphine infusion (APO) in significantly reducing OFF time in PD patients with motor fluctuations despite optimised oral therapy. We report safety and efficacy results including the 52-week open-label phase (OLP).

Methods: All patients completing the DBP (including early switching) were offered OLP entry. The primary objective was evaluation of long-term safety of APO. Efficacy parameters were also collected.

Results: 84 patients entered the OLP (40 previously on APO; 44 APO naïve) and 59 patients (70.2%) completed the study (30 previous APO; 29 APO naïve).

The safety profile of APO was consistent with extensive clinical experience (Table 1). Common treatment-related adverse events (AEs) were mild or moderate infusion site nodules, somnolence and nausea. 14 (16.7%) patients discontinued the OLP due to AEs; such AEs involving >1 patient were fatigue (n=2) and infusion site reactions (n=4); other AEs occurring in individual patients are shown in Table 1.

Reduction in daily OFF time (Figure 1) and improvement in ON time without troublesome dyskinesia (OWTD) (Figure 2) were maintained over 64 weeks. Pooled data for week 64 (n=55) showed a mean (±SD) change from DBP baseline in daily OFF time of -3.66 (2.72) hours and in daily OWTD of 3.31 (3.12) hours. Mean daily levodopa-equivalent dose decreased from DBP baseline to week 64 by >500 mg.

OLP safety set (n=84)	n (%)
Patients with at least one AE	83 (98.8)
AEs related to the study medication	77 (91.7)
Serious treatment-related AEs	8 (9.5)
AEs leading to study discontinuation:	14 (16.7)
• Infusion site reactions	4 (4.8)
• Fatigue	2 (2.4)
• Autoimmune haemolytic anaemia	1 (1.2)
• Delirium	1 (1.2)
• Dementia	1 (1.2)
• Disturbance in attention	1 (1.2)
• Lymphoma	1 (1.2)
• Nausea	1 (1.2)
• Panic attack	1 (1.2)
• Somnolence	1 (1.2)
AEs with a local intolerability (skin changes at injection site)	60 (71.4)
Most common AEs (≥10% frequency)	
• Infusion site nodules	46 (54.8)
• Somnolence	19 (22.6)
• Nausea	19 (22.6)
• Dyskinesia	14 (16.7)
• Fall	14 (16.7)
• Constipation	12 (14.3)
• Insomnia	13 (15.5)
• Dizziness	11 (13.1)
• Infusion site erythema	11 (13.1)
• Headache	9 (10.7)

Table 1. Combined safety results for all patients entering the OLP measured from DBP baseline.

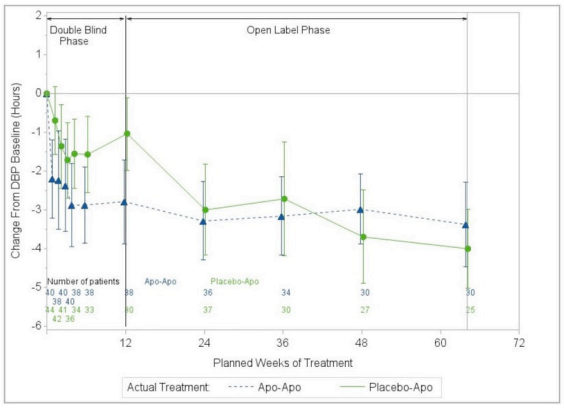

Figure 1. Changes from DBP baseline in daily OFF time over 24 hours (OLP safety set).

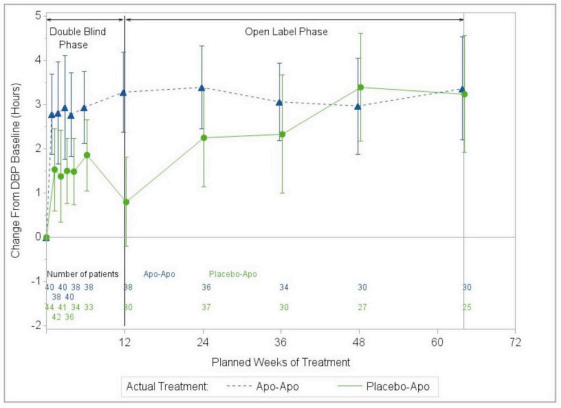

Figure 2. Changes from DBP baseline in daily OWTD (OLP safety set).

Conclusion: Results confirm the safety and efficacy of APO in long-term use while substantially reducing oral PD medication.

Disclosure: Britannia Pharmaceuticals Limited funded the study, registered at ClinicalTrials.gov (NCT02006121).

EPR2059

Preferences of patients with Parkinson's disease for communication about advanced care planning

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Background and aims: There is increasing awareness that patients with progressive chronic neurological disease are in need of palliative care. Advanced care planning (ACP) concerns discussion on the patients' needs, wishes, and preferences regarding treatment of (non) disease-specific and end-of-life issues. ACP was found to enhance quality of life in amyotrophic lateral sclerosis patients. The opinion of PD patients concerning ACP is largely unknown including what is considered optimal timing.
To explore needs, wishes and preferences of PD patients regarding content and timing of ACP in a qualitative manner.
Methods: In-depth interviews with 20 patients conducted in one tertiary PD referral center. Qualitative analysis consisted of open coding and inductive analysis of verbatim typed out interviews.
Results: 13 males and 7 females were interviewed. Mean age was 63 years (range 47-82) and mean disease duration 9 years (range 1-27). None had severe cognitive impairment. Most patients had moderately severe motor symptoms. Nearly all patients expressed the wish to receive more information about the consequences of the diagnosis, in particular regarding daily activities. More than half desired, complimentary to regular neurological care, to be better informed about what to expect in the (near) future, e.g. cognitive impairment, increased disability, and how to anticipate. They experienced difficulty gaining knowledge about available care and what could be planned in advance.
Conclusion: PD patients experience lack of knowledge on individual prognosis and available care. Actively inquiring the need for care and providing guidance in timely decision-making on medical support and treatment may improve patient care during this neurodegenerative illness.
Disclosure: Nothing to disclose

EPR2060

The burden of non-motor symptoms on health-related quality of life among patients with Parkinson's disease: a neurologist/patient real-world assessment in the US

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Background and aims: Parkinson's disease (PD) patients develop motor and/or non-motor symptoms (MS; NMS), e.g. bradykinesia, anxiety, cognitive impairment. While MS are typically more manifest, NMS are frequently overlooked or treated as peripheral issues to MS, yet their burden can affect patient health-related quality of life (HRQoL). We investigated the impact of NMS on HRQoL in real-world PD patients.
Methods: Data were drawn from Adelphi's 2017 Parkinson's Disease Specific Programme, a cross-sectional US study of 109 neurologists and 1,409 of their consulting PD patients, encompassing all disease stages. Patients were divided into two analysis cohorts: those with motor-only (MO) and those with motor plus non-motor (MNM) symptoms, as recorded by their physician. These cohorts underwent propensity-score matching (PSM) for physician-reported age, sex, BMI, numbers of motor/non-motor-related comorbid conditions and H&Y stage, before testing for differences in patient-reported HRQoL measures (EQ-5D, EQ-VAS & PDQ-39) and physician-reported OFF-time presence and aggregation.
Results: 383 MO & 1,019 MNM-patients were available for PSM analysis of physician-reported data; 118 MO & 451 MNM for patient-reported data. 7.5% MO had OFF-time vs. 31.2% MNM-patients ($p<0.001$) with mean daily OFF-hours of 0.19 MO vs. 0.98 for MNM ($p<0.001$). Significantly more favourable scores were seen for MO than MNM-patients across all patient-reported outcome measures.

Table 1 – Patient-reported outcomes

	Motor-only patients (n=118)	Motor plus non-motor patients (n=451)	p-value
EQ-5D-3L Health Utility Score (0=Worst; 1=Best Health)	0.82	0.74	0.005
EQ-VAS (Visual Analog Scale) (0=Worst; 100=Best Health)	78.2	67.8	<0.001
PDQ-39 (Parkinson's Disease Questionnaire): Composite Score (100=Worst; 0=Best Health)	11.9	23.3	<0.001
PDQ-39: Mobility	20.5	30.7	<0.001
PDQ-39: Activities of Daily Living	15.8	24.7	0.016
PDQ-39: Emotional Wellbeing	12.4	29.9	<0.001
PDQ-39: Stigma	11.1	23.2	<0.001
PDQ-39: Social Support	5.9	14.5	0.001
PDQ-39: Cognitions	8.9	23.6	<0.001
PDQ-39: Communication	8.3	15.4	<0.001
PDQ-39: Bodily Discomfort	12.4	24.7	<0.001

Table 1. Patient-reported outcomes.

Conclusion: The addition of non-motor atop motor PD symptoms is associated with significant negative impact upon HRQoL. Higher rates of OFF-time were also present alongside NMS. Further study is required into the effects of the presence of NMS and their association with OFF-time.
Disclosure: Analysis and writing funded by Sunovion Pharmaceuticals Inc., US.

EPR2061

Switching entacapone 'non-responders' to open-label opicapone: change in absolute OFF-time following the 1-year extension BIPARK-I study

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Background and aims: To evaluate the efficacy of opicapone (OPC) in levodopa-treated Parkinson's disease (PD) 'non-responders' patients who switched from placebo (PLC) or entacapone (ENT) to OPC in BIPARK-I open-label part. OPC, a once-daily COMT inhibitor, proved effective in the treatment of motor fluctuations in PD patients in two large, pivotal, multinational trials (BIPARK-I and II) [1,2].
Methods: After completing BIPARK-I double-blind part, PLC- and ENT-patients switched to a 1-year open-label extension under OPC-treatment. This post-hoc analysis investigated the change from open-label baseline in absolute OFF-time in 'non-responders' PLC and ENT 'switchers'. Non-responders, as assessed by Patient Global Impression of Change (PGI-C), were any subjects who had no improvement by double-blind endpoint. A linear mixed-effect model repeated measurement (MMRM) with region as factor and baseline as covariate was applied.
Results: In total, 199 patients switched from PLC (n=99) or ENT (n=100) to 1-year OPC open-label extension. From these, ~45% were PGI-C 'non-responders' for both groups. After 1-year treatment with OPC, for PLC-patients defined as 'non-responders' at double-blind endpoint, switching to OPC resulted in a statistical significant additional reduction of OFF-time (-83.8 min, p=0.0003). Likewise, switching ENT 'non-responders' to open-label OPC resulted in a statistical significant additional reduction of OFF-time (-45.3min, p= 0.0399). 'Non-responders' patients (~23%) originally allocated to OPC-50mg in the double-blind phase also showed greater response but not statistically significant.
Conclusion: Switching entacapone 'non-responders' to open-label opicapone resulted in a statistical significant reduction of OFF-time.
1. Ferreira et al., Lancet Neurology 2016; 15(2):154-165.
2. Lees et al., JAMA Neurol. 2017; 74(2):197-206.
Disclosure: This study has been supported by BIAL - Portela & C[a], S.A.

EPR2062

Mutations in the LRRK2 and Parkin genes and intermediate alleles in the HTT and ATXN1 genes modulate the risk of cancer in Parkinson's disease

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Background and aims: Several researches associate mutations in the LRRK2 and Parkin genes with cancer in PD. Other researches found a negative correlation between the number of polynucleotide repeats and the risk of cancer. We aimed to assess the frequency of cancer in our cohort of PD patients to check whether mutations in the LRRK2 and Parkin genes or the presence of IAs in the HTT and ATXN1 genes modify the risk of cancer in PD.
Methods: This is a retrospective study where we revised the clinical records of all PD cases in search of history of any cancer. All cases were screened for mutations in the LRRK2 and Parkin genes and the number of CAG repeats in HTT and ATXN1 genes. The relative risk of cancer was computed for carriers and non-carriers of these genetic variants and compared between groups.
Results: The relative risk of cancer among carriers of mutations in the LRRK2 and Parkin genes and among carriers of IAs in the ATXN1 gene was higher than among non-carriers of genetic variants, while the relative risk of cancer among carriers intermediate alleles in the HTT was lower than among non-carriers of genetic variants.
Conclusion: Mutations in the LRRK2 and Parkin genes and IAs in the ATXN1 gene seem to increase the risk of cancer while IAs in the HTT gene decrease the risk of cancer in PD.
The study of larger cohorts is needed to assess the influence of these and other genetic variants on the risk of specific cancer cell lines in PD.
Disclosure: Nothing to disclose

EPR2063

Endemic parkinsonism associated with the rare haplotype of LRRK2 gene

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Background and aims: The increased prevalence of neurodegenerative parkinsonism was detected in population of a small isolated region of south-eastern Czech Republic. The aim of the study was to investigate a co-occurence of rare variants in set of genes frequently associated with parkinsonism.
Methods: The molecular genetic examination was performed in 32 probands with parkinsonism and 20 asymptomatic controls. Coding sequences, exon/intron regions and 5'/3'UTR sequences of genes associated with parkinsonism were tested with MPS method using Ion Torrent technology and confirmed by Sanger sequencing. In total, 93% of gene sequences were covered. Variants were filtered using parameter MAF<0.01. SIFT; PolyPhen-2 prediction software was used for missense variants evaluation. PhyloP algorithm was used to assess the phylogenetical conservation.
Results: The joint occurence of 4 intron variants (rs11564187, rs36220738, rs200829235, rs3789329) and 1 exon variant (rs33995883) were identified in LRRK2 gene in 6 probands; none of these variants was found in controls. Using prediction tools (SIFT, PolyPhen-2) the exon variant was evaluated as pathogenic, the variant rs200829235 resulted in a break of the splice site and in activation of an exonic cryptic donor site and potential alteration of mRNA splicing , rs11564187 led to creation of a new donor site.
Conclusion: Based on data of 1000 Genomes project, the frequency of the joint occurence of these variants in the population is almost exclusive, so we assume that these variants are in haplotype. Therefore, they may be associated with Parkinson's disease and may be one of the causes of the increased prevalence of parkinsonism in this region.
Disclosure: Supported by grants: AZV- Ministry of Health of the Czech Republic Nr. 15-32715A, IGA-LF-2018-009 and MH CZ – DRO (FNOL 00098892) – 2018

EPR2064

"Trust the patient not the doctor": non-motor symptoms and quality of life in cervical dystonia

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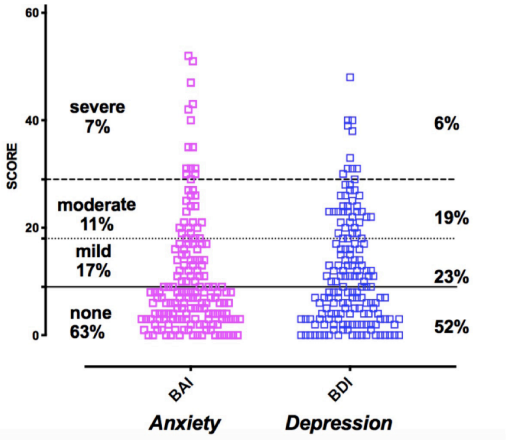
Background and aims: Mood disorder is common amongst cervical dystonia (CD) patients and can impact on quality of life (QoL). It often precedes the onset of CD and does not improve with botulinum toxin therapy. We hypothesize that mood disorder is part of the primary pathogenic process causing CD. The aim is to assess the prevalence of mood disorder and measure QoL in relation to severity, disability and pain in CD patients receiving botulinium toxin therapy with good effect.

Methods: We prospectively collected data using assessment tools including TWSTRS questionnaires for pain, severity and disability; CDIP-58 and Euro-QoL VAS questionnaires for QoL and BAI, BDI-II & HADS for mood disorder assessment.

Results: In 160 patients with mean age 62 years (SD: 12.67), using the BAI and BDI-II, 38% had depression, 42% had anxiety and 50% reported anxiety and/or depression. There was a significant correlation between the severity of mood disorder and quality of life using CDIP-58 {(Anxiety: R2=0.39; p<0.0001) and (Depression: R2=0.33; p<0.0001)}. There was weak correlation between disease severity, disability and quality of life; R2=0.09; p<0.0002 and R2=0.18; p<0.0001 respectively.

BAI & BDI Scores			
Anxiety scores by BAI (160 patients)			
none 0-9	mild 10-18	moderate 19- 29	severe 30+
99 (63%)	31 (20%)	17(11%)	13 (7%)
Depression scores by BDI (159 patients)			
0-9	10-18	19-29	30+
83 (52%)	36 (23%)	30 (19%)	10 (6%)
(either anxiety or depression in 81/160 – 50%)			

BAI & BDI Scores



Mood assessment using BAI & BDI

CORRELATION WITH CDIP-58

	TWSTRS - DISABILITY	TWSTRS - PAIN	TWSTRS - SEVERITY	BAI	BDI	HADS - Anx	HADS - Dep	EQoL
No. of values	159	176	182	161	160	147	142	144
R square	0.1793	0.2026	0.09066	0.3955	0.3258	0.09973	0.1554	0.2513
p value	<0.0001	<0.0001	0.0002	<0.0001	<0.0001	0.0001	<0.0001	<0.0001
Deviation from zero?	Significant	Significant	Significant	Significant	Significant	Significant	Significant	Significant

Correlations between Quality of Life and measures of mood disorders, severity, pain and disability

Conclusion: There was a significant correlation between reported mood disorder and QoL in CD but a weak association with measures with the severity, pain and disability scales. This shows that patient-reported measures, in particular, the CDIP-58, are a source of significant disability reporting which is not determinable by standard recommended measures of CD severity, administered by the neurologist. As such it is important to trust the patient.

Disclosure: Nothing to disclose

Movement disorders 6

EPR2065

A totally data-driven whole-brain multimodal pipeline for the discrimination of Parkinson's disease, multiple system atrophy and healthy control

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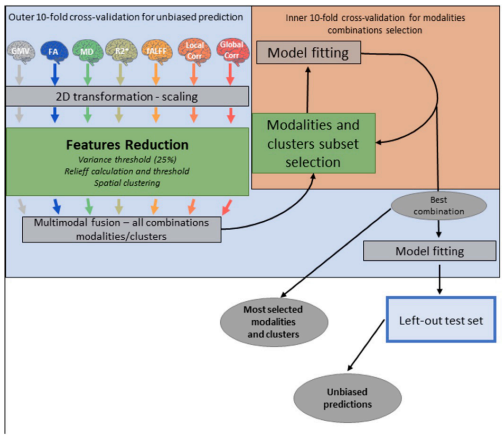
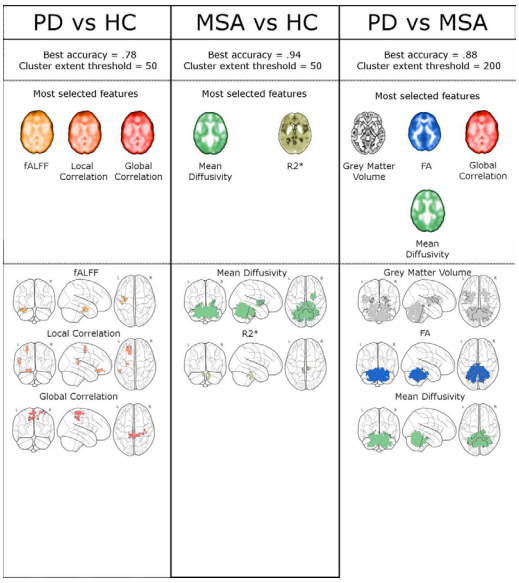
Background and aims: Parkinson's disease (PD) and multiple system atrophy (MSA) are two parkinsonian syndromes that share many symptoms, albeit having different prognosis. Although previous studies have proposed multimodal MRI protocols combined with multivariate analysis to discriminate between these two populations and healthy controls, studies combining all MRI indexes relevant for these disorders (i.e. grey matter, fractional anisotropy, mean diffusivity, iron deposition, brain activity at rest and connectivity) with a completely data-driven voxelwise analysis for discrimination are still lacking.

Methods: In this study, we used such a complete MRI protocol and adapted a fully-data driven analysis pipeline to discriminate between these populations and a healthy controls (HC) group. The pipeline combined several feature selection and reduction steps to obtain interpretable models with a low number of discriminant features that can shed light onto the brain pathology of PD and MSA.



Colored brains represent indexes, same color represent indexes from the same modality. Outer malva square: outer 10-folds-CV; inner orange square: inner 10-folds CV to find the best combination. Green squares: features selection steps. Grey squares: preprocessing,fitting and prediction. Grey ovals: outcomes

Results: Using this pipeline, we could discriminate between PD and HC (best accuracy =.78), MSA and HC (best accuracy =.94) and PD and MSA (best accuracy =.88). Moreover, we showed that indexes derived from resting-state fMRI alone could discriminate between PD and HC, while mean diffusivity in the cerebellum and the putamen alone could discriminate between MSA and HC. On the other hand, a more diverse set of indexes derived by multiple modalities was needed to discriminate between the two disorders.



Performance of the best model for each discrimination task (upper panel). Modalities most frequently selected for each discrimination task (middle panel).Cluster most frequently observed (>50 folds) for each of the most observed modalities (lower panel).

Conclusion: We showed that our pipeline was able to discriminate between distinct pathological populations while delivering sparse model that could be used to better understand the neural underpinning of the pathologies.

Disclosure: Nothing to disclose

EPR2066

Safety and tolerability of apomorphine sublingual film during titration in patients with Parkinson's disease and "off" episodes: a pooled analysis

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Background and aims: Apomorphine sublingual film (APL-130277; APL) was well tolerated and effective as acute, intermittent treatment for "OFF" episodes in patients with Parkinson's disease (PD) in a phase-3 trial. Safety and tolerability during titration were further examined using pooled clinical data.

Methods: Adult levodopa-responsive patients with PD and "OFF" episodes exposed to ≥1 dose of APL (10–60 mg/dose) during titration across 4 clinical trial were included in this pooled safety analysis. Treatment-emergent adverse events (TEAEs) were reported using descriptive statistics.

Results: Among the 408 unique patients in the pooled titration phase, median exposure was 21 days (range, 1–109 days) and most patients (81%) received ≤5 individual APL doses. Overall, 60% of patients reported ≥1 TEAE; the most common (≥5%) were nausea (21%), somnolence, yawning, dizziness (11% each), and headache (8%). TEAEs led to APL discontinuation in 9% of patients; the most common (≥2%) were nausea (3%), and dizziness and somnolence (2% each); there was no apparent trend between APL dose level and discontinuation. Among categories of adverse events of special interest (AESIs), the most common (≥5%) were hypotension/orthostatic hypotension (15% [11% due to dizziness]); daytime sudden onset of sleep (12% [11% due to somnolence], stomatitis, oral ulcers, oral irritation OR allergic/sensitivity response to the formulation (10% [4% due to oral mucosal erythema]), and falls and injuries (5% [2% due to fall]).

Conclusion: APL was well tolerated and TEAEs were generally mild. Safety findings were consistent with known effects of apomorphine and dopamine agonists except for local site reactions associated with sublingual administration.

Disclosure: This study was funded by Sunovion Pharmaceuticals Inc. (Marlborough, MA).

EPR2067

The cost-effectiveness of levodopa carbidopa intestinal gel in advanced Parkinson's disease in a Norwegian setting

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Background and aims: Levodopa/carbidopa intestinal gel (LCIG) has been on the Norwegian market since 2004, however the cost-effectiveness of LCIG treatment has not been assessed by the Norwegian Medicines Agency before. We aimed to determine the cost-effectiveness of LCIG vs. standard of care (SoC) for the treatment of advanced Parkinson's disease (aPD) in Norway.

Methods: A Markov model was used where health states were defined based on Hoehn & Yahr (H&Y) scale combined with percent of day spent in OFF-state and death. A cohort of aPD patients having H&Y III-V and experiencing >50% of their awake time in OFF was selected. SoC included oral therapy±subcutaneous apomorphine injections - the relevant comparator in relation to the indication of LCIG. Data informing the model were derived from a comprehensive clinical trial program and real world data which included Norwegian patients. Utilities were derived using generalized estimating equations. Costs were estimated from patient-level data and inputs from Norwegian clinical experts. Time horizon was 20 years. Both one-way and probabilistic sensitivity analyses were conducted.

Results: The results show a considerable incremental increase in quality adjusted life years (QALY) and that LCIG is cost-effective. The probabilistic sensitivity analysis indicates that there is a 93% probability of LCIG being cost effective with a payer threshold of 51,600 EUR. The model was most sensitive to health state costs. Complete data on QALY and the incremental cost effectiveness ratio (ICER) will be presented.

Conclusion: LCIG is a cost-effective treatment compared with SoC in patients with aPD in Norway.

Disclosure: CT and ATP contributed equally to the work. The authors will like to acknowledge Matthew Madin-Warburton, Seyavash Najlerahim and Christina-Jane Crossman Barnes and Prasanna Lakshmi Kandukuri for their assistance in model development. Financial support for their contribution was provided by AbbVie. CT, ATP, YJJ and KN are employees of AbbVie and may own stocks/shares in the company. CL has served as a consultant to Nordic Infucare, Medtronic and AbbVie, and has received research funding and speaker fees from AbbVie. This study was supported and funded by AbbVie Inc.

EPR2068

Incongruity of functional tremor predicts better response to transcranial magnetic stimulation treatment

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Background and aims: Patients with functional tremor (FT) experience their abnormal movements as involuntary. However, FT characteristics suggest its generation relies on structures involved in control of voluntary movements. In fact, findings incongruent with organic tremors, including tremor entrainment or amplitude variability with attentional shift, reflect physiological aspects of voluntary movements. Not all FT patients show these incongruent features, suggesting that mechanism of FT generation is heterogeneous. Apparently, central nervous system may become "overtrained" by FT, which then becomes more automatic movement, resistant to interference of contralateral movements or attention. We hypothesised that patient whose FT has more "voluntary" aspects may respond better to rTMS.
Methods: Ten patients with FT underwent 5-day repeated sessions of cTBS over the motor cortex contralateral to more affected hand. On the first and the last day of stimulation, electromyography and accelerometry of postural tremor was performed, without and with mass loading. Additionally, patients performed battery of tests including tapping task (3 different frequencies) and cognitive load task, that determined FT score for each patient. Response to cTBS was measured subjectively and objectively as change in tremor amplitude.
Results: 7/10 patients reported no subjective improvement. Objectively, 5 patients were responders and 5 non-responders. Responders had higher FT score comparing to non-responders ($p= 0.016$). There was a significant positive correlation between FT score and reduction of tremor amplitude with cTBS ($rs=0.711$; $p=0.048$).
Conclusion: More the tremor looks functional/non-organic, more likely it will respond to treatment, possibly as its generations still largely depends on voluntary non-automatic motor network.
Disclosure: Nothing to disclose

EPR2069

In vivo increased striatal iron deposition in Parkinson's disease dementia and dementia with Lewy body

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Background and aims: Patients with Parkinson's disease (PD) have demonstrated increased iron deposition in the basal ganglia at post-mortem, which is linked to neurodegeneration and alpha-synuclein aggregation. In vivo imaging of alpha-synuclein pathology is currently unavailable, but iron concentration can be measured with susceptibility weighted imaging (SWI) MRI. We hypothesize that iron concentrations, as measured by SWI, will be increased in patients with Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) compared to idiopathic PD (iPD) and healthy controls.
To evaluate iron deposition with SWI MRI in the basal ganglia of PDD and DLB patients compared to iPD patients and healthy controls.
Methods: We enrolled 11 PDD/DLB patients (5 PDD and 6 DLB), 11 iPD patients, matched for disease duration with the PDD/DLB patients, and 22 age- and gender-matched healthy controls.
Results: PDD/DLB patients demonstrated increased iron deposition in caudate nucleus and putamen compared to iPD patients (caudate: $P=0.014$, putamen: $P=0.015$) and compared to healthy controls (caudate: $P=0.017$, putamen: $P=0.036$). A trend of increase in striatal iron deposition has been found between iPD and healthy controls (+9%) and between DLB and PDD patients (+5%).
Conclusion: Our findings demonstrate that SWI iron can be used as a marker of basal ganglia pathology in alpha-synuclein disease and that PDD and DLB patients have a higher burden of striatal pathology compared to PD patients and healthy controls.
Disclosure: Nothing to disclose

EPR2070

Diagnostic utility of CSF NfL in patients referred to a tertiary movement disorder clinic with a diagnosis of atypical parkinsonism

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Background and aims: Differentiating among the parkinsonian syndromes is difficult, particularly in early disease stages. Previous studies have identified cerebrospinal fluid (CSF) concentrations of neurofilament light (NfL) as a useful biomarker for differentiating Parkinson's disease (PD) from atypical parkinsonian syndromes (APS). In this study we assess the value of CSF NfL as a part of the diagnostic work-up in patients with parkinsonism referred to a tertiary movement disorder clinic and evaluate the diagnostic utility of CSF NfL in a relatively large cohort of clinically well-characterized patients.
Methods: A total of 147 patients referred to the Bispebjerg Movement Disorder Clinic, Bispebjerg University Hospital, Copenhagen, with a working diagnosis of APS were consecutively enrolled over a 6-year period. CSF concentrations of NfL, Aβ42, t-tau, and p-tau were determined as a part of the diagnostic work-up. Clinical follow-up was performed after 25 months (range: 2 – 65 months) and diagnoses were made according to clinical criteria (MSA= 20, PSP=33, DLB= 20, CBS= 9, PD= 31).
Results: Patients diagnosed with PD at follow-up time, although they were initially suspected of atypical parkinsonism, had significantly lower CSF NfL compared to patients fulfilling the criteria for MSA ($p<0.001$) and PSP ($p<0.011$) at follow-up.
Conclusion: Our results suggest that CSF NfL may be useful in differentiating patients with PD from patients with MSA and PSP, even when PD patients clinically present with phenotypes mimicking APS in early disease stages.
Disclosure: Nothing to disclose

EPR2071

Quality of life is worse in Parkinson's disease (PD) patients with 5-2-1 positive criteria: a simple screening tool for identifying advance PD cases who need an optimization of Parkinson's treatment

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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) criteria have recently been proposed by a Delphi expert consensus panel for diagnosing advanced Parkinson's disease (PD). The aim of the present study is to compare quality of life (QoL) in PD patients with vs patients without "5-2-1 positive criteria" (defined as meeting ≥1 of the criteria).
Methods: This is a cross-sectional, observational, monocenter study. Three different instruments were used to assess QoL: the 39-item Parkinson's disease Quality of Life Questionnaire Summary Index score (PDQ-39SI); a subjective rating of perceived QoL (PQ-10) on a scale from 0 (worst) to 10 (best); and the EUROHIS-QOL 8-item index (EUROHIS-QOL8).
Results: From a cohort of 102 PD patients (65.4±8.2 years old, 53.9% males; disease duration 4.7±4.5 years), 20 (19.6%) presented positive 5-2-1 criteria: 6.9% for 5, 17.6% for 2, and 4.9% for 1. The 37.5% (12/32) and 25% (5/20) of patients with motor complications and dyskinesia, respectively, presented 5-2-1 negative criteria. Both health-related (PDQ-39SI, 25.6±14 vs 12.1±9.2; $p<0.0001$) and global QoL (PQ-10, 6.1±2 vs 7.1±1.3; $p=0.007$; EUROHIS-QOL8, 3.5±0.5 vs 3.7±0.4; $p=0.034$) was worse in patients with 5-2-1 positive criteria. Patients with motor fluctuations and 5-2-1 positive criteria (n=20) trended to have worse QoL that those with motor fluctuations but negative criteria (n=12) (PDQ-39SI, 25.6±14 vs 19.2±7.3; $p=0.157$).
Conclusion: QoL is worse in patients meeting ≥1 of the 5-2-1 criteria. These criteria could be useful for identifying patients in which it is necessary to optimize Parkinson's treatment.
Disclosure: Nothing to disclose

MS and related disorders 3

EPR2072

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 is crucial to understanding the long-term benefit–risk profile of ocrelizumab. The safety and efficacy of ocrelizumab have been characterised in one Phase II study in relapsing-remitting multiple sclerosis (MS) (NCT00676715), two identical Phase III trials in relapsing MS (RMS; OPERA I/II [NCT01247324]/[NCT01412333]) and the Phase III trial in primary progressive MS (PPMS; ORATORIO [NCT01194570]), and their extensions. These analyses report ongoing safety evaluations from ocrelizumab clinical trials and open-label extension (OLE) periods up to July 2018.

Methods: Safety outcomes were reported for all patients receiving ocrelizumab during the controlled treatment and OLE periods of the Phase II/III MS clinical trials, plus the Phase IIIb trials VELOCE, CHORDS/CASTING and OBOE (ocrelizumab all-exposure population; updated data-cut to include ENSEMBLE). The number of post-marketing patients exposed to ocrelizumab is based on estimated total number of vials sold and US claims data. To account for different exposure lengths, the rate per 100 patient years (PY) is presented.

Results: In clinical trials, 3,811 patients with MS received ocrelizumab, resulting in 10,919 PY of exposure, as of February 2018. Reported rates per 100 PY (95% confidence interval) were: adverse events (AEs), 242 (239–245); serious AEs, 7.23 (6.73–7.75); infections, 74.5 (72.9–76.1); serious infections, 2.00 (1.74–2.28); and malignancy 0.45 (0.33–0.60). Updated cross-trial information and post-marketing data as of July 2018 will be presented.

Conclusion: Reported rates of events per 100 PY in the ocrelizumab all-exposure population continue to be generally consistent with the controlled treatment period in the RMS/PPMS populations.

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

EPR2073

Progression of cortical thinning over time differs across phenotypes and is clinically relevant: a multicentre study

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Background and aims: Grey matter atrophy is a crucial component of multiple sclerosis (MS) and provides clinically relevant information. We investigated the distribution and regional evolution of cortical thickness (CTh) reduction in MS patients in a multicentre dataset.

Methods: T2- and 3D T1-weigthed images were acquired at 3T from 81 MS patients (65 relapsing-remitting MS [RRMS], 10 progressive MS [PMS] and 6 clinically-isolated-syndrome [CIS]) and 31 healthy controls (HC) at 3 European sites, at baseline and after one-year of follow-up. Patients were classified as clinically stable or worsened according to their disability change. Baseline CTh differences and changes over time were assessed using Freesurfer. Correlations between CTh and T2 lesion volume changes were assessed.

Results: At baseline, temporal and occipital atrophy was found in MS patients vs HC. RRMS patients mainly showed CTh loss in bilateral superior temporal, secondary visual and posterior cingulate regions, while PMS patients showed additional CTh reduction vs RRMS mostly in frontal regions. At follow-up, CTh decreased in all MS patients in occipital, cingulate and temporal cortices vs HC. Such decrease was mainly driven by CIS and RRMS patients, while PMS patients presented predominant superior parietal and sensorimotor cortex thinning vs RRMS. Cortical thinning was higher in bilateral frontal and left temporo-parietal regions in clinically worsened vs stable MS patients. A higher CTh decrease over time in occipital regions was correlated with higher changes of T2 lesion volume.

Conclusion: One-year cortical thinning progression was variable across MS phenotypes, partially correlated with concomitant lesion volume change and contributed to explain clinical worsening.

Disclosure: Nothing to disclose

EPR2074

No increased risk of spontaneous abortion and ectopic pregnancy after exposure to interferon-beta prior to or during pregnancy: results from register-based Nordic study among women with MS

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Background and aims: Women with multiple sclerosis (MS) are often diagnosed at childbearing age. Previous small observational studies suggested that interferon-beta (IFNβ) exposure does not increase the risk of early pregnancy loss, though an abortive effect with high doses has been reported in pre-clinical studies. Our aim was to assess the prevalence and risk of spontaneous abortion and ectopic pregnancy in IFNβ-exposed pregnant women with MS.
Methods: Finnish and Swedish health register data between 1996-2014 were used to study women with MS treated with 1) only IFNβ within 3 months prior to or during pregnancy (IFNβ-exposed) and 2) without any MS disease modifying drugs (MSDMDs) (unexposed). The prevalence of spontaneous abortion and ectopic pregnancy among all pregnancy events was compared between the exposed and unexposed with multivariate log-binomial regression, adjusted for confounders including maternal age and comorbidities.
Results: Among 3054 pregnancies, 8.1% (95% confidence interval (CI) 6.3-10.2%) of the IFNβ-exposed and 11.1% (95%CI 9.7-12.7%) of the unexposed had spontaneous abortion, with no statistical difference between the groups (risk ratio (RR) 0.83; 95%CI 0.63-1.08). The prevalence of ectopic pregnancy was 1.6% (95%CI 0.9-2.7%) among IFNβ-exposed versus 2.9% (95%CI 2.2-3.8%) among the unexposed. A numerically decreased risk (RR 0.55; 95% CI 0.30-1.01) was observed among the IFNβ-exposed, compared to those unexposed.
Conclusion: This largest population-based observational study in pregnant women with MS treated with IFNβ found no increase in the risk of spontaneous abortion or ectopic pregnancy in women with MS exposed to only IFNβ, compared to those unexposed to MSDMDs.
Disclosure: Funding for the analysis, project management and medical writing was provided by Bayer AG, Biogen, Merck KGaA and Novartis Pharma AG.

EPR2075

Assessment of disease progression in patients with secondary progressive multiple sclerosis (SPMS) using a novel functional composite endpoint

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Background and aims: Physical disability, as measured by the Expanded Disability Status Scale (EDSS) score, and cognitive decline, as assessed by a measure of cognitive processing speed, the Symbol Digit Modalities Test (SDMT), are functional domains of high clinical relevance for patients with SPMS. We evaluated a novel composite endpoint (CEP), using both EDSS- and SDMT-related events, to characterise disease progression in a more comprehensive manner in patients with SPMS.
Methods: We analysed time to clinically meaningful changes in EDSS and SDMT, i.e., 6-month confirmed disability progression on EDSS (1.0-point worsening from ≤5.0 baseline score or 0.5-point worsening from >5.0 baseline score; 6mCDPEDSS), SDMT (4.0-point confirmed worsening from baseline; 6mCWSDMT), and on the proposed CEP in patients from the EXPAND trial (siponimod vs. placebo; N=1645).
Results: EDSS- and SDMT-related progression, when assessed separately, was well-balanced with minimum overlap of events: 358 patients had EDSS progression, of which 279 (78%) had no progression on SDMT; 287 had SDMT progression, of which 208 (72%) had no progression on EDSS; 79 progressed on both EDSS and SDMT. Compared to placebo, siponimod reduced the risk of physical and cognitive progression when assessed individually by EDSS and SDMT events and on the CEP (Table 1). At the end of the core study, 62.2% of siponimod-treated patients versus 52.3% on placebo remained CEP free.
Conclusion: CEP allowed assessment of two key disease outcomes for measuring disability that are complementary

but largely independent of each other. Siponimod showed a significant beneficial effect on this novel CEP, especially relevant to patients with SPMS.

Table 1. Risk of physical and cognitive disability when assessed individually and on the CEP

Parameter	HR[#] (95% CI)	p value
$6mCDP_{EDSS}$	0.74 (0.60; 0.92)	0.0058
$6mCW_{SDMT}$	0.75 (0.59; 0.95)	0.0163
CEP*	0.75 (0.63; 0.88)	0.0008

*[#]Hazard ratios and 95% confidence intervals using a Cox proportional hazards model are presented; *The combined endpoint shows greater power to assess treatment group difference, as is evident from the lower p value for the CEP and would allow for lower sample sizes in future clinical trials.*
6mCDP, 6-month confirmed disability progression; 6mCW, 6-month confirmed worsening; CEP, composite endpoint; CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; SDMT, Symbol Digit Modalities Test

Table 1. Risk of physical and cognitive disability when assessed individually and on the CEP

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EPR2076

Serum NMR spectroscopy metabolomic profiles indicate progressive multiple sclerosis

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Background and aims: Converging evidence suggests that pathophysiological processes may shift during the course of multiple sclerosis (MS), i.e. from predominantly inflammatory components to prevailing neurodegeneration in progressive MS. Analysis of metabolomic networks in body fluids, which may reflect underlying pathophysiologic mechanisms, could be helpful in order to better define MS disease phenotypes. We therefore applied 1H nuclear magnetic resonance spectroscopy (NMRS) to determine serum metabolomic signatures in MS patients with different disease phenotypes compared to controls.

Methods: We analysed serum samples from 92 MS patients (mean age 30.3, SD 9.2 years) (clinically isolated syndrome (CIS; n=30), relapsing remitting MS (RRMS; n=30), progressive MS (PMS; n=32) and 41controls with other non-inflammatory neurological diseases (OND; mean age 35.4, SD 11.9 years) by high-resolution NMRS.

Results: Orthogonal Partial Least Squares Discriminant Analysis (O-PLS-DA) models correctly discriminated CIS/MS (R2=0.567, Q2=0.497) and PMS (R2=0.755, Q2=0.678) from OND (Figure 1 A-B). Using this approach, significantly different metabolite profiles were seen comparing PMS and CIS/MS patients (R2=0.672, Q2=0.462) (Figure 2). Altered metabolites leading to the clustering were increased glutamine and glutamate levels in PMS compared to CIS/MS and controls, and reduced creatinine levels in CIS/MS and PMS compared to OND.

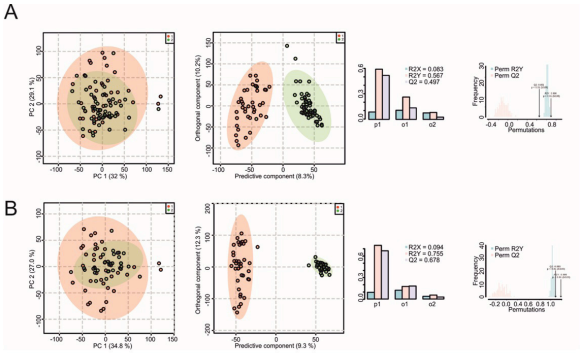

Figure 1: Principle Component Analysis (PCA) and O-PLS-DA analysis of serum samples. A. Control vs. CIS/MS B. Control vs. SPMS

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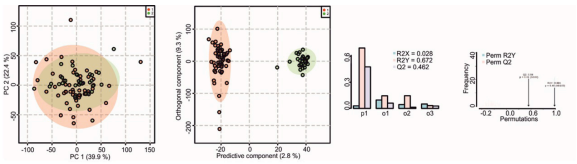

Figure 2: Principle Component Analysis (PCA) and O-PLS-DA analysis of serum samples. CIS/MS vs. SPMS

Figure 2: Principle Component Analysis (PCA) and O-PLS-DA analysis of serum samples. CIS/MS vs. SPMS

Conclusion: Analysis of serum metabolomic profiles by NMRS represents a promising non-invasive tool for discrimination of different disease phenotypes in MS. Future studies should test whether this approach also has potential for an early diagnosis of progressive MS forms beyond clinical phenotyping to provide pathophysiologic insights and steer therapeutic considerations.

Disclosure: Nothing to disclose

EPR2077

Increased serum neurofilament light chain levels are associated with relapse, MRI disease activity, and need for additional alemtuzumab courses in patients from CARE-MS I

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Background and aims: In CARE-MS I (NCT00530348) and 2 subsequent extension studies (NCT00930553; NCT02255656), alemtuzumab demonstrated efficacy in treatment-naive RRMS patients that was maintained through 8 years (y), with a consistent and manageable safety profile. This analysis examines associations between serum neurofilament light chain (sNfL) levels over 7 y and MS disease outcomes over 8 y in alemtuzumab-randomised patients (n=354 with sNfL data).

Methods: Subgroups with or without the following events were considered: 1) ≥1-point EDSS increase from baseline to Y8; 2) EDSS increase from baseline to Y8 of ≥1.5 points if baseline score was 0, ≥1 point for baseline score 1.0-5.5, or ≥0.5 points if baseline score was ≥6.0; 3) relapse through 8 y; 4) MRI disease activity on the Y8 scan (new gadolinium-enhancing or new/enlarging T2 lesions); or 5) ≥1 additional alemtuzumab course for both relapses and MRI disease activity. P values were derived using ranked ANCOVA.

Results: sNfL levels generally did not differ significantly in those with vs without EDSS increase. Significantly higher (P<0.05) median sNfL levels were observed in those with vs without relapses (Y4: 17.6 vs 14.3 pg/mL; Y5: 17.9 vs 14.5; Y6: 20.2 vs 15.4), MRI disease activity (Y5: 17.8 vs 14.9; Y6: 19.4 vs 15.7; Y7: 19.8 vs 12.3), or ≥1 additional alemtuzumab course (Y3: 17.5 vs 13.6; Y4: 27.0 vs 15.1; Y5: 20.3 vs 15.8; Y6: 24.4 vs 16.4; Y7: 19.7 vs 11.2).

Conclusion: Increased sNfL under alemtuzumab treatment was associated with relapse, MRI disease activity, and a need for additional treatment courses.

Disclosure: Study/supported by Sanofi and Bayer HealthCare Pharmaceuticals.

EPR2078

Individual risk of multiple sclerosis in clinically isolated syndromes: a multicenter prospective Italian study

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Background and aims: The early identification of patients with clinically isolated syndromes (CIS) at high risk of multiple sclerosis (MS) represents the main purpose of diagnostic criteria and of clinicians in everyday clinical practice. However, the clinical and neuroradiological parameters do not predict with accuracy progression and severity of the disease in a single CIS patient.

Methods: This is a multicenter, prospective study aimed at the integration of clinical, neuroradiological and neurophysiological data with functional genomics observations with the purpose of building an integrated risk model for MS development and progression in CIS patients.

Results: At baseline 71/150 (47%) patients fulfilled McDonald 2017 MS and started a disease modifying drug. During follow-up (mean 28.5 months), 24/150 (16%) patients developed clinically definite MS, while 118/150 (78.7%) satisfied McDonald 2017 MS. Fifty-two patients (34.7%) presented evidence of disease activity (EDA), defined as evidence of clinical relapses and/or active lesions at MRI and/or disability worsening. The number of T2 lesions at MRI ($p < 0.01$), the presence of enhancing lesions ($p < 0.01$) and the presence of oligoclonal bands ($p < 0.01$) were the most relevant prognostic factors not only for McDonald 2017 MS, but also for EDA. The ongoing transcriptomics analysis will define a predictive algorithm for a personalized diagnostic approach, but on the basis of the prognostic factors evidenced up to now a significant improvement in the definition of prognostic risk classes has been obtained.

Conclusion: The multidisciplinary analysis of CIS patients may lead to a personalized treatment approach in patients with CIS.

Disclosure: This project has been funded by the Italian Ministry of Health (RF-2011-02349698).

MS and related disorders 4

EPR2079

A whole-genome epigenomic approach in multiple sclerosis multiplex families revealed new epigenetic traits involved in the disease

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Background and aims: The genetic component of multiple sclerosis (MS) is now set to 201 common variants and 32 signals from HLA. However, these variants are able to explain only <40% of disease heritability, supporting the role of other mechanisms in disease risk including epigenetics.

Methods: We studied 26 affected and 26 unaffected relatives belonging to 8 MS multiplex families (≥3 affected relatives, of whom ≥2 with first-degree relationship) as part of a multicentric Italian cohort study using Methylated DNA immunoprecipitation sequencing (MeDIP-Seq) run on an Illumina® HiSeq 2500 (2x100 bp). Technical validation in 6 of 8 original families and biological replication in 2 additional families (FDR ≤ 0.05 and concordant fold change, FC) was performed in suggestive differentially methylated regions (DMRs) between affected and unaffected relatives using SeqCap Epi Choice Enrichment (Roche®).

Results: Signals from MeDIP-Seq were meta-analyzed across 8 families, leading to 162 signals with FDR ≤ 0.1 and a concordant FC in ≥6 families. Technical validation and biological replication lead to 3 DMRs of hypermethylation located at 16q22.1, 5q12.1 and 8q24.3 and 3 of hypomethylation located at 14q24.3, 5q35.3 and 6q12 (mean size: 3.1 kb).

Conclusion: Multiplex families represent a privileged setting for the study of regions of differential methylation as they reduce the impact of potential confounders like shared genetics and environmental factors. We are now exploring the role of the 6 identified regions since they contain genes of potential interest that are under investigation, and test their role in additional familial cases.

Disclosure: (code RF-2011-02350347). Finalised research the Ministry of Health.

EPR2080

Quantitative EEG differentiates multiple sclerosis with and without cognitive impairment from healthy controls at the beginning of the disease: preliminary data

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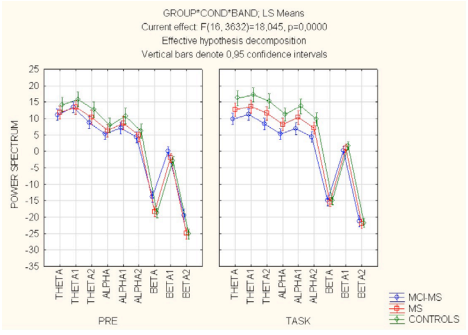
Background and aims: The present study aims to assess possible qEEG differences between newly diagnosed multiple sclerosis (MS) patients with or without cognitive impairment (CI).

Methods: We enrolled 22 patients (18-55-years-old) treated with first-line drugs for <6 months, and 11 healthy controls. All subjects underwent neuropsychological assessment including BICAMS and BDI. EEG recordings were performed during a cognitive task (computerised "SDMT" subtest of BICAMS) and at rest. Based on neuropsychological assessment, patients were considered as affected (MSCI group) or not (MS group) by cognitive impairment. We analysed data comparing MSCI patients matched by sex, age (±5years) and education to an MS patient and a control. Power spectrum analysis (theta, alpha and beta bands and sub-bands) was performed (EEGLAB extension for Matlab). Data were log-transformed and analysed through repeated measures ANOVA.

Results: A significant interaction group (MSCI, MS, Controls) x condition (rest, task) x band (alpha, beta, theta) was observed. Post-hoc analyses showed significant differences between MSCI and both MS and Controls in all the bands at rest ($p<.05$). In task condition MSCI significantly differed from controls in alpha and theta bands ($p<.05$) but not beta ($p=.9$). Moreover, while a significant power spectrum difference was found in all bands in both MS and Controls between rest and tak condition, MSCI didn't show any difference in alpha power ($p=.6$).



Conclusion: If confirmed in larger series, our results seem to support the hypothesis that qEEG differences exist among MSCI, MS and healthy controls, opening to a possible neurophysiological hallmark of cognitive impairment in MS patients.

Disclosure: Nothing to disclose

EPR2081

Rapid myelin quantification reveals diffuse demyelination linked to multiple sclerosis disability

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Background and aims: Magnetic resonance imaging (MRI) is essential for diagnosing and monitoring multiple sclerosis (MS). Conventional MRI is, however, not specific to demyelination. Rapid Estimation of Myelin for Diagnostic Imaging (REMyDI), is a new robust MRI technique allowing clinically feasible myelin quantification. We aimed to determine if REMyDI was sensitive to demyelination in normal-appearing tissue and its association to physical and cognitive disability in relapsing-remitting MS (RRMS).

Methods: RRMS patients (N=39) and age/sex-matched controls (N=21) underwent 3T MRI with REMyDI, exemplified in Figure 1. Lesions were semi-automatically segmented and subtracted from white and grey matter masks generating normal-appearing white (NAWM) and grey (NAGM) matter masks. Myelin volumes were extracted and normalized by intracranial volume. Clinical disability was assessed using the Expanded Disability Status Scale (EDSS), Symbol Digit Modalities Test (SDMT), EuroQol-5 dimension (EQ5D) and Multiple Sclerosis Impact Scale (MSIS). Demographics, clinical disability metrics and MRI measures are detailed in Table 1.

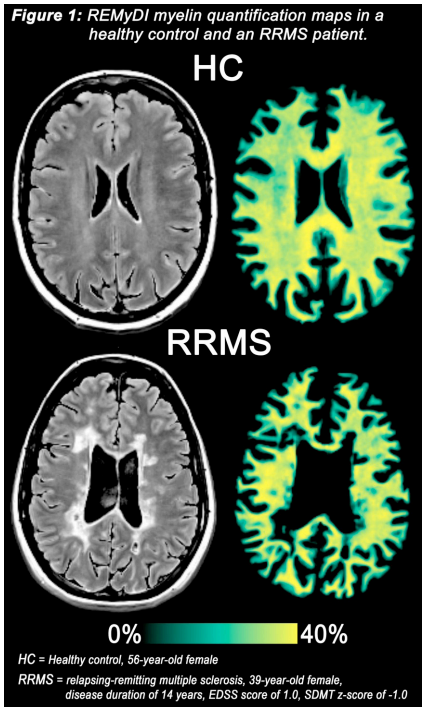

Figure 1: *REMyDI myelin quantification maps in a healthy control and an RRMS patient.*

Table 1: *Participant demography, clinical metrics and MRI measures.*

		Relapsing-Remitting Multiple Sclerosis	Healthy Controls (HC)
Demography	Participants, N	39	21
	Sex (F/M), N	28/11	12/9; $P = 0.25^{*}$
	Age, years	36.7 ± 10.4	35.9 ± 13.8; $P = 0.80^{\dagger}$
	Disease duration, years	9.13 ± 6.87	N/A
Clinical metrics	EDSS score: N, median	39, 1.5 ± 1.0	N/A
	SDMT score: N, mean	37, -1.10 ± 1.11	N/A
	MSIS score: psychological: N, median	31, 1.89 ± 1.34	N/A
	physical: N, median	31, 1.40 ± 0.80	N/A
	EQ5D score: N, median	30, 0.85 ± 0.28	N/A
MRI myelin quantification	Whole-brain myelin fraction	11.7 ± 1.40; $\boldsymbol{P = 0.004}^{\dagger}$ vs. HC	12.6 ± 0.9
	NAGM myelin fraction	1.74 ± 0.14; $P = 0.56^{\dagger}$ vs. HC	1.72 ± 0.1
	NAWM myelin fraction	9.49 ± 1.54; $\boldsymbol{P = 0.001}^{\dagger}$ vs. HC	10.6 ± 1.0

All myelin fractions are given as % after normalisation to the intracranial volume.
All values are given as mean ± standard deviation unless otherwise specified as median ± interquartile range.
**P-value, by Chi-square test (two-tailed).*
†P-value, by unpaired t-test (two-tailed, equal variances not assumed).
EDSS = expanded disability status scale; EQ5D = EuroQol-5 dimension; MSIS = multiple sclerosis impact scale; NAGM = normal-appearing grey matter; NAWM = normal-appearing white matter; SDMT = symbol digit modality test.

Results: RRMS patients had lower normalized myelin fractions in the whole-brain (11.7±1.40 vs. 12.6±0.9; P=0.004) and NAWM (9.49±1.54 vs. 10.6±1.0; P=0.001), relative to controls. REMyDI myelin fractions correlated with: SDMT in whole-brain (r=0.48, P=0.003) and NAWM (r=0.45, P=0.005); MSIS-physical in whole-brain (ρ=-0.39, P=0.032) and MSIS-psychological in whole-brain (ρ=-0.50, P=0.004) and NAWM (ρ=-0.47, P=0.007), as further described in Table 2.

Table 2: *Clinical correlations of REMyDI myelin quantification and clinical disability metrics.*

MRI myelin quantification (*N*=39)	Clinical disability metrics: EDSS (*N*=39)		SDMT (*N*=37)		MSIS: physical (*N*=31)		MSIS: psychological (*N*=31)		EQ5D (*N*=30)	
	ρ	$P^{\ddagger}$	r	$P^{\dagger}$	ρ	$P^{\ddagger}$	ρ	$P^{\ddagger}$	ρ	$P^{\ddagger}$
Whole-brain	-0.096	0.56	**0.48**	**0.003**	**-0.39**	**0.032**	**-0.50**	**0.004**	0.21	0.069
NAGM	-0.027	0.87	<0.001	0.99	0.13	0.15	0.20	0.27	-0.27	0.15
NAWM	-0.095	0.57	**0.45**	**0.005**	-0.34	0.058	**-0.47**	**0.007**	0.19	0.30

EDSS = expanded disability status scale; EQ5D = EuroQol-5 dimension; MSIS = multiple sclerosis impact scale; NAGM = normal-appearing grey matter; NAWM = normal-appearing white matter; SDMT = symbol digit modality test.
†P-value by Pearson correlation, between two normally distributed variables.
‡P-value by Spearman's correlation, between one or two non-normally distributed variables.

Conclusion: REMyDI captures diffuse demyelination in whole-brain and normal-appearing tissue at the RRMS stage and the myelin quantification measures are related to patients' clinical disability.

Disclosure: This research was supported by the Stockholm City Council and Karolinska Institutet (ALF 20120213 and 20150166).

EPR2082

Effects of fingolimod and natalizumab on brain T1/T2-weighted and magnetization transfer ratios: a 2-year study

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Background and aims: Fingolimod and natalizumab are highly effective treatments for relapsing-remitting multiple sclerosis (RRMS). We compared the effects of these drugs on brain T1/T2-weighted ratio (T1T2r) and magnetization transfer ratios (MTR) in RRMS after two years of treatment.
Methods: RRMS patients starting fingolimod (n=25) or natalizumab (n=30) underwent 3T brain scans at baseline (T0), month-6 (M6), year-1 (Y1) and year-2 (Y2). T1T2r and MTR maps for white matter (WM) lesions, normal-appearing (NA) WM and gray matter (GM) were estimated using in-house implemented methods and compared using linear mixed models.
Results: No baseline between-group difference was found. At M6 vs T0, fingolimod-patients had increased lesional MTR (p=0.05), whereas natalizumab-group showed increased lesional MTR (p=0.008) and T1T2r (p=0.02), without between-group differences. At Y2 vs M6, lesional values stabilized in fingolimod-group, whereas T1T2r decreased in natalizumab-group (p=0.002). At M6 vs T0, both groups showed stable NAWM T1T2r and MTR, whereas at Y2 vs M6 fingolimod-patients showed higher NAWM T1T2r values (p=0.01), without between-group differences. At M6 vs T0, fingolimod-patients showed reduced GM T1T2r (p=0.04), which recovered at Y2 (p=0.04), while T1T2r and MTR were stable in natalizumab-patients. At Y2 vs T0, fingolimod-patients had increased lesional (p=0.002) and GM MTR (p<0.001); these measures were stable in natalizumab-group, with a higher increase of GM MTR in fingolimod-patients (p=0.02).
Conclusion: Natalizumab promotes an early recovery of lesional damage and limits microstructural damage accumulation in normal-appearing brain tissue. Fingolimod enhances recovery of tissue damage that is visible 6 months after treatment start.
Disclosure: Nothing to disclose

EPR2083

An evaluation of axonal and myelin damage in multiple sclerosis lesions in living patients using myelin water and multi-shell diffusion MRI

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Background and aims: Multiple sclerosis (MS) is an autoimmune disease of the central nervous system, affecting both myelin and axons. The goal of this study was to quantify the concomitant presence of axonal and myelin injury in MS.
Methods: Ten MS patients and eight healthy controls (HC) underwent myelin water (MW) and neurite density and orientation dispersion imaging (NODDI) at 3T (Figure 1). Mean MW fraction (MWF) and NODDI parameters (neurite density index- NDI and orientation dispersion index- ODI) were extracted in white matter (WM) MS lesions (MSLs), normal appearing WM (NAWM) and WMHC.
By using analysis of variance (Hp01-2) and paired t-test (Hp03) we tested: Hp0-1 MW and NODDI metrics are similar in MSLs compared to NAWM and WMHC; and Hp0-2 myelin damage is as extensive as axonal damage in MSLs. For Hp0-2, we manually segmented the mirror contralateral region of 17 MSLs to evaluate the percentage of myelin (%MWF) and axonal density reduction (%NDI).

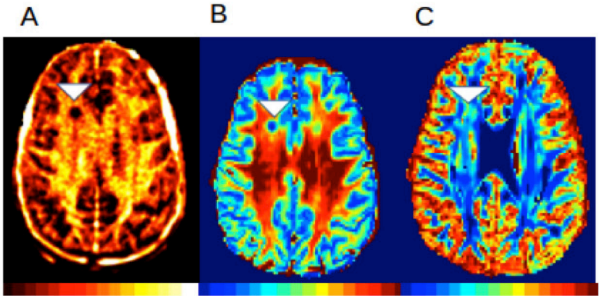

Figure 1. Myelin Water Fraction (MWF), Neurite Density Index (NDI) and Orientation Density Index (ODI) maps in one exemplary MS patient with a periventricular lesion (arrowheads) (A, B and C).

Results: We segmented 120 MSLs. MWF was significantly lower in MSLs compared to NAWM and WMHC ($p<0.0001$ and $p<0.001$). NDI was also significantly lower in MSLs compared to NAWM and WM HC ($p<0.0001$ for both). ODI in MSLs was higher than in NAWM ($p<0.001$) and WMHC ($p<0.01$) (Figure 2).%MWF reduction was significantly higher than%NDI in WM MSLs ($p<0.0001$, Figure 3).

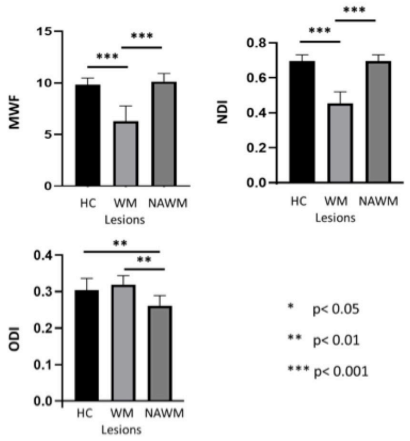

Figure 2. Average Myelin Water Fraction (MWF), Neurite Density Index (NDI) and Orientation Density Index (ODI) in MS lesions, normal appearing white matter (NAWM) and WM in Healthy Control (HC).

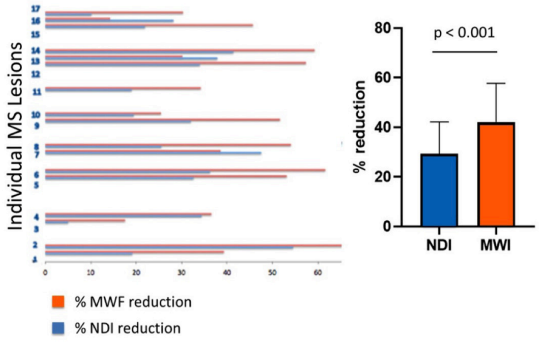

Figure 3. Percentage of reduction for Neurite Density Index (NDI, blue rectangles) and Myelin Water Fraction (MWF- orange rectangles) in individual MS lesions (Left) and on average (Right).

Conclusion: In this cohort of patients, MWF and NODDI metrics show a significant reduction in myelin and axonal density in MSLs compared to NAWM and WMHC. Furthermore, myelin damage appeared more extensive than axonal damage in WM MSLs.
Disclosure: Nothing to disclose

EPR2084

Thalamic energy dysregulation drives microstructural changes of thalamo-cortical projections in multiple sclerosis

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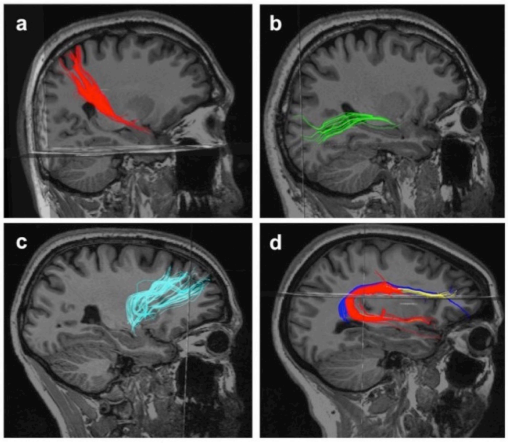
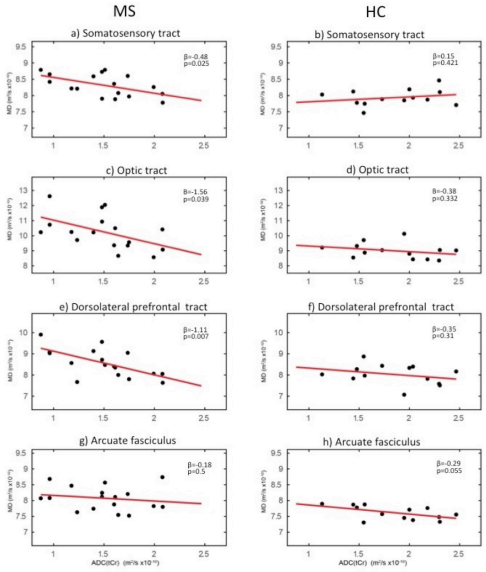
Background and aims: Neuronal energy dysfunction in multiple sclerosis (MS) has been proposed as a key driver of axonal degeneration. Diffusion-weighted 1H magnetic resonance spectroscopy (DW-MRS) can measure the diffusivity of creatine-phosphocreatine (Cr/PhCr), whose reduction in the MS thalamus has been proposed to reflect limited energy reserves. We tested in-vivo whether thalamic energy dysregulation is associated with microstructural degeneration of its projection tracts in MS.
Methods: Seventeen patients and thirteen healthy controls (HCs) underwent 3T MRI scan including DW-MRS and DW sequences. From DW-MRS, Cr apparent diffusion coefficient (ADC(tCr)) was extracted in the bilateral thalami. Thalamic projections to somatosensory, dorsolateral prefrontal cortexes and optic radiations (case tracts) and the arcuate (non-thalamic control tract) were manually drawn in TrackVis (Fig.1). Fractional anisotropy (FA) and mean diffusivity (MD), reflecting microstructural damage, were extracted for each tract. Associations between ADC(tCr) and microstructural parameters were tested using linear mixed-effect models.



T1-weighted images showing the tracts of interest manually drawn in TrackVis: somatosensory tract (a), optic tract (b), dorsolateral prefrontal tract (c) and arcuate fasciculus (frontoposterior [blue] + temporoposterior [red]+ frontotemporal [yellow] branches, d).

Results: In MS, lower thalamic ADC(tCr) was associated with lower mean FA and higher mean MD of pooled thalamo-cortical tracts after adjusting for disease duration, gender and tract-specific lesion load (p=0.033 and p=0.047). No correlation was found in HCs. Unadjusted tract-by-tract analysis confirmed the correlation between thalamic ADC(tCr) and MD in patients. The arcuate tract, not connected to the thalamus, showed no correlation (Fig.2).



Scatter plots showing unadjusted tract-by-tract results for the relationship between thalamic ADC(tCr) (x axis) and mean MD (y axis) in patients with MS (a-c-e-g) and HCs (b-d-f-h).

Conclusion: Thalamic ADC(tCr) was associated with specific microstructural damage of thalamo-cortical tracts in MS, suggesting that energy dysfunction in this crucial hub - through an impaired Cr/PhCr transport/utilization - may disrupt thalamo-cortical networks by inducing the selective anterograde degeneration of connected fibers.
Disclosure: Nothing to disclose

EPR2085

Predictors of long term brain atrophy among multiple sclerosis patients

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Background and aims: Brain atrophy is an important determinant of multiple sclerosis (MS) progression. We aimed at assessing predictors of the global cortical thinning in the long-term.
Methods: Among 219 relapsing remitting (RR) MS patients, followed for 7.9 mean years, we used regression analysis to assess factors affecting the global cortical thickness (Cth) loss.
Results: Fifty-nine (27%) patients converted to secondary progressive (SP) MS, in 6.1 mean years; this subgroup had, at onset, lower mean global Cth (SP=2.51mm, RR=2.58mm p=0.004), higher number of cortical lesions (CLs) (SP=6.5, RR=1.8 mean lesions; p<0.001), and displayed faster cortical thinning (SP=-1.31%, RR=-0.96% mean loss/year; p<0.001). Factors associated with more severe grey matter loss/year were gender (male=-0.74%, female=-0.60%; p=0.03), number of CLs at onset (0 CLs=-0.56%, 1-3 lesions=-0.63%, 4-6 lesions=-0.73%, ≥7 lesions=-0.78%, p<0.001) and number of relapses during the first two years (1 relapse=-0.47%, 2 relapses=-0.79%, ≥3 relapses=-0.94%; p<0.001). The white matter lesions number did not affect the rate of brain atrophy (lesions: ≤ 4=-0.68%, 5-8=-0.60%, 9-11=-0.67%, ≥12=-0.72%; p=0.13). In the multivariate model, larger accumulation of CLs (OR=3.47; p=0.01), faster cortical thinning during the first two years (OR=1.43; p=0.001), and ≥3 early relapses (OR=8.41; p<0.001) independently predicted a more severe global Cth loss over time.
Conclusion: Patients at higher risk of SPMS have more severe early cortical pathology and demonstrate faster rate of cortical thinning. The early focal cortical damage and early relapses affects the severity of grey matter loss in the long term and can be used to identify groups potentially benefitting from early aggressive treatment.
Disclosure: Nothing to disclose

Muscle and neuromuscular junction disease 1

EPR2086

MicroRNAs as serum biomarkers in Becker muscular dystrophy

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Background and aims: Becker muscular dystrophy (BMD), a neuromuscular disorder due to mutation in the gene encoding dystrophin, is characterized by progressive proximal muscles involvement and wide clinical variability. MicroRNAs (miRNAs) are small non coding RNAs acting as post-transcriptional regulators. Levels of miRNAs selectively involved in muscular pathways have been found upregulated in serum of patient affected with muscular dystrophies and have been called myomirs (miR-1, miR-31, miR-133a, miR-133b, miR-206).
Methods: We analysed serum levels of these five miRNAs in 12 BMD patients and 6 healthy controls of the same age. MicroRNAs, purified from serum, were dosed trice per patient, using RT-PCR and pre-amplification. Levels obtained as mean of threshold cycle were normalised, using miR-223 as endogenous control and Ct method, and expressed as relative variation compared to healthy subjects.
Results: The mean age of the patients was 40.3±11.8 years and the majority of them carried a deletion of exons 45-47. MiR-1 (x 10; p=0.024), miR-133a (x 11; p <0.001), miR-133b (x 8; p=0.001) and miR-206 (x 29; p=0.003) were overexpressed in the serum of BMD patients, while miR-31 dosage did not revealed significant differences.
Conclusion: Our data confirmed an upregulation of serum levels of these miRNAs in patients with Becker muscular dystrophy, as previously reported in other small studies. Therefore, serum myomirs seems to be a promising non-invasive biomarker in BMD, that may be used also in clinical trials. Further evaluations are still needed in order to correctly correlate their changes with the clinical stage.
Disclosure: Nothing to disclose

EPR2087

Age of onset, cardiovascular pathologies and genotype affect prognosis of type 1 myotonic dystrophy (DM1): longitudinal experience from 21 years of a neuromuscular clinic

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Background and aims: Myotonic dystrophy type 1(DM1) has progressive course with multiorgan involvement. Cardiovascular, respiratory dysfunctions are major causes of morbidity and death.
Methods: This study included 33 DM1 with abnormal CTG expansion of DMPK gene referred to our Center between 1998 and 2018. Participants were assessed with following criteria: (1)CTG repeat number, (2)Muscular Impairment Rating Scale (MIRS), Medical Research Council Scale (MRC),modified Rankin Scale (mRs). Probability of death, invasive ventilation (IV) and neurological worsening were the primary outcomes, estimated by binomial, multinomial, logistic regression and survival analysis. Multiple imputation model was used in cases of missing values. Variance analysis compared scores among groups at baseline and end of follow-up. P-value <0.05 was considered significant.Independent variables were gender, age of onset, CTG-repeat number, cardiovascular co-pathologies, EMG changes, CPK level.
Results: Thirty-patients were included.Male/female ratio was 1:1.Median follow-up time was 100 months (Range 24-220).CTG-repeat number was either NE1 or NE3 in 30%;13 cases were classified as NE2.Cardiovascular pathology occurred in 67%, cognitive dysfunction in 37%, endocrine in 51%. Death occurred in 12% at mean age of 62; 36% of patients needed IV at mean age of 48. Age of onset above or below 30 was an independent predictor of IV (HR 4.96,p=0.04). Worsening on MIRS was significant (p=0.0003) and significantly affected by CTG-repeat number (HR 3.42, p=0.001).Cardiovascular pathologies increased risk of IV (OR 11.4, p=0.03).
Conclusion: CTG repeat number,cardiovascular co-pathologies, earlier age of onset are independent predictors of prognosis in DM1.
Disclosure: Nothing to disclose

EPR2088

Clinical burden of myasthenia gravis in England: results of a longitudinal, retrospective, observational study using linked data from CPRD and HES

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Background and aims: Data on the long-term clinical burden of myasthenia gravis (MG) are critical to inform decision-making about its treatment, but few longitudinal studies have been performed.

Methods: We took advantage of the Clinical Practice Research Datalink and linked data from the Hospital Episode Statistics database collected during 1997–2016 to quantify diagnosis of comorbidities and incidences of exacerbations, crises, and hospitalisation after MG diagnosis in adult patients in England. Patients with MG were classified as refractory to conventional treatment based on receipt of immunosuppressive therapies and hospital treatments (Figure 1).

Results: 1,149 patients with MG were included, of whom 66 (5.7%) were classified as refractory, along with 252 non-MG control patients matched 4:1 with the refractory MG patients for age, sex, and general practice (Figure 1). Data were available for a median of 88.2 months before and 47.2 months after the index episode. After the index episode, patients with refractory MG more often developed diabetes (with or without complications) and congestive heart failure than non-MG control patients and more often developed renal disease, hypertension, psoriasis, and psoriatic arthritis than both non-refractory MG patients and non-MG control patients (Figure 2). Although incidences of respiratory crises, exacerbations, and MG-related hospitalisations decreased over time for refractory and non-refractory MG patients, rates remained higher for refractory MG patients for up to a decade after the index episode (Figure 3).

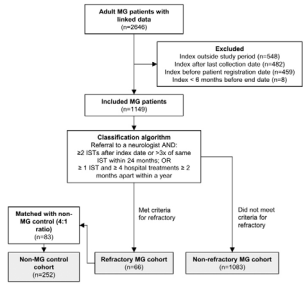

Figure 1. Patient selection and classification
Patients were included in the study if they had a diagnosis code for MG according to a Read code in Clinical Practice Research Datalink or an ICD-10 code in the Hospital Episode Statistics, were ≥ 18 years of age at their first MG diagnosis (index date), were registered with their general practitioner during the study period, had data in the Clinical Practice Research Datalink, and belonged to a general practice that was linked to the Hospital Episode Statistics database. MG patients were identified as refractory to conventional treatment using an algorithm from a US study (Engel-Nitz et al. Muscle Nerve, 2018 Feb 27) adapted for the English setting. The non-MG control cohort comprised patients without a diagnosis of MG randomly matched in a 4:1 ratio to patients in the refractory MG cohort for age, sex, and general practice. Patients included in the non-MG control cohort had to be ≥ 18 years of age at the reference date (i.e. index date of the matched refractory MG patient) and have ≥ 12 months between the up-to-standard date and the matched reference date without a diagnosis of MG. Abbreviations: IST, immunosuppressive therapy; MG, myasthenia gravis.

Figure 1. Patient selection and classification

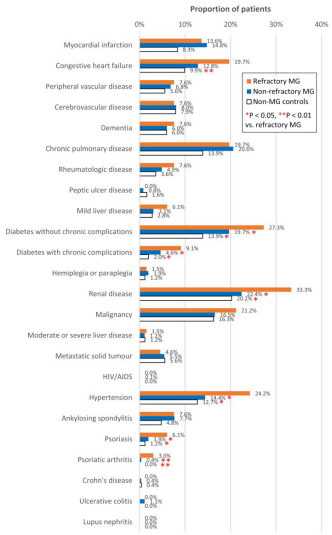

Figure 2. Comorbidities diagnosed after the index MG episode.
Abbreviation: MG, myasthenia gravis.

Figure 2. Comorbidities diagnosed after the index MG episode

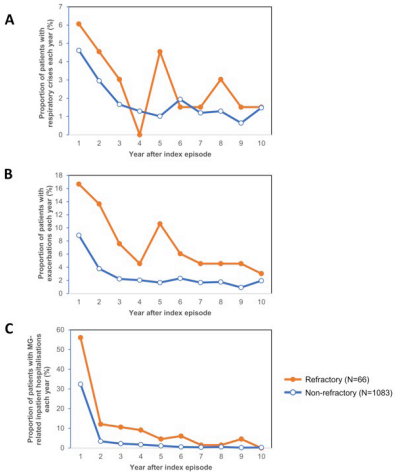

Figure 3. Annual incidence of respiratory crises (A), MG exacerbations (B), and MG-related inpatient hospitalisations (C) after the index episode in patients with refractory MG and non-refractory MG. Abbreviations: MG, myasthenia gravis.

Figure 3. Annual incidence of respiratory crises (A), MG exacerbations (B), and MG-related inpatient hospitalisations (C) after the index episode in patients with refractory MG and non-refractory MG

Conclusion: These results show that, despite receiving immunosuppressive therapies, patients with refractory MG develop more comorbidities and continue to experience more severe events than non-refractory patients.

Disclosure: This study was funded by Alexion Pharmaceuticals.

EPR2089

Multiplex ligation-dependent probe amplification in undiagnosed autosomal recessive limb girdle muscular dystrophies

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Background and aims: Limb girdle muscular dystrophies (LGMD) type 2A and 2B are genetic disorders associated with biallelic mutations in CAPN3 and DYSF genes. Sequencing of CAPN3 and DYSF is laborious and time-consuming due to the large size of coding sequence and the absence of mutational hot spots. Although next-generation sequencing (NGS) has improved the diagnostic rate, the molecular diagnosis in few LGMD2A/2B patients remains elusive.
Methods: Multiplex ligation-dependent probe amplification (MLPA) allows the detection of deletions/duplications of one or more exons within a single reaction. We applied this method to a cohort of LGMD patients displaying a clinical suspect of LGMD2A (n=18) or LGMD2B (n=13). Western blot analysis confirmed the reduction of calpain-3 and dysferlin protein levels. Conventional or Next-generation sequencing resulted in one or no candidate/causative mutations.
Results: MLPA improved the molecular diagnosis in 5 of 26 patients (19%). MLPA detected: i) an heterozygous CAPN3 deletion including exons 1-6 in a LGMD2A patient; ii) heterozygous DYSF deletion of exons 25-27 in two patients; ii) homozygous DYSF deletion of exon 55 in two subjects. Segregation was confirmed in available samples. No duplication was found.
Conclusion: MLPA analysis has been demonstrated to be useful in selected cases. MLPA allowed a firm diagnosis in 31% of undiagnosed LGMD2B patients. It should not be used as a screening technique because it is tailored for the suspected candidate gene. It is strongly suggested in cases with only one mutation identified and/or in case of protein absence at Western blot analysis. In the latter scenario, MLPA could precede gene sequencing.
Disclosure: Nothing to disclose

EPR2090

Patient reported outcome measures in myotonic dystrophy type 2

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Background and aims: Myotonic dystrophy type 2 (DM2) actually lacks of disease-specific, validated, outcome measures and patients' reported outcomes (PROs). This represents a limit for monitoring disease progression and response to symptomatic therapies. Our aim was to identify the most appropriate patient reported outcomes to be adopted in future clinical trials on DM2
Methods: 62 DM2 patients fulfilled the following PROs: DM1-Activc, R-Pact, Fatigue and daytime sleepiness Severity Scale (FDSS), McGill-pain questionnaire, Brief-pain inventory (BPI), Beck depression inventory (BDI), Myotonia behaviour scale (MBS). Internal consistency and correlated with clinical features and motor function scales were performed
Results: DM1-active and R-Pact maintained a trend of increasing difficulty and high correlation (r=0.93), despite being built for myotonic dystrophy type 1 and Pompe disease respectively. A ceiling effect was however observed in up to 15% of patients. The BPI performed better than McGill and a good correlation with depression was observed (r=0,67). Fatigue confirmed to be a core symptom of DM2, fatigue-subscale of FDSS negatively correlated with endurance measures (as 6MWT or FI-2). No correlation was found between the MBS and the subpart muscle stiffness of the INQoL and neither with other clinical features, suggesting that MBS and myotonia INQoL might not properly depict the mild myotonia of DM2 patients affecting leg muscles rather than hands.
Conclusion: This pilot study represents the first attempt to identify and validate scales in DM2. In order to complete this first step of validation, a retest of the DM2 group and a control group assessment are ongoing.
Disclosure: Nothing to disclose

EPR2091

Outcome of patients with sustained hyperCKemia after statin treatment

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Background and aims: Musculoskeletal manifestations are frequent side effects of statins that usually resolved after its withdrawal. There is a subgroup of patients that persist with subclinical (hyperCKemia) or progressive myopathy. In some cases it's related to an inflammatory myopathy but in most of them the background remained unknown.
To describe the profile and outcome of a series of patients with persistent hyperCKemia post-statin.
Methods: Study of patients with persistent asymptomatic/paucisymptomatic hyperCKemia post-statin in a Neuromuscular Unit between 2010-2018. Demographic, clinical, laboratory, muscle MRI, biopsy and genetic studies (custom NGS panel) data were collected.
Results: The series included 68 patients, 49 were male, median age of 47 years. 49 patients remained asymptomatic/paucisymptomatic during the follow up, 19 patients developed weakness. 38 patients had CK level >3xUNL and 30 between 1.5-3x. CK elevation was maintained in the same level in 37 patients. Anti-HMGCR antibodies were positive in six out of 10 inflammatory myopathies. MRI showed abnormalities in 21 patients, including STIR hyperintensity in most of the inflammatory myopathies. Muscle biopsies were classified as unspecific features (30), mitochondrial proliferation (16), inflammatory myopathy (10) and other specific features (6). Genetic studies found causative mutations in 5 patients and probable pathogenic mutations in 10.
Conclusion: Post-statin hyperCKemia is a category of relative importance in the neuromuscular diagnoses (it represents 15% of a large series of hyperCKemia) and its management requires following the diagnostic protocol recommended in hyperCKemias. The causes are varied, among which are some serious and potential treatable cases. Pathogenesis is also diverse, often induced by the drug.
Disclosure: Nothing to disclose

EPR2092

Myopathy due to muscle glycogen synthase deficiency with adult onset: report of two unrelated cases

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Background and aims: GSD0 is a very rare metabolic myopathy due to glycogen synthase (GS) deficiency. So far, this condition have been described in few patients with childhood onset and severe cardiac involvement leading to sudden death in the first decade of life.
Methods: We report two unrelated adult subjects (pt1, F/43 and pt2, F/53) who were admitted to our Unit because of exercise intolerance and myalgia after physical exertion. Clinical examination revealed in both neck flexors and girdle muscles weakness at four limbs.
Results: Blood investigations were normal. Electromyography showed a myopathic pattern in both patients. Forearm test evidenced no rise of serum lactate. ECG, cardiac ultrasound and heart MRI were normal. Muscle MRI showed adipose substitution in thigh, gluteus and paraspinal muscles. Muscle biopsy revealed a marked depletion of glycogen at PAS stain. Muscle GS activity was virtually absent (0.001 and 0.002-n.v.12.5±1.2 nmol/min/mg). Muscle glycogen was markedly reduced (6.5% and 8% of n.v.). Sequence analysis of GYS1 revealed in pt1 a homozygous c.630G>C (p.D145H), in pt2 a IVS4+1 G>C homozygous mutation. In pt2, the parents and an healthy sister were heterozygous. On western blotting GYS1 protein was absent in skeletal muscle from both patients.
Conclusion: Our data showed that muscle GSD0 can present in a more benign form than previously reported, with pure myopathy, adult onset without cardiac involvement. These findings highlight the opportunity to considering this very rare condition in the evaluation of metabolic myopathies.
Disclosure: Nothing to disclose

Neurogenetics 2

EPR2093

withdrawn

EPR2094

Clinical and genetic spectrum of Leber's hereditary optic neuropathy caused by rare mutations of the mitochondrial DNA

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Background and aims: Leber's hereditary optic neuropathy (LHON) is the most common primary mitochondrial DNA disorder and frequently results in bilateral, severe central vision loss. Only 90% of LHON is explained by three primary causal mutations of the mitochondrial DNA (mtDNA).
Methods: Single-centre cross-sectional analysis of prospective cohort study. Patients seen in our outpatient clinic with clinical diagnosis of LHON and one rare causal LHON mutation were identified. All underwent complete mtDNA sequencing. Patients with rare mtDNA variants of uncertain significance or having one other known LHON causal mutation were excluded.
Results: In our cohort of 418 LHON patients, we identified 17 patients (4.1%) from 12 families. Ten rare causal mtDNA mutations were found in genes ND1, ND6 and ND4L. Five patients were female (29.4%). Age at onset was 6.0 to 59.0 years (mean 21.1±15.3). Seven had clinical onset at or before 16 years old. Two female patients with childhood onset of mild to moderate visual loss could be retrospectively diagnosed in adulthood, after LHON was diagnosed to their sons. No patient presented with additional neurological features. Clinically significant improvement was documented in six patients. Four of eight patients treated with idebenone had follow-up longer than six months; three of them showed significant clinical improvement.
Conclusion: There was phenotypical variability in age at onset, severity and prognosis. Awareness of causal rare LHON mutations is essential. By high clinical suspicion of LHON and no frequent causal mutation, complete mtDNA sequencing is warranted. Prompt confirmation of a LHON diagnosis is essential, given availability of potential disease-modifying treatment.
Disclosure: C. Catarino received speaker honoraria and travel costs from santhera pharmaceuticals, and travel costs from Gensight Biologics.

EPR2095

Ethnicity-specific genome-wide association study in Parkinson's disease

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Background and aims: Most genome-wide association study (GWAS) of Parkinson's disease (PD) have been centered on populations of European descent and new PD-susceptibility loci have been limited on non-European populations. We aimed to identify new ethnicity-specific genomic variants that are associated with Parkinson's disease (PD).
Methods: Study subjects included patients with PD (N=1,070) and healthy controls (N=5,000) who were unrelated and ethnic Koreans. Genomic data was produced by the Korean Chip (K-CHIP), Affymetrix Axiom KORV1.1 (variants number of 827,400), which contains the imputation GWAS grid (505,000 Asian-based grid), functional variants of nonsynonymous exome content (84,000 Korean-based grid and 149,000 cSNPs and InDels selected from 2,000 whole-exome sequencing and 400 whole-genome sequencing data that are polymorphic in Korean), pharmacogenetics variants, variants in genes involved in absorption, distribution, metabolism and excretion (ADME) of drugs, and expression quantitative trait loci (eQTL). Genomic analysis was performed after stringent sample and SNP quality controls.
Results: The SNCASNP rs3796661 had the most significant association with PD (OR=0.69, CI=0.62-0.76,P=3.79Í10-13). The SLC41A1SNP rs708726 was the second most significant loci (OR=0.75, CI=0.68-0.83, P=1.61Í10-8). Other variants in Chromosome 1 and Chromosome 6 showed the significant association with PD after Bonferroni correction.
Conclusion: This ethnicity-specific GWAS confirmed the association of the SNCAand PARK16with PD and suggested other variants in chromosome 6 as new risk loci for PD.
Disclosure: Nothing to disclose

EPR2096

withdrawn

EPR2097

Stroke-like onset of Creutzfeldt-Jakob disease in a patient with the PRNP V203I mutation

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Background and aims: Creutzfeldt-Jakob disease (CJD) is the most common human prion disease; it is usually sporadic, but about 10–15% of cases are familial (genetic CJD (gGJD)).
Methods: We report the case of a patient affected by gCJD characterized by stroke-like onset and tumultuous progression until death in four weeks.
Results: The patient was a 64-year-old man with an unremarkable clinical and familiar history, who had conducted a normal social and working life until symptoms appeared. The patient was admitted to the neurological ward with word-finding difficulties occurred suddenly four days earlier. After three days, the patient presented involuntary chewing movements. He underwent a brain MRI resulted negative for pathological findings. Few days later, the clinical general conditions rapidly worsened with deterioration in the state of consciousness that progressed to coma. A second brain MRI showed DWI hyperintensity of basal ganglia, insula and bilateral cerebral cortex, consistent with CJD diagnosis. This hypothesis was further supported by increased levels of 14.3.3 protein in cerebrospinal fluid and an EEG pattern of pseudoperiodic generalized triphasic slow waves. The patient died after three weeks; the autopsy finally confirmed the CJD diagnosis. The genetic analysis revealed the V203I point mutation in the PRNP gene, an extremely rare genetic variant with unknown penetrance, described so far in few patients in Europe and Asia (two in Italy).
Conclusion: We present a case of gCJD with some interesting peculiarities: the acute onset with expressive aphasia, never reported before for this genetic variant; the rarity of mutation; the dramatically rapid course of illness.
Disclosure: Nothing to disclose

EPR2098

Analysis of neurologic symptoms, diagnostic patterns, and provider perspective of acute hepatic porphyria among EU-5 countries

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Background and aims: Acute hepatic porphyria (AHP) is a family of rare genetic diseases, the most common being acute intermittent porphyria (AIP). AHP results from enzyme deficiencies involved in haem synthesis, leading to accumulation of neurotoxic haem intermediates, aminolaevulinic acid (ALA) and porphobilinogen (PBG), causing potentially life-threatening attacks and chronic symptoms. The study described neurologists' experience diagnosing AHP and characterized patients from United Kingdom, France, Italy, Germany, and Spain (EU-5).
Methods: EU-5 physicians (n=100) who actively managed AHP patients in the preceding year completed an online survey probing demographics, familiarity with diagnostic tests, and symptoms. Physicians reviewed a subset of patients' charts (n=304) and shared anonymized data (demographics, medical history, attacks, and symptoms).
Results: Physicians practiced a mean of 19 years and 18% were neurologists. Neurologic symptoms deemed AHP-related included abdominal pain (88%), neuropathy (61%), vomiting (63%), tachycardia (61%), seizures (57%), muscle pain (57%), and palpitation (57%). Patients were aged 40 years (mean), female (52%), with AIP (83%). Neurologists considered urinary PBG (78%), ALA (67%) and several non-specific tests indicative of AHP. For most patients (68%), diagnoses were assessed as uncertain (41%) or incorrect (27%). Misdiagnoses included polyneuropathy (56%), psychosis (44%), and fibromyalgia (47%). Patients had a mean of 1.9 attacks and 1.1 hospitalizations in the past year. Chronic symptoms were primarily pain (60%), weakness (59%), and fatigue (57%).
Conclusion: This study highlights the challenges diagnosing AHP due to non-specificity of symptoms and limited understanding of diagnostic procedures. AHP patients reported acute attacks and chronic symptoms, implicating both in the disease.
Disclosure: Study funded by Alnylam Pharmaceuticals.

Neurogenetics 3

EPR2099

Value of diagnostic plasmatic biomarkers for Niemann-Pick type C disease in adolescent/adult patients with selected neuropsychiatric symptoms: the NOX study

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Background and aims: Niemann-Pick type C (NP-C) is a lipid storage disorder with autosomal recessive inheritance. A treatment is available (miglustat), which demonstrated the best response if started early with minimal neurological disability. The objective of this study is to evaluate the usefulness of plasmatic NP-C diagnostic biomarkers (NDB) cholestane-5β,3α,6β-triol (C-Triol), 7-ketocholesterol (7-KC) and lyso-SM-509 within the diagnostic approach among adolescent/adult patients with selected neuropsychiatric symptoms.
Methods: Patients ≥-12-year-old were prospectively recruited from several French centers if they had at least one of the following cardinal manifestations (CM): 1) unexplained cerebellar ataxia or dystonia; and/or 2) unexplained cognitive decline; and/or 3) atypical psychosis. Patients were considered "complex" if they had ≥two CM. NBD were measured in all patients and, if positive, a genetic testing (NPC1 and NPC2 genes) was performed.
Results: 241 patients were screened for C-triol and 7-KC, and among them 132 for Lyso-SM-509 (this study is ongoing). 105 patients presented ataxia or dystonia as CM, 124 presented cognitive decline and 132 presented atypical psychosis. Biomarkers were considered positive in six patients: two had bi-allelic NPC1 mutations, three had no mutation, and one was lost to follow up. The two confirmed NP-C patients were "complex", as 100 other patients.
Conclusion: NBD proved to be useful in our selected population, with high yield of diagnosis especially among "complex" patients (2/102, 2%) and low false positive rate (3/240, 1.2%), with Lyso-SM-509 being the most accurate biomarker. Systematic NBD measurement in this population may accelerate NP-C diagnosis allowing earlier treatment initiation.
Disclosure: YN: honorarium for speeches from Amicus, Actelion, Orphan Europe, grants for research from Actelion, Leadiant Pharmaceuticals.

EPR2100

The spectrum of late-onset hereditary leukoencephalopathies among Russian patients

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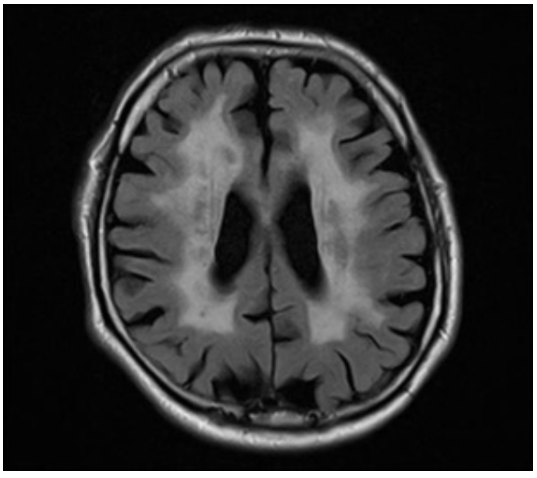
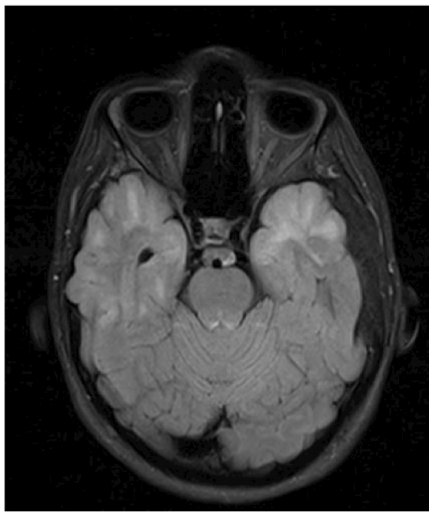
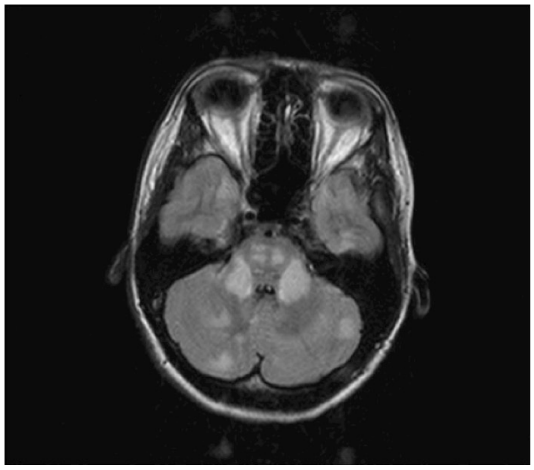
Background and aims: Leukoencephalopathies (LE) is a heterogenous group of the diseases affecting white matter and characterizing by similar clinical and neuroimaging features. Different conditions including vascular, demyelinating, mitochondrial as well as monogenous can cause LE.
The aim of this study was to reveal the most common types of hereditary LE, their frequency, clinical, neuroimaging and genetic features among adult patients of Russian ethnicity.
Methods: 243 adult patients with suspected hereditary LE underwent neurological and psychometric examination, neuroimaging and genetic testing.
Results: 30 cases of CADASIL, 11 cases of late-onset LE with lactate elevation, 2 cases with LE with spheroids, 1 case of FXTAS and 1 case of late-onset Krabbe disease were found. More than a half of the patients initially had a diagnosis of multiple sclerosis and received inadequate treatment.
All the patients had different combination of non-specific neurological (pyramidal, cerebellar, pseudobulbar) and neuropsychological (cognitive decline, depression, fronrtal dysfunction) symptoms.
Brain MRI revealed white matter hyperintensity in all the cases, but also some specific signs of CADASIL and LE with lactate elevation were found (Fig.1,2). White matter changes were found even on the early srages of the disease (Fig.3).



66 y.o. male patient, T2 FLAIR. Deep white matter hyperintensity



20 y.o. female patient, T2 FLAIR. Bilateral temporal pole hyperintensity



43 y.o. female patient, T2 FLAIR. Massive pons and middle cerebellar peduncles lesion

Conclusion: One can conclude that hereditary forms of LE are not as rare as supposed to be. Some early-onset forms can manifest in the adulthood and present without specific clinical signs. It often leads to misdiagnosis and wrong treatment. In is of great importance to be aware of hereditary LE, look for the "red flags", accurately collect family history and investigate neuroimaging features.
Disclosure: Nothing to disclose

EPR2101

Massive parallel sequencing as the important step in understanding the genetic etiology of cerebral palsy in Russian children

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Background and aims: Cerebral palsy (CP) is the most common cause of physical disability in children and it is usually caused by such factors as birth asphyxia, stroke and infection in the developing child's brain. Genetic studies have shown that more than 10% of CP cases can be caused by single gene mutations.
Methods: Study includes 83 children (35 girls, 48 boys), who applied for treatment with a directional diagnosis: CP and perinatal central nervous system damage. After medical genetic counseling all patients were subjected to molecular genetic testing by massive parallel sequencing.
Results: Mutation were detected in 68 cases out of the 83 children. 55 (81%) patients had dominant inheritance. 12 had mutations causing various forms of epilepsy, 29 had rare monogenic syndromes, 4 had mutations leading to myopathy, and the remaining 10 patients had different diagnoses including neurofibromatosis, various forms of ataxia and genetically determined forms of mental retardation. 13 (19%) patients had recessive inheritance. 10 of these children had different inherited metabolic diseases, two boys had pyridoxine-dependent epilepsy and another boy had pontocerebellar hypoplasia type 2A. Interestingly, among all 97 variants in 93 different genes only 44 variants have been previously described .
Conclusion: Our research shows a wide variety of masks - genetically heterogeneous diagnoses, behind that CP can be hiding. The use of modern diagnostic methods allows us to understand and explore the nature of CP better. A large number of previously undescribed mutations may indicate a insufficient knowledge and significant variability of the populations inhabiting the territory of Russia.
Disclosure: Nothing to disclose

EPR2102

Cross-sectional and longitudinal data of 36 patients harboring the mitochondrial m.3243A>G mutation

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Background and aims: In the Munich cohort, 36 patients were found to harbor the m.3243A>G mutation in the mitochondrial DNA (mtDNA). This pathogenic variant is often associated with mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS). We present results of the cross-sectional and longitudinal data analysis.
Methods: 102 data sets of 36 patients from the Munich center were analyzed with regards to disease manifestations, functional parameters and quality of life.
Results: The cohort consists of 22 (61%) women and 14 (39%) men with an average age of 44.3 years at baseline. The age at onset ranged from 3.7-72.5 years of age with an average of 29.4 years. The mothers of 19 (52.7%) patients were found to be symptomatic as well. The average time to genetic diagnosis was 14.7 years. Eight (22%) patients suffered from at least one stroke-like episode, 10 (28%) reported seizures with an overlap of 5 (14%) patients. Other manifestations are hypacusis (24;67%), glucose intolerance (17;47%), depression (12;33%), gastrointestinal symptoms (12;33%), ataxia (10;28%) and muscle weakness (8;22%). The average functional read-outs remained relatively stable across the cohort while the quality of life decreased over time.
Conclusion: Clinical manifestations of the most common MELAS mutation m.3243A>G are very heterogeneous. Hypacusis was the most common symptom followed by glucose intolerance and depression. Only 22% of patients suffer from the characteristic stroke-like episodes while seizures occurred in nearly a third of all patients. Across the cohort quality of life deteriorated over time albeit functional impairment remained comparably stable, which will be subject to further investigation.
Disclosure: Nothing to disclose

EPR2103

SMANDOP: new phenotype of homozygote POLG gene mutation in consanguineous moroccan patient

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Background and aims: Sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) syndrome is characterised by a triad of sensory or cerebellar ataxia, dysarthria and opthalmoparesis. However, there is a wide phenotypical variation among patients.
This disorder most often results from mutations in the POLG1 gene.
Methods: A 25-year-old Moroccan man presented with symptoms of ophthalmoparesis. He developed further sensori-motor ataxic neuropathy, and dysarthria. Nerve conduction studies found a severe axonal sensori-motor polyneuropathy.
Results: Skeletal muscle biopsy revealed ragged red fibers, and genetic testing showed a compound homozygous mutation in the POLG1 gene consistent with the diagnosis of SANDO syndrome with severe motor symptoms and psychiatric disorders (depressive mood, suicidal attempts and ideas) that we call "SMANDOP"for sensory motor ataxia with neuropathy dysarthria ophtalmoplegia and psychiatric disorders.
Conclusion: Clinical presentation of "SANDO syndrom" with POLG mutation is very heterogenous underlying interest of POLG gene sequencing in all SANDO spectrum to search for new mutation in despite different phenotype.
Disclosure: Nothing to disclose

EPR2104

Homozygous pathogenic variant in BRAT1 associated with non-progressive cerebellar ataxia

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Background and aims: To confirm the pathogenicity of a novel homozygous BRAT1 variant in two siblings with non-progressive cerebellar ataxia through functional studies on primary and immortalized patient cell lines.
Methods: BRAT1 protein levels in patient and control fibroblasts and lymphocytes were assessed by western blotting. DNA damage repair was evaluated by quantifying double and single strand DNA breaks in patient and control cells post treatment with established genotoxins. ATM activation was measured in patient and control cells after irradiation with 5Gy. The impact of the BRAT1 variant on mitochondrial function was assessed by comparing PDH-E1α phospho293 (S293) expression and oxygen consumption rates between patient and control cells.
Results: Two male siblings with non-progressive cerebellar ataxia, mild intellectual disability and isolated cerebellar atrophy were found to be homozygous for a c.185T>A (p.Val62Glu) variant in BRAT1 by whole exome sequencing. Western blotting revealed significantly decreased BRAT1 protein levels in both lymphocytes and fibroblast cells from both affected siblings compared to control cell lines. There were no differences in single or double strand DNA breaks, or ATM activation in fibroblasts or lymphocytes in the patients compared to controls. Mitochondrial studies were initially suggestive of a defect in regulation of pyruvate dehydrogenase (PDH) activity, but there was no evidence of increased phosphorylation of the E1α subunit of the PDH complex. Measurement of oxygen consumption rates revealed no differences between patient and control cells.
Conclusion: Bi-allelic pathogenic variants in BRAT1 can be associated with non-progressive cerebellar ataxia, a phenotype considerably milder than previously reported.
Disclosure: Nothing to disclose

Neuroimaging 1

EPR2105

Functional network connectivity predicts spreading of cortical atrophy in Parkinson's disease

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Background and aims: To decipher the mechanisms of network-based neurodegeneration in Parkinson's disease (PD) investigating the relationship between functional network connectivity (FC) in healthy brain connectome and cortical thinning in patients at the early disease stage, and to develop a predictive model for atrophy spreading in PD.
Methods: 86 early-stage PD patients performed 3D T1-weighted MRI at baseline and every year for 3 years. Resting state functional MRI (rs-fMRI) was obtained from 60 age- and sex-matched controls at baseline. Mean volumes for each region were calculated for PD patients and controls on 3D T1-weighted images. Regional percentage of atrophy in PD patients relative to controls was calculated at each time point: [1-(mean patient volumes/mean control volumes)]*100. Functional healthy connectome was estimated from rs-fMRI in controls. In PD patients, the "disease exposure" (DE) to pathology of each brain region at each time point was defined as a function of FC of the region with the whole brain in healthy connectome and the atrophy of the connected regions. DE during the first and second year of follow-up was used to predict atrophy at the subsequent time points.
Results: In early-stage PD patients, regional DE at 1-year follow-up predicted atrophy accumulation at 2-year follow-up relative to baseline. Although atrophy at 3 years was increased relative to 2-year follow-up, its variation didn't correlate with DE at any time point.
Conclusion: Our study suggests that disease propagation in PD follows functional network connectivity.
Disclosure: Supported by: Ministry of Education and Science Republic of Serbia (Grant #175090).

EPR2106

Amide as an imaging biomarker of amyotrophic lateral sclerosis

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Background and aims: There is a lack of objective imaging indicators for amyotrophic lateral sclerosis (ALS) diagnosis and assessment. This study aims to explore the value of amide proton transfer (APT) in ALS patients as a possible image biomarker of disease diagnosis, and the correlation between APT and diffusion imaging.
Methods: Amide proton transfer imaging, diffusion tensor imaging, and conventional MRI were performed on 32 participants at 3T. Lorentz fitting was introduced to quantify the amide effect. Analysis of covariance for APT was calculated between patients and controls, and between different regions within ALS patients. Correlations between APT and diffusion parameters were also measured.
Results: Within ALS patients, the amide peak was significantly different between the motor cortex and other grey matter territories. Compared with controls, the APT signal intensities in ALS were significantly reduced in motor cortex ($P<0.001$) and corticospinal tract ($P=0.046$), which were undetectable under routine imaging methods. In addition, APT was negatively correlated with FA ($r=-0.477$, $P=0.006$) and positively correlated with apparent diffusion coefficient (ADC) ($r=0.629$ and $P<0.001$).
Conclusion: To our knowledge, this is the first study demonstrating changes of APT in the motor cortex and corticospinal tract of ALS patients, which has the potential to be an objective imaging biomarker for ALS diagnosis. The combination of APT and DTI can simultaneously detect changes of metabolism and microstructure in ALS patients.
Disclosure: This study was supported by Canadian Institutes of Health, the ALS Society of Canada and Brain Canada, the Natural Science Foundation of China (NSFC81471730, 31870981), and the Natural Science Foundation of Guangdong Province (2018A030307057).

EPR2107

Elaboration of a radiologic score using a combination of brain imaging findings in idiopathic intracranial hypertension: a pilot study

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Background and aims: Although the association of brain imaging findings in idiopathic intracranial hypertension (IIH) could improve the ability to diagnose this condition, very few studies investigated the diagnostic values of the combination of these signs. The aim of this study is to investigate which combination of radiologic signs best diagnose IIH, and to elaborate a radiologic diagnostic score for this condition.

Methods: We conducted a retrospective study which included all patients diagnosed with IIH using the Dandy modified criteria, from 2010 to 2018 in our department. All cases were reviewed for the presence of brain imaging features of IIH. These signs were combined and the best model was selected.

Results: Ninety tree patients with IIH and 63 controls were included. The most specific signs of IIH were the presence of posterior flattening of the globe, distension of the optic nerve sheath and bilateral transverse sinus stenosis ≥50% in each sinus (98.2, 90.9 and 89.1%, respectively ; table I). The final radiologic score included the 3 above mentioned signs, an empty sella (≥category III of Yuh) and a vertical tortuosity of the optic nerves. We assigned 1 point for each sign. A global score ≥3 predicted IIH with a 86.5% sensitivity (95%CI 77.6-92.8) and a 96.4% specificity (95%CI 87.5-99.6 ; table II and figure).

Table I : Characteristics of individual brain imaging findings in IIH compared to healthy controls

	IIH patients with finding, n/N (%)	Sensitivity (%)	Control patients with finding, n/N (%)	Specificity (%)	*p*-value
Empty sella > category II	80/93 (86.0)	85.7	21/63 (33.3)	66.7	<0.001
Empty sella > category III	66/93 (71.0)	71.9	11 (17.5)	83.6	<0.001
Vertical tortuosity of the optic nerves	78/93 (83.9)	83.1	17/63 (27.0)	72.7	<0.001
Distension of optic nerve sheath	83/93 (89.2)	88.8	6/63 (9.5)	90.9	<0.001
Posterior flattening of the globe	69/93 (74.2)	74.2	1/63 (1.6)	98.2	<0.001
Combined Stenosis score ≤ 4	76/89 (85.4)	85.4	10/56 (17.9)	83.6	<0.001
Combined Stenosis score ≤ 5	81/89 (91.0)	91.0	17/56 (30.4)	69.6	<0.001
Combined Stenosis score ≤ 6	85/89 (95.5)	95.5	32/56 (57.1)	42.9	<0.001
Bilateral transverse sinus stenosis (score ≤ 2 in each sinus)	68/89 (76.4)	76.4	6/55 (10.9)	89.1	<0.001

Table 1

Table II : Items and performance of the radiological diagnostic score for IIH

	Score
Moderate empty sella (category ≥ III)	
Absent	0
Present	1
Vertical tortuosity of the optic nerve	
Absent	0
Present	1
Distension of the optic nerve sheath	
Absent	0
Present	1
Posterior flattening of the globe	
Absent	0
Present	1
Bilateral transverse sinus stenosis (≥ 50% in each sinus)	
Absent	0
Present	1
Total score ≥ 3	
Sensitivity	86.5% (95%CI 77.6-92.8)
Specificity	96.4% (95%CI 87.5-99.6)
Positive predictive value	97.5% (95%CI 90.8-99.3)
Negative predictive value	81.5% (95%CI 72.2-88.2)
Accuracy	90.3% (95%CI 84.2-94.6)

Table 2

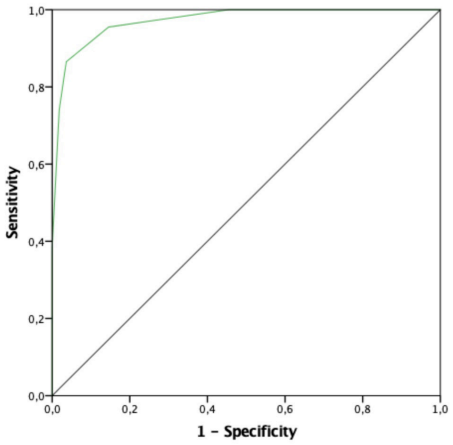

Figure : ROC curve of the radiologic diagnostic score for IIH.

Figure

Conclusion: The proposed radiologic score could help diagnose difficult cases and patients with IIH that do not fulfill the criteria, but should be validated by prospective studies.

Disclosure: Nothing to disclose

EPR2108

Composite UHDRS shows extensive spatial correlation with grey matter and white matter volume in Huntington's disease gene carriers

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Background and aims: Symbol digit modalities test (SDMT), Stroop word-reading test and total motor score (TMS) the most reliable clinical measures in Huntington's disease (HD). Recently a composite measure of motor, cognitive and functional outcome (cUHDRS) has been proposed as a sensitive clinical tool in early HD.
This work sought to determine the structural correlates of variability in cUHDRS in HD gene expansion carriers (HDGC).
Methods: Participants were recruited from the TRACK-HD study which included 120 premanifest (preHD) and 123 early HD patients. Clinical assessments were performed at four sites. 3T MRI data were acquired according to a standardized protocol. Nine participants were excluded from the analysis due to poor quality scan or incomplete clinical assessments leaving a total of 234 HDGCs (118 preHD and 116 early HD). Correlation analysis was performed using voxel-based morphometry (VBM) in SPM12. We studied the correlation between SDMT, Stroop, TMS and cUHDRS scores with grey matter (GM) and white matter (WM) volumes at baseline.
Results: Clinical impairment in HDGC was correlated with GM volume in caudate and putamen as well as. This correlation between cUHDRS and both GM (image 1) and WM volumes was spatially extensive and statistically significant.
Results were considered significant at cluster-level $p<0.05$ (FWE-corrected).

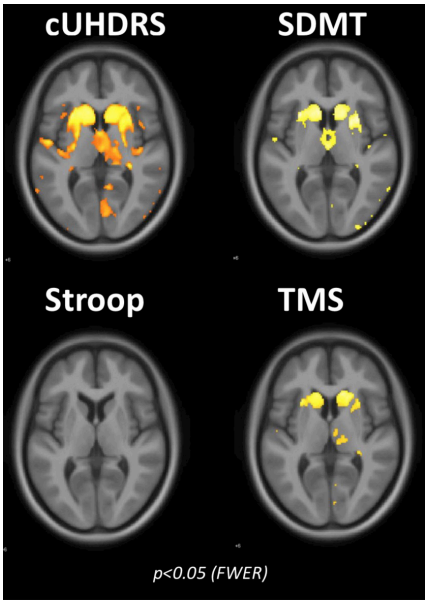

Image 1

Conclusion: In HDGCs, cUHDRS shows a significant correlation with GM and WM volumes in a fashion that extends throughout the basal ganglia and surrounding WM, suggesting this composite clinical measure links closely with underlying HD pathology.
Disclosure: Nothing to disclose

EPR2109

Progression of Parkinson's disease: a longitudinal MRI study of functional brain connectome in a large cohort of patients

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Background and aims: To investigate functional neural pathway organization and its changes over-time in Parkinson's disease (PD) patients.

Methods: 146 PD patients performed clinical and cognitive evaluations and resting-state functional MRI at baseline and every year for 4 years. Cluster analysis identified two PD subtypes: 86 "early" and 60 "mild-to-severe" patients. Within the "early" subtype, two clinical groups were identified: "early-motor-predominant" and "early-diffuse", the latter having greater cognitive deficits and more frequent non-motor manifestations. 60 age- and sex-matched controls performed baseline assessments.

Results: "Early" PD patients showed a preserved global functional architecture at baseline and over-time. "Mild-to-severe" patients showed altered functional topological properties of the sensorimotor and parietal areas relative to controls. Longitudinal analysis showed a progressive deterioration of global functional features in "mild-to-severe", with a involvement of the sensorimotor, frontal, parietal and temporal regions. At baseline, a widespread pattern of decreased FC involving the basal ganglia, sensorimotor, frontal, parietal and temporal networks was found in "mild-to-severe" and "early-diffuse" patients relative to controls and in "mild-to-severe" relative to "early-motor-predominant" cases. When FC changes over-time were compared between subtypes, five patterns of progression were identified: 1) different trend of change; 2 & 3) similar trend of change, with or without FC difference between the groups; 4) different but stable FC over time in the two subtypes; 5) stable FC with no difference between groups.

Conclusion: Connectomics might represent a powerful approach to understand the pathophysiological process associated with PD progression.

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

EPR2110

Structural and functional organisation of the brain connectome in patients with different motor neuron diseases: a multicenter study

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Background and aims: To investigate structural and functional neural organization in amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS) and progressive muscular atrophy (PMA).

Methods: 173 ALS, 38 PLS, 28 PMA patients and 79 controls were recruited from three different centers. Subjects underwent 3DT1-weighted, Diffusion Tensor and resting-state functional MRI. Graph analysis and connectomics assessed global and local structural and functional topological network properties and regional structural and functional connectivity (FC).

Results: Compared to controls, ALS and PLS patients showed altered structural global network properties, while PMA patients showed unchanged global structure. All patient groups showed preserved global and local FC in each comparison. ALS and PLS patients showed altered structural local properties in sensorimotor, basal ganglia, frontal and parietal areas relative to controls, while only PLS patients demonstrated altered local structural alterations in sensorimotor network relative to PMA group. Widespread structural changes were observed in ALS and PLS patients relative to controls: decreased fractional anisotropy within the sensorimotor networks and in connections to the medial and lateral prefrontal cortex. ALS patients showed increased FC involving precentral, middle and superior frontal gyri, while PLS patients in the sensorimotor, basal ganglia and temporal networks relative to controls. ALS and PLS patients also showed decreased fractional anisotropy relative to PMA cases within the sensorimotor and frontal networks.

Conclusion: Network-based advanced MRI analyses provide an objective in vivo assessment of motor neuron disease related pathological changes, delivering potential diagnostic and prognostic markers.

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EPR2111

Life-long effects of extreme stress on brain structures – a holocaust survivor MRI study

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Background and aims: The neurobiological markers of extreme stress in Holocaust survivors (HS) compared to Czech age- and gender-matched control subjects (CS) without a personal or family history of Holocaust were investigated. Posttraumatic stress symptoms and posttraumatic growth were significantly more frequent in HS than CS.

Methods: 46 subjects (HS: 19 females, 9 males, median age 79,5 years; CS: 18 females, 10 males, median age – 80,0 years) underwent structural MRI study on 3T siemens prisma scanner.

Results: Voxel-based morphometry (VBM) displayed a significant grey-matter volume reduction in HS in the orbitofrontal cortex, insula, anterior cingulum, gyrus frontalis superior/medius, perirhinal and entorhinal cortex. The HS group was divided into two subgroups regarding the age at the end of the stressful period - under and above the age of 12 years in 1945. The reduction of grey matter was significantly more expressed in older probands.

VBM showed the decreased volume of grey-matter in HS in regions of salient network structures. The smaller volume of the cingulum and insula was repeatedly found in combat veterans with PTSD or in people with early-life stress experience. The age-dependent difference in the grey matter volume in the HS is unclear. This finding may be related to the time of duration of the stress exposure or different perceptions of the stress environment in very early childhood.

Conclusion: A significant reduction of grey matter volume in regions known to be involved in stress response, memory, limbic system, and salient system persists over 70 years after the long-lasting exposition to life-threatening stress.

Disclosure: Supported by Ministry of Health of the Czech Republic, grant No. NV18-04-00559 A.

Neuroimmunology 1

EPR2112

How to remove disease-causing autoantibodies - precision treatment for anti-MAG neuropathy

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Background and aims: Anti-myelin-associated glycoprotein (MAG) neuropathy is characterized by IgM autoantibodies that target the human natural killer-1 (HNK-1) carbohydrate epitope present in myelinated nerve fibres on MAG. The progressive demyelination and axonal damage of peripheral nerves causes patients to suffer neuropathic pain, tremors, sensory loss, and ataxia. While the reduction of anti-MAG IgM titers has been shown to clinically improve the symptoms, current treatment options are unselective and often inefficient. We developed a therapeutic glycopolymer that presents mimetics of the HNK-1 epitope multivalently on a polymer backbone. It specifically binds and eliminates the antibody in an immunological mouse model and abrogates the myelin binding. Here we investigated the IgM-glycopolymer binding characteristics, their elimination pathway, and potential immunomodulatory effects.
Methods: We characterized the tissue distribution, cellular uptake, and B cell binding by fluorescence microscopy and flow cytometry. The stoichiometry was determined by size exclusion chromatography, fluorescent analytical ultracentrifugation, and electron microscopy.
Results: The glycopolymer bound the IgM antibody in a stoichiometry of 1:1-1:2, forming small complexes that were quickly taken up by the mononuclear phagocyte system (MPS) of the liver and spleen in mice. Using human macrophages, we confirmed the active endocytic uptake. The glycopolymer neither activated nor suppressed B cells of anti-MAG patients or healthy controls and showed a favourable safety profile in rats and dogs with a dose-depended half-life of 30±10 min.
Conclusion: The targeted degradation of the pathogenic IgM autoantibodies through the MPS enables an antigen specific treatment option for anti-MAG neuropathy that can potentially be adapted for other antibody-mediated disorders.
Disclosure: B.E., P.H., and R.H. are co-founders of the University of Basel spin-off, Polyneuron Pharmaceuticals AG, whose activity is related to the subject matter of this abstract. B.E. is also a member of the board of directors. B.E. and R.H. are named as co-inventors on relevant patent applications.

EPR2113

Prevalence of MOG antibodies in a large cohort of multiple sclerosis patients: a multicentre cross-sectional study

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Background and aims: Myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) have been reported in adult patients with acquired demyelinating diseases, mainly associated to optic neuritis (ON) or neuromyelitis optica related phenotype. Although MOG-Ab-associated disease seems to define a separately entity from multiple sclerosis (MS), evaluation of presence and frequency of MOG-Ab in a large unselected MS cohort is still lacking.
Our aim is to address frequency of MOG-Ab among MS patients.
Methods: Cross-sectional study performed in two tertiary referral MS centers between December, 2017 and June, 2018. Patients aged≥18 years with a definite diagnosis of MS according to McDonald 2010 criteria were tested for MOG-ab by cell-based assay, and subsequently included.
Results: Serum samples from 686 consecutive MS patients were analysed for MOG-Ab. Median age of disease onset and at sampling was 28.5 (interquartile range [IQR], 22.1-37.2), and 42.8 (IQR, 33.7-51.0) years, respectively. Five per cent had a clinically isolated syndrome, 61.5% Relapse Remitting, 19.2% Secondary Progressive and 14% Primary Progressive MS. Two (0.29%) patients resulted to be MOG-Ab-positive after a median disease duration of 11.4 (IQR, 5.8-17.7) years. The two patients were female, aged 42 and 38 at disease onset, and were diagnosed with secondary and primary progressive MS, respectively. No history of typical symptoms of MOG-Ab-associated disease (ON, myelitis or brainstem symptoms) was found in both patients, therefore questioning the specificity of autoantibodies in these 2 cases.
Conclusion: MOG-Ab are not associated to MS and then should not be tested in typical MS presentation.
Disclosure: Nothing to disclose

EPR2114

Antibodies against NF155 are associated with severe and chronic forms of Guillain-Barré-Syndrome in children

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Background and aims: The identification of autoantibodies to paranodal epitopes of the peripheral nervous system in immune mediated neuropathies, including Guillain-Barré-syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) has led to new insights and therapeutic implications regarding these diseases. A systematic screening of children with immune mediated neuropathies associated with paranodal antibodies hasn't been performed yet.
Objective: To report the clinical course and its correlation to antibody status of children with GBS/CIDP.
Methods: 50 children with a history of immune mediated neuropathies, who were referred from different hospitals in Germany and Austria between 2006 and 2018 were included in this retrospective study. From the majority of children, a complete clinical data set including CSF and nerve conduction studies (NCS) and documented course of the disease was available. Serum samples were screened for autoantibodies (abs) against different epitopes including neurofascin 155 (NF155) and contactin1 (CNTN1) by use of tissue-based and cell-based assays.
Results: Patients' mean age was 10 years (range 1-18) male to female ratio was 31:19.
26 had AIDP, 6 AMAN/AMSAN, 4 MFS, 2 MFS/GBS overlap and 8 CIDP. Four patients with GBS couldn't be sub-classified due to lack of NCS.
NF155 abs were detected in two children, both of whom had a long and protracted disease course requiring different forms of immunomodulation.
Conclusion: In a small subgroup of children with severe GBS and subsequent chronic course, anti-NF155-abs were found. Studies of adult patients suggest the treatment with rituximab.
Disclosure: R. Höftberger receives grants from the "Jubiläumsfonds der Österreichischen Nationalbank", Project Number 16919 D. De Simoni receives grants from the GBS/CIDP Foundation International.

EPR2115

Diagnosing autoimmune encephalitis in clinical practice: application of the diagnostic algorithm in a single-centre cohort

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Background and aims: A syndrome-based approach to diagnose autoimmune encephalitis (AE) has been recently proposed (Graus, 2016). Little is known in literature about its application and no published study to date has analyzed in detail potential reasons for lack of criteria fulfillment in suspected AE. Our aims are to test feasibility of such criteria in a real world setting and to analyze the most relevant factors in criteria fulfillment.
Methods: We retrospectively applied such criteria to our cohort of AE patients (n=33; 19 autoantibody-positive in serum and/or CSF), following step-by-step the diagnostic process to final diagnosis.
Results: All the patients fulfilled criteria for possible AE (pAE). Final diagnosis was attributed as follows. Eighteen patients (55%) matched criteria for definite autoimmune limbic encephalitis (dALE); of these, 15/18 were autoantibody-positive and 3/18 were negative. Three patients fulfilled criteria for probable anti-NMDA-R AE (pNMDA). After recognition of the autoantibody, definite anti-NMDA-R encephalitis (dNMDA) was diagnosed in 4 patients, but surprisingly none of these had fulfilled criteria for pNMDA. Among 11 patients who didn't meet criteria for dALE or dNMDA, only one matched criteria for autoantibody-negative but probable autoimmune encephalitis (prAE-), while the others remained classified as pAE. Detailed criteria fulfillment analysis showed that CSF data contributed less often to reach final diagnosis, while EEG and MRI had a more relevant role.
Application of the algorithm and final diagnosis.
Conclusion: CSF showed limited value in diagnosing AE. Criteria for pNMDA encephalitis showed low sensitivity. Criteria for prAE- may be too restrictive. Data from our cohort of patients suggest the need for a potential criteria revision.
Disclosure: Nothing to disclose

EPR2116

CXCL13 Levels in LGI1- and CASPR2-autoantibody syndromes

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Background and aims: C-X-C Motif chemokine ligand 13 (CXCL13) is a cytokine secreted by stimulated antigen presenting cells which modulates B and plasma cell function and homing to germinal centres (GCs), mainly via the chemokine receptor 5. Plasma CXCL13 levels have been shown to be a marker of germinal centre activity1, and CXCL13 levels are elevated in the CSF of patients with multiple sclerosis[2], NMDA-R-antibody encephalitis[3],[4], and neuromyelitis optica[5].
Our objectives were to compare concentrations of CXCL13 in patients with LGI1- and CASPR2-antibody mediated syndromes, and correlate levels with clinical parameters and explore the concept of active GC reactions in these patients6.
Methods: Serum CXCL13 levels were determined by sandwich ELISA in 143 samples from 31 subjects: LGI1 (n=86 from 19 patients) and CASPR2 (n=37 from 12 patients), and healthy controls (HC, n=20), and evaluated with the Mann-Whitney test.
Results: LGI1-antibody patients showed higher serum levels of CXCL13 compared to CASPR2-antibody patients and HCs ($p<0.0001$, Figure). No differences were observed between CASPR2-antibody patientsand HCs ($p=0.1627$). While, overall, non-relapsing versus relapsing LGI1-antibody patients showed no differences, within individual patients the trends of CXCL13 gave informative dynamic data over time.

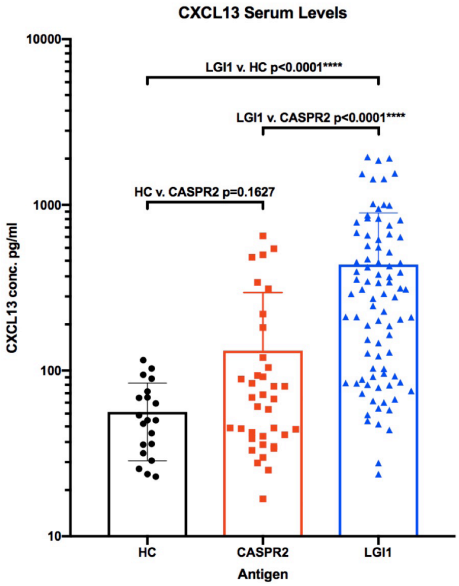

Figure: CXCL13 Serum Levels in LGI1- and CASPR2-Antibody Patients

Conclusion: Highest CXCL13 levels were detected in LGI1-antibody patients. There were clear dynamic changes, with markedly high levels at onset, and sharp rises during relapses. Overall, these findings suggest that sustained, ongoing GC-reactions may occur, particularly in LGI1-antibody syndromes, highlighting disparate mechanisms of disease perpetuation in the closely linked entities of LGI1- and CASPR2-antibody diseases, akin to dichotomous findings of HLA-associations in these patient groups7.

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Disclosure: Nothing to disclose

Neuro-oncology

EPR2117

Post-irradiation parkinsonism: an institutional series

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Background and aims: Large field irradiation is recognized as a well-known cause of leukoencephalopathy and cognitive decline. Few cases only of secondary parkinsonism in patients after brain tumor irradiation have been reported.
Methods: We collected from the database of the Department of Neuro-Oncology of Turin 6 patients with gliomas and 1 with single brain metastasis, who developed extrapyramidal signs during follow-up, that were not correlated to tumor involvement of basal ganglia.
Results: All patients underwent surgical resection and adjuvant radiotherapy. The onset of extrapyramidal disturbances occurred within the first year from radiotherapy in 5 patients, and after more than 16 years in the remaining 2. Neurological symptoms included bradykinesia, bradyphrenia and hypomimia in 4 patients, abnormal gait with camptocormia, and intermittent freezing in 2 others. Four patients also developed progressive cognitive decline, with apathy and memory deficits. In 5 out of 7 patients we observed a fast deterioration in the first months after the onset with a subsequent stabilization. MRI showed in all patients a widespread FLAIR hyperintensity of white-matter. DAT-SCAN scintigraphy was made in one patient and it was normal. Levodopa yielded a moderate improvement only in all patients.
Conclusion: These cases demonstrate that white-matter diffuse damage related to brain radiotherapy may be a cause of parkinsonism. In comparison with idiopathic Parkinson disease, parkinsonism following radiation displays a slow or absent progression, but is associated with cognitive decline and limited response to levodopa.
Disclosure: Nothing to disclose

EPR2118

An in vitro blood-brain barrier model for studying brain tumour metastasis

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Background and aims: Brain metastasis is one of the most common causes of death among patients suffering from cancer. A crucial step in brain metastasis formation is tumour cell transmigration and disruption of the blood-brain barrier (BBB). BBB structure complexity in vivo constitutes a great challenge for the development of suitable in vitro models. A transwell model has been developed which is composed of human endothelial cells, astrocytes and pericytes, with collagen IV which is a major basement membrane brain microvasculature constituent.
Methods: Barrier function was assessed by measuring permeability to FITC-albumin. In additional, trans-endothelial electrical resistance (TEER) was measured using chopstick electrodes and Voltammeter.
Results: Our model showed a 35-fold decrease in permeability (from 402 to 12 relative fluorescent units, $p<0.0001$) and a significant increase in TEER (from 138Ω to 197Ω, $p<0.005$) when compared to the empty insert control. No significant differences between the 3-cell type model and a simple monolayer of endothelial cells were noted. As validation, treatment of the in vitro barriers with 100μM histamine decreased TEER from 200Ω to 171Ω.
Conclusion: This 3-cell type transwell model shows low permeability and relatively high TEER, which makes it a suitable model for studying tumour cell extravasation into the brain. In addition, it is sensitive to histamine treatment, which indirectly confirms the presence of tight junctions. Further confirmation of tight junction formation and functional polarization of the cells is required to fully evaluate the model.
Disclosure: Grant support from FORCE Cancer Charity Exeter.

EPR2119

A collaborative study on the treatment of epilepsy in patients with glioblastoma

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Background and aims: Glioblastoma multiforme (GBM) is the most common glioma in adults and the most aggressive primary brain tumor. We investigated the occurrence of epileptic seizures secondary to GBM and the treatment with antiepileptic drugs (AEDs).
Methods: All adult patients with a primary diagnosis of GBM and at least one epileptic seizure related to the glioma were included at Haukeland University Hospital, Bergen, Norway or at the National Institute for Cancer Regina Elena, Rome, Italy. The total study population were 72 males and 28 females with median age 54 years at GBM diagnosis. All patients underwent surgery, of which 12 had a diagnostic biopsy only. Of 92 patients who received radiotherapy, 89 received concomitant temozolomide. Epileptic seizures were debut symptom in 49 patients. Levetiracetam was the first AED in 68 patients. Retention time was estimated with Kaplan-Meier method and differences assessed with log-rank test.
Results: Change because of inefficacy (p=0.91) was absent after one year in 85% (95%CI 75-95) of patients on levetiracetam compared to 76% (CI 61-91) of patients on other AEDs. Change because of adverse effects (p=0.05) was absent after one year in 93% (CI 86-100) of patients on levetiracetam compared to 76% (CI 58-94) of patients on other AEDs. Neither having epileptic seizures at onset nor treatment with levetiracetam improved the overall survival.
Conclusion: Change of AEDs because of adverse effects was less frequent with levetiracetam than other AEDs while change because of inefficacy was not significantly different between AEDs. There was no survival benefit neither from debut with epileptic seizures nor from treatment with levetiracetam.
Disclosure: This study was funded by Norsk epilepsiforbund and University of Bergen (PhD scholarship). The authors have no further disclosures.

EPR2120

D-dimer in Glioma: a possible predictor of overall survival

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Background and aims: Several studies over the last decade found a detrimental effect of coagulant thrombin and fibrinogen in primary brain tumors enabling tumor cell seeding and metastasis and leading to increased tumor cell growth and angiogenesis. To evaluate whether d-dimer, marker of fibrin turnover, may be increased in glioma patients compared to other neurological disorder and if its level may be related to particular disease features or be predictive for patient's survival.
Methods: This is a single-center, retrospective, longitudinal study. Serum d-dimer level (normal range 0-243ng/mL) of 139 consecutive glioma patients (46F/93M, median age 56.4 years) was compared with that of 48 consecutive relapsing-remitting multiple sclerosis patients (35F/13M; median age 40.2 years). The possible correlations of d-dimer level with glioma's and clinical characteristics were evaluated.
Results: D-dimer was significantly higher in glioma compared to multiple sclerosis patients (330±578 vs 134±107. P<.0001). D-dimer was higher in patients with Karnofsky-performance-status lower than 70 (491±826 vs 211±223, p=.01). D-dimer was not different in glioma subgroups divided according to gender, glioma grading, MGMT methylation and IDH1 mutation status, presence of recurrence, heparin and steroid therapy. Glioma patients with d-dimer level lower than median (<180ng/mL) showed a significant trend for a longer overall survival (27 vs 22.2 months, p=.08) and not significantly longer progression-free survival (14.5 vs 11.4 months, p=.16).
Conclusion: Our data showed an increased turnover of fibrin in glioma compared to multiple sclerosis patients as well as a predictive value of d-dimer for patient's survival regardless of their specific glioma or clinical characteristics.
Disclosure: Nothing to disclose

EPR2121

Characterization of chimeric astrocytic/neuronal cell cultures and neurospheres formation from human anaplastic astrocytoma and glioblastoma multiforme

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Background and aims: Grade III anaplastic astrocytoma (III-AA) and glioblastoma multiforme (GBM) exhibit increased cellularity, with stem-like properties. These cells show high propensity to form neurospheres, under specific culture conditions. Here, we studied neurospheres formation and cell differentiation in one III-AA (Pt1) and three GBM (Pts2-4) whose cells were grown either in serum or in serum-free medium+bFGF.
Methods: Tissues were minced, trypsinized and the cell suspensions centrifuged. Cells were then plated using two different culture media: i)DMEM+10%CS; ii)serum-free DMEM/F12 containing bFGF. The cell proliferation and neurospheres formation were evaluated. Furthermore, cell differentiation was studied using both glial-specific GFAP and neuron-specific NF-H Abs.
Results: All tumors showed IDH1/IDH2 mutations. In presence of serum, cells attached and proliferated. In DMEM/F12 medium+bFGF, clusters of cells formed that fluctuated over a layer of attached cells. Most of the cell clusters then became neurospheres, being more abundant in III-AA with respect to the GBM 2-4. When the neurospheres were dissociated and cultured, most cells acquired a plane morphology, with several showing neurite-like extensions. Cells, either primarily cultured in serum or derived from the neurospheres, strongly expressed both GFAP and NF-H.
Conclusion: In our four tumor samples, the propensity to form neurospheres was much higher in grade III astrocytoma than the other three GBM, and that it does not depends on IDH1/IDH2 genotype. This suggests that neurospheres might represent a further biomarker tumor growth. Furthermore, we show that tumor cells show a chimeric glial/neuronal phenotype, irrespective of the culture conditions. Next step will be to differentiate these cells towards a neuron-specific phenotype.
Disclosure: Nothing to disclose

Monday, July 1 2019
Ageing and dementia 4

EPR3001

Differential diagnosis of Creutzfeldt-Jakob's disease based on the metabolic brain imaging and network analysis

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Background and aims: Differentiation of Creutzfeldt-Jakob's disease (CJD) from other causes of rapidly progressive dementia may be challenging. Brain FDG-PET may help differentiate among neurodegenerative causes. A CJD-specific metabolic pattern (CJDRP) was identified previously (Fig.1), its expression was significantly higher in CJD compared to normal controls, Alzheimer's disease (AD) and behavior variant-frontotemporal dementia (bvFTD) patients on a group level. For distinguishing among these syndromes on a single-subject level, an expression of multiple metabolic patterns should be measured. Our aim was to build a logistic regression model to discriminate patients with CJD from AD and bvFTD based on the syndrome-specific metabolic brain patterns.

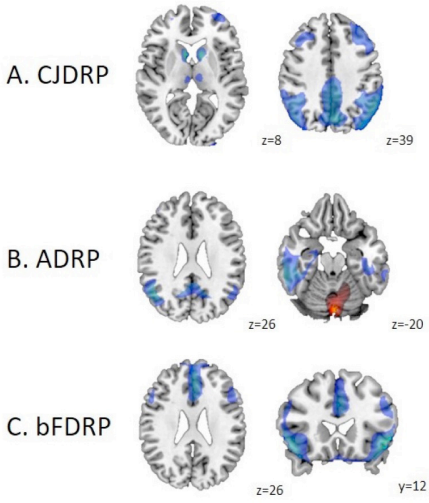

Figure 1. (A) CJD-related pattern was identified using multivariate SSM/PCA analysis of FDG-PET scans from 10 definitive CJD patients and 10 age-matched controls. The pattern expression correlated with disease duration, MMSE, clinical and functional scales. (B) AD-related pattern (Mattis, 2016). (C) bvFTD–related pattern (Nazem, 2018).

Methods: FDG-PET images from 10 pathologically confirmed sCJD, 40 AD and 25 bvFTD patients were analyzed. The expressions of CJDRP, AD-related pattern (ADRP) and bvFTD-related pattern (bFDRP) were calculated. A logistic regression model was built with CJDRP, ADRP and bFDRP z-scores as predicting variables and diagnosis of CJD and combined AD/bvFTD as a dependent variable. The model was validated on 5 sCJD, 17 amyloid-positive AD and 22 bvFTD patients. ROC analysis and discriminative measures were calculated for both models.

Results: The expressions of CJDRP, ADRP and bFDRP are presented in Fig.2. The logistic model classified correctly all but one CJD and two AD/bvFTD patients in the identification and all patients in the validation group. Predictive probabilities, cut-off values and ROC analysis are presented in Fig.3.

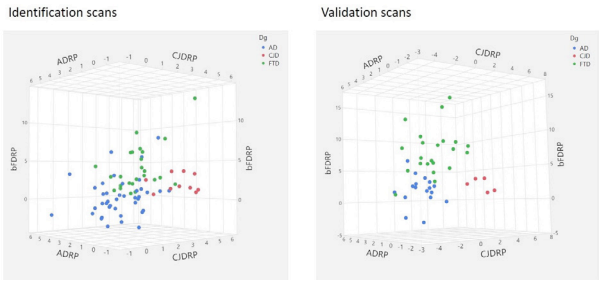

Figure 2. Tree-dimensional graph presenting CJDRP, ADRP and bFDRP z-scores for AD, CJD and bvFTD patients for identification (A) and validation group (B).

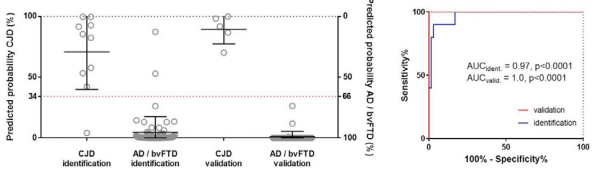

Figure 3. Predicted probabilities for CJD and alternative neurodegenerative cause (combined AD/bvFTD) calculated by logistic model. Optimal cut-off is presented with red line (p>34%; sensitivity 90%, specificity 97%). ROC curve for CJD is presented. AUC – area under the curve. The model achieved 100% sensitivity and specificity at validation.

Conclusion: FDG-PET brain imaging upgraded with network analysis and predictive modeling seems to be a reliable tool to improve the early differential diagnosis of CJD.

Disclosure: Nothing to disclose

EPR3002

Optical coherence tomography predicts cognitive decline in AD and MCI patients

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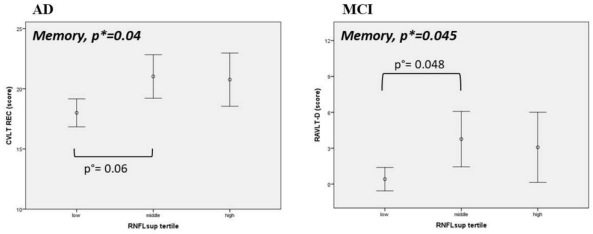
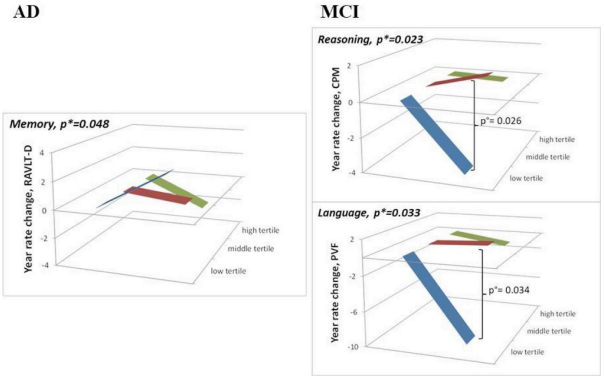
Background and aims: Neurodegeneration markers are needed to monitor the response to treatment in Alzheimer's disease (AD). The Neuro-retina represents a CNS tissue easily accessible for direct and non-invasive imaging through optical coherence tomography (OCT). Here we investigated whether the peripapillary retinal nerve fiber layer (RNFL) thickness at baseline may be associated with cognition and rate of cognitive decline at 6-18 month follow up in AD and mild cognitive impairment (MCI) patients

Methods: We measured the RNFL thickness, both the global value (RNFL G) and in the single quadrants (superior: RNFLsup; temporal: RNFLtemp; inferior: RNFLinf; nasal: RNFLnas) in a sample of 59 AD and 47 MCI. A full neuropsychological assessment was obtained at baseline and at 6-18 month follow-up. For each neuropsychological test, adjusted for age and education, a year rate of cognitive decline was calculated.



Cognitive performances of AD (left) and MCI (right) patients divided in tertiles depending on the RNFL thickness



Year rate cognitive changes in AD (left) and MCI (right) patients divided in tertiles depending on the RNFL thickness

Results: Both AD and MCI patients in the RNFLsup thinnest tertile performed worse than subjects in the higher ones in tests about the memory domain. AD patients in the thinnest RNFLtemp tertile showed a slower rate of cognitive decline in the memory domain. Contrarily, MCI subjects in the thinnest RNFLtemp tertile showed a faster decline on tests about language and reasoning

Conclusion: Peripapillary RNFL seems to mirror cognition in a disease stage-dependent manner. In the full-blown dementia, a thinner baseline RNFL is associated with a slower cognitive decline, probably due to a floor effect. On the contrary, in the early stages the thinner the baseline RNFL the faster the cognitive decline was, probably reflecting a more severe underlying neurodegenerative process.

Disclosure: Nothing to disclose

EPR3003

TOMM40 polymorphism is associated with cerebral β-amyloid load and clinical pathology in Alzheimer's disease dementia

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Background and aims: Mitochondrial protein dysfunction has been hypothesized as a driver of β-amyloid (Aβ) deposition in Alzheimer's disease (AD). We aimed to investigate the relationship between TOMM40 rs10524523 polymorphism and disease pathology in mild cognitive impairment (MCI) and AD.
Methods: We stratified a total of 44 MCI and 45 AD patients according to their TOMM40 rs10524523 carrier status of short (S), long (L) and very long (VL) into homozygous (S/S, L/L, VL/VL) and heterozygous (S/L, S/VL, L/VL) groups. We compared cerebral grey matter (GM) Aβ load and cognitive function between these groups and assessed the relationship between specific TOMM40 variants and disease burden.
Results: Groups carrying the S variant exhibited reduced cortical GM Aβ load globally ($P<0.02$) compared to other groups. Groups carrying the L variant exhibited increased cortical GM Aβ load in frontal, insular and cingulate regions ($P<0.05$), as well as worse delayed word recall (ADAS–CogQ4, $P=0.026$) compared to other groups. Carrying one or more copies of the S variant was associated with reduced cortical GM Aβ load globally ($r\leq0.2$ $P<0.03$), whilst carrying one or more copies of the L variant was associated with increased cortical GM Aβ load in frontal, parietal, temporal, insular and cingulate regions ($r>0.2$ $P<0.03$), worse cognition and delayed word recall (MMSE, $r=0.22$ $P=0.042$; ADAS–CogQ4, $r=–0.22$ $P=0.039$). No associations were found for the VL variant ($P>0.05$).
Conclusion: Our findings suggest that the S variant of TOMM40 is protective to MCI and AD disease burden, whilst the L variant of TOMM40 is detrimental.
Disclosure: Data collection and sharing for this project 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). Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report.

EPR3004

Mortality in dementia follows the time trend of mortality in the general elderly population: a national registry-based cohort study over twenty years

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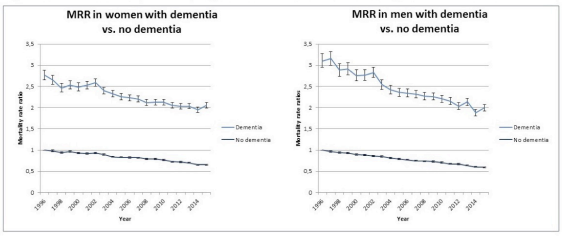
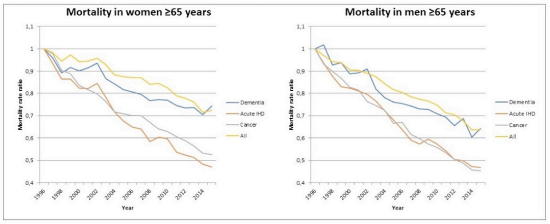
Background and aims: Whether the increased focus on improving health care and caregiving for persons with dementia has affected mortality in persons with dementia remains unclear. The aim was to assess time trends in mortality of dementia based on healthcare data of an entire national population from 1996 to 2015.
Methods: Using a cohort design, we linked longitudinal data on dementia status from nationwide registries on all Danish residents ≥65 years of age from January 1, 1996 to December 31, 2015. We assessed annual mortality rate ratios (MRR) in persons with dementia compared to those without dementia. The reference value of 1.00 was chosen for people without dementia in the year 1996.
Results: Our population comprised 2.00 million persons aged ≥65 years from 1996 to 2015. Of the 152,761 persons registered with a first-time dementia diagnosis in this period, 131,321 persons died. From 1996 to 2015 the age-adjusted MRR declined (women: 2.76 to 2.05; men: 3.10 to 1.99). Similarly, age-adjusted MRR in the general population declined from the reference 1.00 to 0.66 (women) and 0.60 (men).

Figure 1: Time trend of mortality rate ratios (MRR) of dementia vs. no dementia. Error bars represent 95% confidence intervals.



Conclusion: Mortality rates have declined in persons with dementia. However, mortality declined at the same rate in dementia as in the general elderly population, possibly reflecting a general improvement in health. In comparison, mortality in elderly persons with acute ischemic heart disease and cancer declined significantly faster than mortality in the general population during this period. Initiatives for improving health and decreasing mortality in dementia are still highly needed.

Figure 2: Time trend of mortality in all persons ≥65 years, and persons with dementia, cancer or acute ischemic heart disease (IHD).



Disclosure: The Danish Dementia Research Centre is supported by the Danish Ministry of Health, who was not involved in the design or evaluation of the results in this study.

EPR3005

Pathogen-induced autoimmunity and impaired proteostasis in Alzheimer's disease: a data-driven, in silico immunology approach

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Background and aims: The aim of this study is to create a data driven, in silico model of AD pathogenesis, using publicly available, gene expression data.

Methods: We searched GEO Datasets using the keywords /filters "Homo Sapiens", "Azheimer's". Differential gene expression was determined via the GDS viewer built – in analysis tools. Dataset meta-analysis was performed via the ImaGEO. Gene ontology annotations and the construction of protein-protein interaction networks was performed via STRING. BLAST was used to determine protein similarity between different taxons. Protein/oligopeptide antigenicity was determined via the RANKPep and Bepipred-1.0 software.

Results: According to the analysis design, 5 studies were eligible for inclusion in the analyses. 3 Hippocampal Cortex (HC) studies were meta-analyzed via ImaGEO, whereas 1 study of peripheral blood mononuclear cells (PBMC) and 1 involving entorhinal cortex neurons containing neurofibrillary tangles (EC – NFT) were analyzed via the GDS toolset. Significantly enriched pathways across CNS and PBMC datasets included ontologies associated with impaired proteostasis, viral parasitism and bacterial infections. BLAST revealed 853 gene – derived proteins from the EC – NFT study, significantly homologous with E.Coli proteins (minimum p<1.0e-100). Finally, RANKPep and Bepipred 1.0 revealed more than 29000 antigenic oligopeptides, derived from EC – NFT neurons.

Conclusion: By employing a data-driven, in silico approach, we reconstructed gene expression data in an integrated model where viral parasitism and infection mediate impaired proteostasis in AD. Furthermore, we characterized oligopeptides likely to serve as substrates to fuel infection-induced autoimmunity in the CNS.

Disclosure: Nothing to disclose

EPR3006

Comedication patterns in patients with dementia and their effect on all-cause mortality

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Background and aims: Comorbidities in patients with dementia are comparable in age matched cohorts. However, patients with dementia might be affected differently by the same disease or treatment.
Here, the aim was to analyze the pattern of comedication and their influence on all-cause mortality in patients with dementia.
Methods: Insurance claims were obtained from 13 sickness funds covering 98% of the Austrian population. We identified patients treated with anti-dementives in the period of 2005-16 and age- and sex-matched controls in a 1:3 fashion. Cox proportional hazard models were calculated to assess the association of comedication with all-cause mortality. The effect of dementia was assessed through interaction analysis.
Results: We identified 127986 patients with dementia and matched them to 342632 controls. 65.6% of the patients were female and the mean age at inclusion was 78.7 years. Dementia patients were treated with a mean of 5.1 comedications, controls received a mean of 5.7 ($p<0.001$). Dementia patients were less often treated for somatic (mean 3.7 vs 5 comedications) and more often for psychiatric comorbidities (1.4 vs 0.8, Table 1). The association with mortality was similar except for antidepressants and glucose lowering medication, which were associated with a reduced mortality in dementia but not in controls (Figure 1).

Table 1 - Demographics

	Dementia (n = 127986)	Control (n = 342632)	p-value
Age (mean (sd))	78.60 (8.94)	78.75 (8.56)	
Female (%)	83739 (65.4)	224780 (65.6)	
Deceased (%)	53480 (41.8)	110634 (32.3)	<0.001
Comedications (mean (sd))	5.08 (3.19)	5.74 (3.19)	<0.001
Somatic (mean (sd))	3.74 (2.58)	4.97 (2.66)	<0.001
Beta-blocker	38287 (29.9)	147917 (43.2)	<0.001
Diuretic	37030 (28.9)	120781 (35.3)	<0.001
Calcium antagonist	25767 (20.1)	106719 (31.1)	<0.001
RAS antagonist	60066 (46.9)	218160 (63.7)	<0.001
Anticoagulant	62768 (49.0)	192512 (56.2)	<0.001
Lipid lowering	37659 (29.4)	132977 (38.8)	<0.001
Glucose lowering	21197 (16.6)	62103 (18.1)	<0.001
NSAID	39618 (31.0)	209991 (61.3)	<0.001
PPI	68594 (53.6)	228394 (66.7)	<0.001
Analgesic	26910 (21.0)	114289 (33.4)	<0.001
Opiod	16756 (13.1)	63447 (18.5)	<0.001
Ginkgo	22989 (18.0)	73346 (21.4)	<0.001
Anti-parkinson	20390 (15.9)	31119 (9.1)	<0.001
Psychiatric (mean (sd))	1.35 (1.08)	0.78 (0.97)	<0.001
Antidepressant	67449 (52.7)	115701 (33.8)	<0.001
Antipsychotic	59994 (46.9)	55533 (16.2)	<0.001
Benzodiazepine	24828 (19.4)	63500 (18.5)	<0.001
Anticholinergic	28900 (22.6)	78713 (23.0)	0.004

Table 1 - Demographics

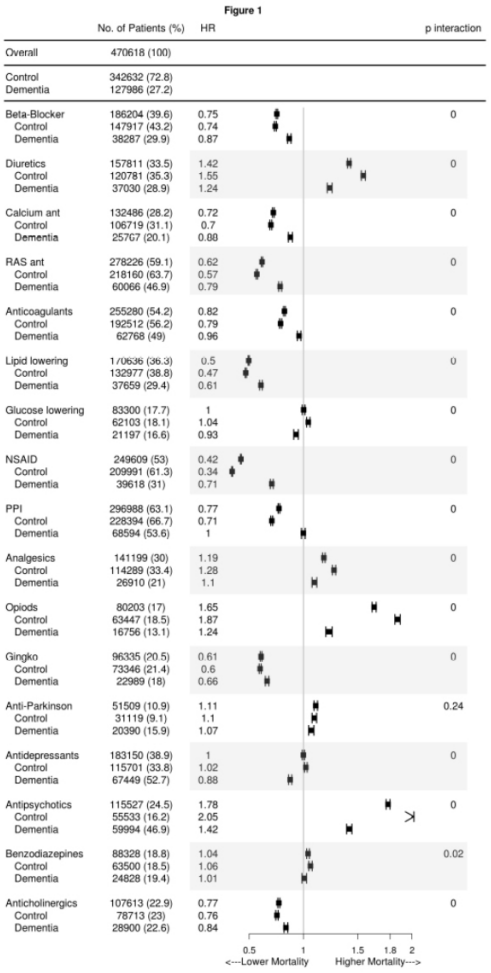

Figure 1 - Comedication and mortality

Conclusion: Insurance claims from a nation-wide database suggest undertreatment of somatic comorbidities in patients with dementia. Additionally, we find signals for a positive effect of antidepressants and glucose lowering drugs specifically in dementia - this warrants further study.
Disclosure: Nothing to disclose

Cerebrovascular diseases 5

EPR3007

TWIST tenecteplase in wake-up ischaemic stroke trial

M.B. Roaldsen[1], M.-H. Søyland[2], M. Jusufovic[3], A. Tveiten[4], E. Lundström[5], J. Petersson[6], J. Putaala[7], J. Kõrv[8], H.K. Christensen[9], D. Jatuzis[10], S. Engelter[11], G.M. de Marchis[11], D. Werring[12], T. Robinson[13], E. Mathiesen[14], E. Berge[15]
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Background and aims: Patients with wake-up stroke have traditionally been considered ineligible for intravenous thrombolytic treatment. Tenecteplase has pharmacological advantages over alteplase, and can be given as a bolus. We are performing a pragmatic, CT-based, randomised-controlled, open-label trial of tenecteplase for patients with wake-up stroke; the tenecteplase in wake-up ischaemic stroke trial (TWIST).
Methods: Patients with wake-up stroke <4.5 hours and without evidence of large infarct or ICH will be randomised to tenecteplase 0.25 mg/kg plus standard care or standard care alone. Plain brain CT and CT angiography will be done before randomisation and repeated on day 2. CT perfusion will be done at selected centres. Follow-up will be done at discharge (or day 7) and by telephone at 3 months. The primary effect variable is functional outcome at 3 months, measured by the modified rankin scale.
Results: The target is to include 500 patients from centres in Norway, Sweden, Denmark, Finland, Estonia, Lithuania, UK, and Switzerland. Start of patient inclusion: June 2017. Study questions to be answered:
1. Can thrombolytic treatment with tenecteplase within 4.5 hours of wake-up improve functional outcome at 3 months?
2. Can findings on CT angiography or CT perfusion identify patients who benefit from such treatment, compared to patients without such findings?
Conclusion: TWIST will show whether patients with wake-up stroke can be treated with tenecteplase within 4.5 hours of awakening, and whether multi-modal CT can be used for identification of patients who benefit from treatment.
Disclosure: Nothing to disclose

EPR3008

How to predict occult atrial fibrillation in patients after acute cryptogenic stroke

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Background and aims: In patients with embolic strokes of undetermined sources (ESUS), 20-37% have episodes of atrial fibrillation (AF) during extended monitoring. Studies of implantable cardiac rhythm monitors (ICRM) have demonstrated detection rates up to 30%. Hence, long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation in patients with ESUS. However, available resources and cost is currently limiting the use of this technology in all patients with ESUS. The present study is conducted to seek to refine and evaluate a novel scoring system that can stratify subjects into high-, intermediate- and low-risk groups for undetected AF in cryptogenic stroke.
Methods: Patients were included if routine work-up including, carotid Doppler and 24 Holter ECG monitoring did not expose the cause of stroke. Upon inclusion additional blood samples were drawn for the purpose of creating a biobank. Transthoracic- and transesophageal echocardiography and implantation of ICRM were performed in all patients during the index hospitalization.
Results: In total 251 patients are included. Among the 147 patients followed up for at least one year, 49 patients (33%) were diagnosed with atrial fibrillation, and were switched from antiplatelet therapy to OAC.
Conclusion: The study confirms that ICRM is a highly effective way to detect silent AF and to initiate adequate secondary prophylaxis in a timely fashion in patients with ESUS. However, it is a costly and resource intensive follow-up strategy. After completion of follow up we will use the results to build a scoring system for risk stratification for AF.
Disclosure: Nothing to disclose

EPR3009

Temporal trends for endovascular treatments in acute ischemic stroke in Italy

V. Saia[1], G. Pracucci[2], P. Nencini[2], D. Inzitari[3], F. Sallustio[4], R. Tassi[5], A. Saletti[6], P. Cerrato[7], R. Musolino[8], L. Chiumarulo[9], M. Magoni[10], F. Zappoli[11], N. Burdi[12], E. Ciceri[13], M. Ruggiero[14], A. Carolei[15], G. Passalacqua[16], S. Marcheselli[17], M. Cappellari[18], A. Cavallini[19], E. Duc[20], A. Sanna[14], A. Casalena[21], D. Toni[22], S. Mangiafico[23]

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Background and aims: Selection criteria for endovascular treatment (ET) in acute ischemic stroke (AIS) are rapidly evolving due to the results of recent trials. We aimed to explore the impact of these changes on clinical practice in Italy.

Methods: The Italian Registry of ET for AIS consecutively collects data of patients treated with ET in 43 comprehensive stroke centres. Efficacy measures are 3-month mRS 0-2, and TICI score 2b-3. Safety measures include symptomatic intracranial haemorrhage (s-ICH), procedural adverse events and death.

Results: From 2011 to 2017, 5559 patients were treated, median age 72 years, 51% male patients. Median baseline NIHSS was 18. TICI 2b-3 was achieved in 75%, and 3-months mRS 0-2 in 46% of patients. S-ICH and procedural adverse events accounted respectively for 8% and 4%. Death rate was 20%. From 2011 to 2017 patients aged ≥80 increased from 8% to 27%, as well as patients sent from Spoke Centres, from 20% to 37%. Time-based contraindication to intravenous fibrinolysis declined from 22% in 2011 to 14% in 2017. The use of thromboaspiration devices steeply raised from 17% in 2011 to 54% in 2017. A significant decline in time-to-groin puncture from 255 to 216 minutes and time-to-end of procedure from 351 to 290 minutes was observed through years.

Conclusion: Our results highlight changes in real-world management of AIS patients treated with ET in our country over time.

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EPR3010

Comparison of different service delivery for endovascular treatment for acute ischemic stroke in Italy

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Background and aims: There is no clear evidence on the best model for delivering endovascular treatment (ET) to eligible acute ischemic stroke (AIS) patients. We aimed to compare outcomes of patients directly admitted to a Comprehensive Stroke Centre (CSC) for ET with those of patients referred from Spoke Centres in Italy.

Methods: The Italian Registry of ET for AIS consecutively collects data of patients treated with ET in 43 comprehensive stroke centres. We divided patients in two groups according to access modality to a CSC, direct or indirect after Spoke selection. Efficacy measures include 3-month mRS 0-2, and TICI score 2b-3. Safety measures are symptomatic intracranial haemorrhage (s-ICH), and death.

Results: From 2011 to 2017, 5559 patients were treated, 72% presented directly to CSC and 28% were referred by a Spoke Centre. Median age was 72 in Hub and 71 in Spoke patients, median NIHSS respectively 17 and 18. Median time-to-groin puncture was 225 minutes in Hub patients vs 290 minutes in Spoke patients. No significant differences between the two groups were observed for outcome measures (TICI 2b-3, 75% vs 74%, and 3-months mRS 0-2, 45% vs 47%), nor for S-ICH (7% vs 9%). Death rate was 21% in Hub vs 18% in Spoke patients.

Conclusion: Despite delay in access to angio-suite for patients referred from Spoke Centres, our data show similar results for outcome in AIS patients treated with ET in both paradigms.

Disclosure: Andrea Zini received speaker fees and consulting fees from Boehringer-Ingelheim and Medtronic, and serves as advisory board from Boehringer-Ingelheim, Stryker and Daiichi-Sankio. Salvatore Mangiafico acts as a consultant for Johnson&Johnson. Danilo Toni received honoraria as member of Advisory Board and speaker honoraria from Abbott, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer. Unrestricted research grant from Boehringer Ingelheim. Other authors declare no potential conflicts of interest.

EPR3011

Long term surveillance for atrial fibrillation in patients with cryptogenic stroke using a implantable loop recorder in community hospital setting-long term results

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Background and aims: Atrial fibrillation (AF) detection rate of 30% has been shown at 3 year follow-up in stroke patients with long term monitoring in crystal AFIB trial. We present our real world community experience with long term surveillance for atrial fibrillation in a cryptogenic stroke cohort.
Methods: We reviewed electronic medical charts of our prospective cohort of cryptogenic stroke patients who underwent implantable loop recorder (ILR) from to March 2014 to December 2018. All patients met ESUS criteria prior to implantation and were enrolled in atrial fibrillation clinic with structured remote follow-up. All patients diagnosed with AF were contacted and offered anticoagulation.
Results: 432 patients underwent ILR insertion but long-term follow-up of at least 3 years was available in 144 patients. AF was found in 48 patients (33.33%) age range 43–88 average 71, 23 female and 25 male. Median time from index event to device insertion was 4 days (range 1–3628). Median time from insertion to AF detection 158.5 days (range 1-1074). Only one patient refused anticoagulation. Median time from detection of AF to anticoagulation was 1 day (range 1-11). Average CHAD2VASC score was 5. All patients had greater than 6 minutes of AF detected. No significant differences amongst age, gender and race noted between patients with and without AF detected.
Conclusion: 48/144 (33.33%) patients developed AF on long-term monitoring with ILR at 3 years follow up similar to findings of CRYSTAL-AFIb trial. All except 1 patient were started on anticoagulation soon after AF detection.
Disclosure: I have received speakers and consultant fees from Medtronic in the past.

EPR3012

The prognostic value of collaterals vessels status in large vessel ischemic stroke treated within the therapeutic window

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Background and aims: Time from symptoms onset is the major determinant for acute treatment decision in stroke. Nevertheless, some patients have a poor outcome even within the early time window. We aimed to describe the relationship between collaterals vessels status and acute treatment outcome in a cohort of acute ischemic stroke (AIS) with large vessels occlusion (LVO).
Methods: From our prospective database we selected patients with the following inclusion criteria: AIS within 6 hours from known symptoms onset, documented anterior circulation LVO, eligible to tPA and or thrombectomy according to current guidelines. Stroke outcome was measured at 90 days with mRS. Imaging features included baseline ASPECTS score, site of LVO and collateral status score evaluated blindly and independently by two experienced raters.
Results: 54 patients fulfilled the inclusion criteria: 19 received mechanical trombectomy, 7 intravenous tPA and 28 combined treatment. Median age was 74 years (IQR 66-78), onset-to-door was 70.7±54 minutes, baseline NIHSS score was 18 (IQR 14-22). Onset-to imaging was 97 (IQR 78-132) minutes with ASPECTS score of 9 (IQR 8-10). Collateral vessel status scored good in 39.0%, intermediate in 27.1% and poor in 33.9%.
Collateral status was independently associated with 3-month mRS ($p=0.035$); the effect of each collateral score one-step worsening on mRS score was estimated at 0.64 (±0.30) mRS units. Collateral status was not influenced by onset-to-imaging.
Conclusion: Our data suggest that collateral vessel status may influence the outcome of AIS patients with LVO treated within approved therapeutic window.
Disclosure: Nothing to disclose

EPR3013

The impact of vascular risk factors on microstructural changes of the brain in patients with cerebral small vessel disease

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Background: Cerebral small vessel disease (CSVD) is one of the main causes of cognitive impairment, ischemic and hemorrhagic strokes. Arterial hypertension (AH) is recognized as its leading risk factor, while the role of other vascular risk factors is not determined.

Aims: Assessment of the impact of vascular risk factors on brain microstructural changes in patients with CSVD.

Methods: The study included 73 patients (mean age 60.1±6.5, 47(64.4%) women) with CSVD according to STRIVE (2013). The control group consisted of 19 volunteers (mean age 56.9±5.4 years, 14 (73.7%) women). Classical vascular risk factors (AH, diabetes mellitus, hypercholesterolemia, obesity, smoking) and diffusion MRI with the region of interest analysis were evaluated in all patients. The relation between the parameters was estimated using multivariate linear regression.

Results: AH (82.4%, p=0.0001) and diabetes mellitus (20.8%, p=0.021) were significantly more common in patients with CSVD. Regression analysis showed the effect of age and hypercholesterolemia on the increase of radial diffusivity in the periventricular white matter hyperintensities (WMH) of posterior frontal lobes (R2=0.550), smoking and hypercholesterolemia - on the increase of axial diffusivity in the juxtacortical WMH of the anterior frontal lobes (R2=0.846). In both models, age and smoking had a positive correlation, hypercholesterolemia - a negative one with DTI parameters.

Conclusion: The results revealed the impact of age on the decrease in myelin density and smoking on the decrease in axonal integrity of white matter of the brain, while hypercholesterolemia showed a protective effect in patients with CSVD.

Disclosure: Nothing to disclose

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EPR3014

Cerebral vascular resistance and pulsatility in patients with carotid atherosclerosis

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Background and aims: Transcranial color-coded duplex sonography (TCCS) enables to detect and measure blood flow characteristics in cerebral vessels through intact scull, including resistance and pusalitility. Study aims to identify factors influencing the TCCS measured pulsatility (PI) and resistance (RI) indices in patients with atherosclerotic plaque in carotids (ClinicalTrials.gov Identifier: NCT02360137).
Methods: Self-sufficient patients with atherosclerotic plaque and stenosis 20-70% in carotid artery were consecutively enrolled to the study. All patients underwent duplex sonography of cervical arteries and TCCS with measurement of carotid artery stenosis, angle corrected blood flow velocities, PI a RI in middle cerebral artery, neurological and physical examinations. Following data were recorded: age, gender, weight, height, body mass index, systolic and diastolic blood pressure, current and previous diseases (arterial hypertension, diabetes mellitus, hyperlipidemia, vascular events, etc.), surgery, medication, smoking and daily dose of alcohol. Univariant and multivariant logistic regression analysis were used for identification factors influencing PI and RI.
Results: Totally 1724 patients (777 males, age 68.73±9.39 years) were enrolled to the study. Independent factors increasing PI/RI were age (odds ratio, OR=1.105/1.108 per 1 year), diabetes mellitus (OR=2.170/1.767), arterial hypertension (OR=1.700 for RI only) carotid artery stenosis (OR=1.260 per 10% stenosis for RI only), and male gender (OR=1.530 for PI only; $p<0.01$ in all cases).
Conclusion: Independent factors influencing cerebral vascular pulsatility and/or resistance are higher age, male gender, diabetes mellitus, arterial hypertension and percentage of carotid artery stenosis.
Disclosure: Study was supported by the Ministry of Health of the Czech Republic, grants No. 16-29148A, 16-30965A and 17-31016A.

EPR3015

Clinical, laboratorial and ultrasonographic interrelations in giant cell arteritis: the "halo sign" associates with more systemic involvement and risk of complications

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Background and aims: Temporal artery biopsy is the gold standard for giant cell arteritis (GCA) diagnosis; its limited sensitivity may be supplanted by "halo sign" in color-duplex sonography (CDS). We aimed to analyze clinical, laboratorial and histopathological findings in GCA patients with and without halo.
Methods: Retrospective study of consecutive patients of our center gathering American College of Rheumatology criteria for GCA that performed CDS. Data on clinical and laboratorial features [C-reactive protein, Erythrocyte Sedimentation Rate (ESR) and hemoglobin (Hgb)] was compared in two groups: with and without halo. T-Test/ Mann-Whitney and $\chi 2$ were applied ($p<0.05$).
Results: Ninety-one patients were included. The main clinical manifestations were headache (81%), systemic symptoms (57%) and optic ischemic neuropathy (50%). Temporal halo was identified in 46% of patients. The number of patients who received steroids before CDS (54%) was significantly higher in the subgroup without halo (62% vs 33%, $p=0.005$). Halo was more often present in older patients (77±7.69vs 73±8.20 years, $p=0.022$), associated with systemic features (58% vs 42%, $p=0.011$), higher ESR values (84±26vs 74±34mm/hr, $p=0.020$), lower Hgb values (10.94±1.5vs 12.12±1.6g/dL, $p<0.001$). In a post hoc analysis, stroke occurred in 17 patients (19%), 76% in the vertebrobasilar territory. CDS specificity was 98% compared with the final clinical diagnosis.
Conclusion: "Halo sign" was present in almost half of our GCA patients. Previous corticotherapy decreased the positive CDS findings. Stroke cases disproportionally affected the posterior circulation. Ultrasonography might signalize systemic involvement and a greater risk of major complications.
Disclosure: Nothing to disclose

EPR3016

Anterior circulation endovascular therapy outcomes according to occlusion site

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Background and aims: The clinical trials that established endovascular treatment (EVT) as a paradigm-changing treatment for acute ischaemic stroke (AIS) included mostly patients with proximal middle cerebral artery occlusions. Nevertheless, in clinical practice, patients with more distal occlusion sites are treated. We aimed to analyse the clinical outcome of these patients.

Methods: We retrospectively included 289 AIS patients submitted to EVT between 06/2015 and 06/2018. We collected demographic, clinical and imaging data. We defined a modified Rankin Scale(mRS) <3 or no deterioration from baseline as good outcome. We analysed predictors of outcome according to occlusion site.

Results: Overall, 117(40.5%) patients achieved a good outcome. Good outcome was associated with younger age [68(58-78) vs 77.5(69.5-83), p<0.001]. lower prevalence of hypertension (58.1% vs 74.4%, p=0.003), higher smoking prevalence (29.9% vs 15.7%, p=0.004), lower pre-stroke disability (78.7% vs 50% mRS 0-1, p<0.001), lower NIHSS at presentation [14(8-17) vs 18(15-21), p<0.001]. No significant differences in patient characteristics or TICI grade were found between patients with M1 or M2 occlusions. Nevertheless, we built an outcome prediction model including gender, age, presentation NIHSS and baseline mRS with an area under the curve (AUC) of 0.78(0.72-0.83). Occlusion site was then added to the model, with similar accuracy. When compared to M1 occlusion(n=199), M2 occlusion(n=42) had similar outcomes(OR=1.06(0.49-2.26), p=0.822). Carotid artery (CA) occlusion(n=43) showed a trend towards worse outcomes (OR=0.50(0.21-1.15), p=0.10).

Conclusion: In our AIS patient cohort, M2 occlusion had a similar impact on patient outcomes when compared with M1 occlusion. This should be considered when deciding to treat patients with more distally affected vessels.

Disclosure: Nothing to disclose

EPR3017

Performance evaluation of AECRS1.0 using stroke risk calculators

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Background and aims: Recently developed risk calcualator called AECRS1.010yr, integrated the carotid ultrasound image-based phenotyoed with convetional risk factors to compute a 10-year cardiovascualar and stroke risk. The AECRS1.010yr reported better performance whene compared against ten conventional cardiovascular risk calculators. However, AECRS1.010yr was not tested against the stroke risk calculators so far. In this study, we evaluated the performance of AECRS1.010yr against two stroke risk calculators.

Methods: 202 Japanese patient's left/right common carotid arteries were examined to obtain 404 ultrasound scans. Given conventional cardiovascular (CV) risk factors (CCVRFs) of these patients, we first computed 10-year stroke risk using two conventional stroke risk calculators (CSRCs) such as MyRisk_Stroke calculator (MRSC) and Framingham stroke risk score (FSRC). Then we computed 10-year stroke risk using the AECRS1.010yr by integrating five current image-based phenotypes and eight CCVRFs. Lastly, the performance of AECRS1.010yr against MRSC and FSRC was evaluated using receiver operating characteristics analysis using an event equivalence response variable as a gold standard. The event equivalence response variable was derived by combining four risk factors: (i) two from CCVRFs (glycated hemoglobin, and hypertension)

and two from carotid ultrasound image (maximum intima-media thickness and plaque score).
Results: Area-under-the-curve for AECRS1.010yr (AUC=0.80) was higher compared to the two MRSC (AUC=0.63) and FSRC (AUC=0.65).
Conclusion: AECRS1.010yr reported better performance compared to MRSC and FSRC thus it could potentially be implemented as a new stroke risk calculator.
Disclosure: Nothing to disclose

EPR3018

Neurofilament light chains for outcome prediction in ischemic stroke

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Background and aims: Serum neurofilament light chains (sNFL) are a marker of axonal loss in various neurologic diseases. We aimed to address their prognostic value in patients following acute ischemic stroke.
Methods: We selected patients from the Find-AF trial (ISRCTN46104198) with available serum samples 24h after hospital admission and further brain imaging (MRI or CT-Scans). sNFL levels were measured using the SIMOA technique. Infarct size on brain imaging was classified as lacunar (<10cm3) or non-lacunar (>10cm3). We assessed whether sNFL was associated with: (I) clinical severity on admission (II) lesion volume in brain imaging and (III) functional outcome after 3 and 12 months.
Results: 58 patients fulfilled the inclusion criteria with a median age of 73 years (IQR61-79). Among patients with acute ischemic stroke, sNFL levels were not associated with clinical severity (measured by NIHSS and mRS; p=0.83 and p=0.43, respectively) or lesion size in brain imaging at baseline (lacunar 80.3 pg/ml, non-lacunar 122.9 pg/ml, p=0.16). Nevertheless, baseline sNFL levels correlated with functional outcome as measured by mRS after 90 days: mRS≤2, 75.9 pg/ml; mRS>2, 110.8 pg/ml; p=0.018. This prognostic ability of sNFL was preserved for functional outcome measurements after 12 month: mRS≤1, 71.3 pg/ml; mRS>1, 99.7 pg/ml; p=0.044. The prognostic accuracy for prediction of stroke outcome is reflected by an AUC of 0.71 for the 3-month outcome and an AUC of 0.69 for the 12-month outcome (see Figure1).
Conclusion: sNFL levels after ischemic stroke predict clinical outcome after 3 and 12 months.

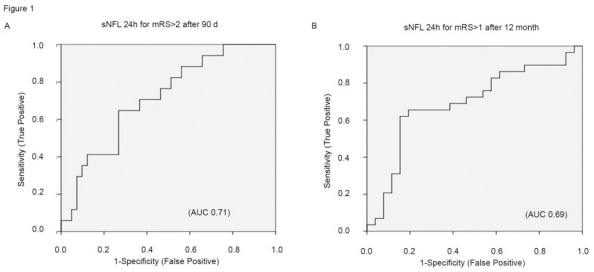

Figure 1

Disclosure: Nothing to disclose

EPR3019

Antiphospholipid antibodies as ischemic stroke prognostic factors

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Background and aims: Antiphospholipid syndrome (APS) is an autoimmune condition characterized by thrombosis and/or pregnancy morbidity and persistent positivity for antiphospholipid antibodies. It is one of the cause of ischemic stroke, usually in young, female patient. We aimed to seek the relationship between initial positivity of antiphospholipid antibodies in acute ischemic stroke patients and functional outcome.
Methods: We consecutively collected 562 patients with first-ever acute ischemic stroke within 7 days of initial symptom from January 2016 to October 2018. We retrospectively obtained the clinical and laboratory data of the patients from medical records. Antiphospholipid antibodies were measured the day after admission and the presence of at least one antibody was regarded as positive antiphospholipid antibody. We analyzed the effect of antiphospholipid antibody on the favorable function outcome of ischemic stroke defined as discharge modified Rankin score 0-1.
Results: Among 562 patients, 98 (17.4%) had positive antiphospholipid antibody initially. Positive antiphospholipid antibody was associated with older age, severe stroke symptom and the presence of atrial fibrillation. Three hundred twelve patients (56%) had favorable outcome at discharge. Unfavorable outcome was associated with older age ($p<0.001$), initial NIHSS score ($p<0.001$) and the presence of antiphospholipid antibody ($p=0.035$).
Conclusion: Antiphospholipid antibody after acute ischemic stroke was associated with poor outcome. Although many patients did not meet the criteria of antiphospholipid syndrome, antiphospholipid antibody alone can be used as prognostic factors. Strict follow up with those initial positive patients could provide more conclusive results.
Disclosure: Nothing to disclose

EPR3020

Comparison of rupture risk between familial and sporadic intracranial aneurysms: an individual patient data meta-analysis

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Background and aims: The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is higher in persons with than in those without a positive family history of aSAH. This higher incidence is in part explained by a higher prevalence of unruptured intracranial aneurysms (UIA), but it is unclear whether persons with a positive family history also have a higher risk of rupture of UIA. One study showed a 17-times higher rupture risk for patients with a family history of aSAH and a history of smoking or hypertension compared to patients with a sporadic UIA. We assessed rupture risk of familial versus sporadic UIA taking into account other risk factors for rupture.
Methods: We pooled individual patient data for 9,143 patients (853 familial patients, 9.3%) with 11,208 UIA and 22.003 person-years follow-up using data from 6 prospective cohort studies. Rupture rates per patient were analyzed with a Cox proportional hazard regression model stratified per cohort and adjusted for the PHASES score.
Results: Rupture occurred in 19 patients with familial UIA (rupture rate: 0.85%/person-year) and 187 patients with sporadic UIA (0.95%/person-year). The hazard rate (HR) for familial aneurysms compared to sporadic aneurysms was HR 0.98 (95% CI: 0.61-1.59) and the adjusted HR 1.39 (95% CI: 0.86-2.25).
Conclusion: We found a slightly but not statistically significantly increased risk of aneurysm rupture for familial compared to sporadic UIA. When assessing the risk of rupture in familial UIA, the family history is not as pivotal as previously assumed.
Disclosure: Nothing to disclose

Clinical neurophysiology; Neurological manifestations of systemic diseases

EPR3021

Resting state network functional connectivity abnormalities in systemic lupus erythematosus: correlations with neuropsychological and neuropsychiatric variables

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Background and aims: Neuropsychiatric manifestations are highly prevalent in patients with systemic lupus erythematosus (SLE), but their neural substrates still have to be elucidated. We investigated modifications of resting state (RS) functional connectivity (FC) in patients with SLE and their correlations with neuropsychiatric involvement.
Methods: Thirty-two SLE-patients and 32 age- and sex-matched healthy controls (HC) underwent brain 3T dual-echo, 3D-T1 and RS fMRI acquisition. A neuropsychological and neuropsychiatric assessment was performed for all SLE patients. Independent component analysis was used to derive the main large-scale cognitive functional networks. Between-group comparisons and correlations between RS FC abnormalities, neuropsychological and structural brain damage measures were performed.
Results: Compared to HC, SLE patients exhibited increased RS FC in the right middle cingulate cortex and decreased RS FC in the left precuneus within the default mode network (DMN), increased RS FC in the left cerebellar crus I and decreased RS FC in the left angular gyrus (L-AG) within the working-memory networks (WMNs) and decreased RS FC in the right middle frontal gyrus within the executive control network. Compared to non-depressed (n=21), depressed SLE patients (n=11) showed decreased FC in the L-AG within WMNs. In SLE patients, RS FC abnormalities were correlated with worse memory and executive functions (r from -0.48 to 0.42, p from 0.001 to 0.04).
Conclusion: Significant RS FC alterations in relevant cognitive functional networks occur in SLE patients and are correlated with neuropsychological variables. The assessment of RS FC might contribute to improve our understanding of the heterogeneous manifestations of SLE.
Disclosure: Nothing to disclose

EPR3022

Complaint, cognitive performance and brain metabolism in PCA patients: a FGD-PET controlled study

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Background and aims: Posterior cortical atrophy (PCA) is a neurodegenerative disease characterized by predominant visual impairment. PCA is classified as an atypical form of Alzheimer's disease (AD). However, diagnosis of PCA remains complicated with a delay of several years between first symptoms reported and diagnosis. The aim of the present study is to better characterize PCA patients' complaints, cognitive deficits and their neuronal substrates.
Methods: Fifteen PCA patients were recruited and matched with 18 healthy controls. For each participant, an evaluation of daily visual difficulties as well as a full neuropsychological assessment and FDG-PET were performed. We compared glucose metabolism between PCA patients and heathy controls. Correlation between complaint scores and cognitive performance was performed. Voxel-wise correlation between metabolism and performance was also conducted.
Results: Major impairment of cognitive functions was found in PCA patients specifically in visual domains. A predominant right sided hypometabolism in ventral and dorsal streams was found. Positive correlations were found between visual impairments and hypometabolism in right temporo-parieto-occipital cortices. However, we do not report correlation between PCA patients' complaint and visual impairment.
Conclusion: Our main results suggest there is a consistent relation between clinical impairment and brain metabolism. However, patient's complaint and visual performance are not linked. Combining literature and ours results, it seems that patients are generally aware to have difficulties but are misinterpreting them. This misinterpretation may be at the origin of the delayed diagnosis.
Disclosure: Nothing to disclose

EPR3023

Effects of age, height, and sex on motor evoked potentials to magnetic stimulation: data from a large Italian cohort in a real-world clinical setting

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Background and aims: Motor evoked potentials (MEPs) to transcranial magnetic stimulation (TMS) are known to be susceptible to several sources of variability. However, conflicting evidences on individual characteristics have been reported. We investigated the effect of age, height, and sex on MEPs of the motor cortex and spinal roots.

Methods: A total of 587 subjects without any clinical and neuroradiological motor impairment were included. MEPs were recorded during slight tonic contraction through a circular coil applied over the "hot spot" of the first dorsal interosseous and tibialis anterior muscles, bilaterally. Central motor conduction time (CMCT) was estimated as the difference between the cortico-muscular latency and the peripheral motor conduction time (PMCT) by cervical or lumbar magnetic stimulation. Peak-to-peak MEP amplitude to cortical stimulation and right-left difference of each TMS index were also measured.

Results: Tables 1 and 2 summarize the demographic features and the descriptive statistics, respectively. After Bonferroni correction, linear regression analysis (Table 3) showed that both MEP latency and PMCT at four limbs positively correlated with age and height. At upper limbs, a negative correlation of the same measures was also observed with sex. CMCT at four limbs and side-to-side differences did not correlate with any physical variable.

	Sex	n	Mean	S.D.
Age ≥ 18 <35 years	F	91	26.8	4.83
	M	63	25.8	4.86
Age ≥ 35 <50 years	F	138	41.7	4.05
	M	68	42.2	4.02
Age ≥ 50 <65 years	F	83	55.8	3.64
	M	71	57.1	4.35
Age ≥ 65 years	F	34	70.6	6.32
	M	39	69.7	4.12
All	F	346	44.0	14.23
	M	241	46.7	16.05
Total		587	45.1	15.05

Legend: n = number of subjects; F = female; M = male; S.D. = standard deviation.

Table. 1. Demographic features of the whole group of participants and of the age subgroups.

	Mean	S.D.	Mean ± 1.96 S.D.	95% confidence interval
Right FDI				
MEP amplitude, mV	7.9	3.21	1.6 / 14.2	2.8 / 15.1
MEP latency, ms	19.5	1.45	16.7 / 22.4	16.9 / 22.5
PMCT, ms	13.6	1.31	11.0 / 16.2	11.2 / 16.2
CMCT, ms	5.9	0.89	4.2 / 7.7	4.3 / 7.6
Left FDI				
MEP amplitude, mV	7.6	3.09	1.6 / 13.7	3.0 / 14.6
MEP latency, ms	19.4	1.45	16.6 / 22.2	17.0 / 22.5
PMCT, ms	13.5	1.32	10.9 / 16.1	11.2 / 16.0
CMCT, ms	5.9	0.87	4.2 / 7.6	4.2 / 7.6
Right-Left difference				
MEP amplitude, mV	0.26	2.23	-4.1 / 4.6	-4.0 / 4.9
MEP latency, ms	0.12	0.69	-1.2 / 1.5	-1.3 / 1.5
PMCT, ms	0.09	0.62	-1.1 / 1.3	-1.3 / 1.3
CMCT, ms	0.026	0.75	-1.4 / 1.5	-1.5 / 1.5
Right TA				
MEP amplitude, mV	5.5	2.30	1.0 / 10.0	2.0 / 10.4
MEP latency, ms	26.5	2.21	22.2 / 30.9	22.7 / 31.2
PMCT, ms	12.7	1.43	9.8 / 15.5	10.2 / 15.8
CMCT, ms	13.9	1.64	10.7 / 17.1	10.9 / 17.1
Left TA				
MEP amplitude, mV	5.3	2.17	1.1 / 9.6	1.9 / 10.0
MEP latency, ms	26.5	2.20	22.2 / 30.8	22.7 / 31.0
PMCT, ms	12.6	1.46	9.7 / 15.4	10.1 / 15.9
CMCT, ms	13.9	1.69	10.6 / 17.2	10.8 / 17.2
Right-Left difference				
MEP amplitude, mV	0.18	2.02	-3.8 / 4.1	-4.0 / 4.5
MEP latency, ms	0.07	1.94	-3.7 / 3.9	-4.4 / 4.1
PMCT, ms	0.07	1.23	-2.3 / 2.5	-2.7 / 2.7
CMCT, ms	0.0002	1.59	-3.1 / 3.1	-3.5 / 3.0

Legend: S.D = standard deviation; FDI = first dorsal interosseous muscle; TA = tibialis anterior muscle; MEP = motor evoked potential; PMCT = peripheral motor conduction time; CMCT = central motor conduction time.

Table. 2. Descriptive statistics of all the variables studied.

	Age		Height		Sex	
	partial correlation	*p*	partial correlation	*p*	partial correlation	*p*
Right FDI						
MEP amplitude, mV	-0.112		0.060		-0.069	
*MEP latency, ms**	***0.284***	***0.000001***	***0.394***	***0.000001***	***-0.212***	***0.000012***
*PMCT, ms**	***0.383***	***0.000001***	***0.381***	***0.000001***	***-0.281***	***0.000001***
CMCT, ms	-0.075		0.099		0.044	
Left FDI						
MEP amplitude, mV	-0.129		0.073		-0.099	
*MEP latency, ms**	***0.301***	***0.000001***	***0.415***	***0.000001***	***-0.243***	***0.000001***
*PMCT, ms**	***0.397***	***0.000001***	***0.405***	***0.000001***	***-0.324***	***0.000001***
CMCT, ms	-0.068		0.092		0.052	
Right-Left difference						
MEP amplitude, mV	0.015		-0.014		0.037	
MEP latency, ms	-0.015		-0.018		0.041	
PMCT, ms	-0.004		-0.024		0.058	
CMCT, ms	-0.010		0.010		-0.008	
Right TA						
MEP amplitude, mV	-0.089		-0.086		-0.220	0.000004
*MEP latency, ms**	***0.317***	***0.000001***	***0.433***	***0.000001***	-0.097	
*PMCT, ms**	***0.323***	***0.000001***	***0.404***	***0.000001***	-0.023	
CMCT, ms	0.119		0.206	0.000025	-0.094	
Left TA						
MEP amplitude, mV	-0.010		-0.038		-0.153	0.0095
*MEP latency, ms**	***0.231***	***0.0000008***	***0.265***	***0.000001***	-0.062	
*PMCT, ms**	***0.253***	***0.000001***	***0.274***	***0.000001***	0.002	
CMCT, ms	0.075		0.101		-0.077	
Right-Left difference						
MEP amplitude, mV	-0.088		-0.055		-0.084	
MEP latency, ms	0.063		0.159	0.00012	-0.026	
PMCT, ms	0.048		0.121		-0.025	
CMCT, ms	0.038		0.098		-0.011	

Legend: correlations with medium-to-large size (≥ 0.30) are indicated in bold and italics lettering. * = Significant after Bonferroni correction (non-significant *p* values are not shown); FDI = first dorsal interosseous muscle; TA = tibialis anterior muscle; PMCT = peripheral motor conduction time; CMCT = central motor conduction time.

Table. 3. General linear regression analysis of the correlation between age, height, and sex and all the variables studied.

Conclusion: Physical variables need to be considered for a more accurate MEPs comparison and meaningful interpretation. Both in clinical practice and research settings, patients and controls should be matched for age, height, and sex. Notably, CMCT was not influenced by any variable here considered, thus representing a stable and reliable TMS index of central motor conductivity.

Disclosure: Nothing to disclose

EPR3024

Neurosarcoidosis: report of 35 cases What about diagnosis dilemma?

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Background and aims: Neurosarcoidosis (NS) is a rare and polymorphic entity. At our knowledge, it is the first time 2018 consensus criteria were applied. We sought to describe a cohort of patient and to establish the relevance of diagnostic investigations.
Methods: A retrospective study of all patients diagnosed with NS was conducted in Rouen University Hospital between 1993 and 2018. We included patients diagnosed with definite, probable and possible NS according to 2018 consensus.
Results: A total of 35 patients were included, 22 (63%) of whom with inaugural NS. Sex ratio male/female was 0.84. The mean age of onset was 48.0 years. NS was considered as definite in four patients (11%), probable in 17 (49%) and possible in 14 (40%). In cases of already known sarcoidosis, neurological symptoms mainly occurred within 6 months after the onset of sarcoidosis (54%). Pulmonary involvement was associated in 26 (74%). Headache (49%), cranial neuropathies (57%) were the most common signs. Only six patients (17%) presented myelitis and four (11%) peripheral nervous impairment. Biological tests showed: lymphopenia (71%). CSF analysis revealed abnormalities in 86%: lymphocytic pleocytosis (48%), high protein content (71%). Diffuse T2 white matter hyperintensities (87%) and focal meningeal enhancement (73%) were the most common brain MRI finding.

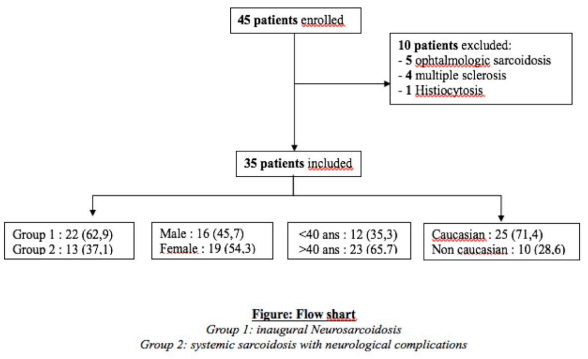

Figure 1

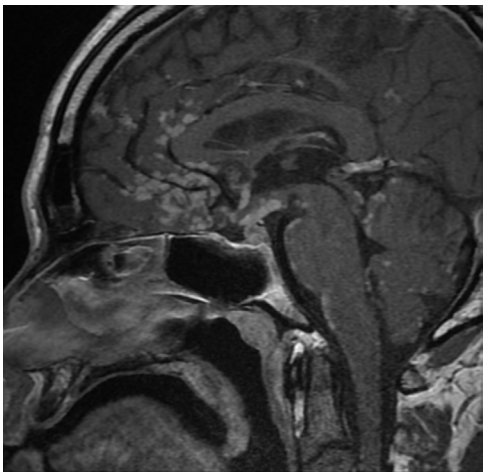

Figure 2

Conclusion: Here we highlight application of 2018 consensus criteria of NS. Probability having at least one of the following (CSF, MRI, EMG) abnormal was 91% showing the interest of these investigations.
Disclosure: Nothing to disclose

EPR3025

Blink reflex recovery cycle in atypical parkinsonian syndromes: cut-off scores to differentiate corticobasal syndrome from progressive supranuclear palsy and multiple system atrophy

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Background and aims: R2 blink reflex recovery cycle (R2BRRC) is a neurophysiological tool used to assess brainstem excitability in several movement disorders. CorticoBasal syndrome (CBS), progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) show an overlap of common clinical features, especially at the early stage of the disease. We evaluated R2BRRC in atypical parkinsonian syndromes, finding optimal cut-off scores to differentiate CBS patients from PSP and MSA patients.
Methods: We prospectively enrolled 67 subjects: 14 CBS patients, 23 PSP patients, 15 MSA patients and 15 controls, investigating Blink Reflex and R2BRRC at interstimulus intervals (ISIs) of 100, 150, 200, 300, 400, 500 and 750 ms. The optimal cut-off value of each ISI in differentiating CBS patients from PSP and MSA patients was calculated.
Results: PSP and MSA patients showed earlier recruitment of R2BRRC as compared to CBS patients and controls (ISI 100, 150 and 200 ms: $p<0.001$). R2BRRC data of the four groups are shown in table 1. A cut-off value of 33% at ISI of 100 ms differentiated CBS patients from PSP patients with a sensitivity of 91.3% and a specificity of 92.9%, whereas a cut-off value of 23% permitted to differentiate CBS patients from MSA patients with a sensitivity of 93.3% and a specificity of 92.9%.

R2 blink reflex recovery cycle (%)	CBS (n=14)	PSP (=22)	MSA (n=15)	CTRL (n=15)	*p*-value*
ISI 100 (ms)	6.4 ± 23.8	68.6 ± 36.6	74.4 ± 47.5	0	**<0.001**
ISI 150 (ms)	3.6 ± 13.6	64.4 ± 32.5	59.7 ± 19.2	0.6 ± 2.3	**<0.001**
ISI 200 (ms)	3.7 ± 13.9	61.8 ± 26.9	67.5 ± 21.8	7.9 ± 13.7	**<0.001**
ISI 300 (ms)	55.9 ± 31.7	62.7 ± 20.1	66.4 ± 28.8	44.0 ± 31.9	0.4
ISI 400 (ms)	53.9 ± 37.1	70.6 ± 32.2	77.9 ± 24.6	50.9 ± 24.7	0.04
ISI 500 (ms)	71.0 ± 40.0	77.5 ± 32.5	90.9 ± 26.2	59.8 ± 32.0	0.08
ISI 750 (ms)	86.4 ± 31.2	87.8 ± 28.6	95.9 ± 24.3	91.7 ± 31.3	0.8

Table 1. R2 blink reflex recovery cycle for CBS, PSP, MSA and control groups. Ratios of conditioned R2 component to unconditioned response (amplitude) are shown as means±standard deviations. CBS=Corticobasal syndrome, PSP=Progressive Supranuclear Palsy, MSA=Multiple System Atrophy, CTRL=controls, ISI=interstimulus interval. *ANOVA

Conclusion: R2BRRC curve may represent a reliable tool in differentiating atypical parkinsonian syndromes.
Disclosure: Nothing to disclose

EPR3026

Plasma adenosine deaminase 2 and serum immunoglobulin M accuracy in adult Sneddon's syndrome

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Background and aims: The association between livedo reticularis (LR) and stroke is known as Sneddon's syndrome (SnS). It's classified as primary SnS (PSnS) if the cause remains unknown or secondary. Recently, a new genetic disorder called deficiency of adenosine-deaminase-2 (DADA2) was described. It is characterized by recurrent fevers and vascular pathologic features, including SnS phenotype. These patients carry recessively inherited mutations in adenosine-deaminase-2 (ADA2) gene, encoding the ADA2 protein. Genetic testing is the standard diagnosis tool for DADA2. However, diagnostic accuracy of more affordable tests remains to be established. We aim to determine whether plasma ADA2 activityand serum immunoglobulin M (IgM) levels can distinguish DADA2 from other adult PSnS patients.
Methods: Plasma ADA2 activity and serum IgM levels were measured in adult patients within the SnS spectrum in a terciary center in Portugal. Genetic results were used as standard reference. The primary outcome measures were sensitivity and specificity derived from receiver operating curve analysis.
Results: 26 PSnS patients with no CECR1 mutation and 6 bi-allelic (DADA2 patients) were included. Plasma ADA2 activityand serum IgM were significantly lower in DADA2 patients than in PSnS. With the use of the best indexes, plasma ADA2 activity differentiated PSnS from DADA2 with a sensitivity and specificity of 100.0% and serum IgM levels differentiated PSnS from DADA2 with a sensitivity of 85.2% and specificity of 83.3%.
Conclusion: Serum IgM levels might be used as a triage tool and plasma ADA2 activity performs perfectly as a diagnostic test for DADA2 in adult patients with SnS.
Disclosure: Nothing to disclose

EPR3027

Visualisation of amyloid deposition within the brain of long-term hereditary transthyretin amyloidosis survivors by 18F- flutemetamol positron emission tomography

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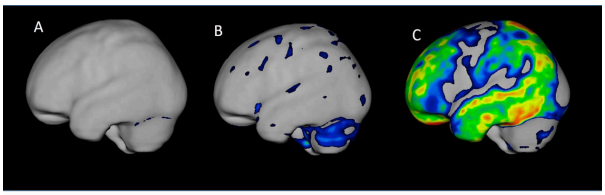
Background and aims: Hereditary transthyretin amyloid (ATTRv) amyloidosis caused by the transthyretin (TTR) Val30Met (p.V50M) mutation is characterised by peripheral neuropathy, and central nervous (CNS) complications has rarely been reported. However, liver transplantation has prolonged the patients' survival, and CNS complications attributed to amyloid angiopathy caused by CNS synthesis of variant TTR have been reported. The aim of the study was to ascertain CNS amyloid deposition in long-term ATTRv survivors

Methods: 20 ATTR Val30Met patients with symptoms from the CNS and a median disease duration of 16 years (9-25 years) together with five Alzheimer (AD) patients, who served as positive controls were included in the study. Amyloid CNS deposits were assessed by 18F- flutemetamol PET/CT examination utilising relative z scores with pons as reference.

Results: Expectedly, all Alzheimer patients had an clearly increased global composite z score above 2.0 compared with 55% of the ATTRv patients. There was an increased local uptake corresponding to cerebellum in 12 ATTRv patients compared to only one in the AD group (fig 1). Four of these ATTRv patients had a global composite z score within the normal range. No correlation between duration after 9 years and amyloid CNS deposition was noted.



A. ATTR V30M patient with 15 years of disease, No increased uptake

B. ATTR V30M patient with 16 years of disease, increased uptake cerebellum

C. AD patient with generalised increased upptake in frontoparietotemporal regions.

figure 1

Conclusion: Amyloid deposition within the brain after long-standing ATTRv amyloidosis is increased and is often noted in the cerebellum. However, not all patient display amyloid CNS deposition, thus, additional causes for CNS complications should always be considered.

Disclosure: Nothing to disclose

Cognitive neurology/neuropsychology 2

EPR3028

Relationship between cognitive impairment and MRI brain abnormalities in benign multiple sclerosis: a multiparametric study

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Background and aims: Mechanisms responsible of cognitive dysfunction in benign multiple sclerosis (BMS) are unclear. We used a multiparametric MRI approach to investigate whether cognitive impairment (CI) in BMS patients is associated with specific patterns of structural and functional abnormalities.
Methods: Thirty-eight BMS patients (EDSS ≤3.0 and disease duration ≥15 years) underwent structural and functional MRI scans and neuropsychological assessment, with derivation of a cognitive impairment index (CII). Gray matter (GM) atrophy, white matter (WM) microstructural damage and resting state (RS) functional connectivity (FC) were investigated for whole brain, within relevant regions (cortex, lobes, subcortical nuclei and WM tracts), and functional networks. MRI measures were included into univariate, multivariate and combined models to identify independent predictors of cognitive abnormalities.
Results: In BMS patients, the median CII was 9 (IQR:4-16). Higher CII correlated with: higher T2 lesion volume; atrophy of several deep GM structures (caudate putamen nuclei, left thalamus, left amygdala) and bilateral parietal lobe; and a distributed pattern of decreased fractional anisotropy (FA), involving temporo-parietal-occipital WM tracts ($p<0.05$). At multivariate analysis, right (R) caudate nucleus atrophy ($R2=0.34$, $p=0.008$) and R posterior corona radiata (PCR) FA reduction ($R2=0.43$, $p=0.001$) were independent predictors of CI. The combined model identified integrity loss of the R PCR ($R2=0.43$, $p=0.001$) as the only predictor of CI.
Conclusion: Several structural MRI measures, taken separately, were associated with CI in BMS. At multimodal investigation, damage to the WM of parietal regions emerged as predominant predictor of worse cognitive performances in these patients.
Disclosure: Partially supported by FISM – Fondazione Italiana Sclerosi Multipla – cod. 2018/S/3, and financed or co-financed with the '5 per mille' public funding.

EPR3029

Effect of cognitive reserve on resting-state functional connectivity in adult healthy subjects

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Background and aims: Early and recurring involvement of cognitive abilities and exposure to leisure activities during early-life experiences is a prerequisite to reach a high level of cognitive reserve. We investigated the associations between cognitive reserve and resting-state functional connectivity (RS-FC) in healthy controls (HC).
Methods: RS functional MRI scans were obtained from 51 HC (24M; mean age=36; range=19-64). For all subjects Cognitive Reserve Index (CRI), including education, leisure activities and IQ, was also assessed (higher scores reflect higher cognitive reserve). Independent component analysis identified nine independent RS networks. Global-CRI and its sub-domains (cognitive/social/physical) scores were correlated with network RS-FC using linear regression models.
Results: Higher global-CRI was correlated with lower RS-FC of left (L) postcentral gyrus and right (R) rolandic operculum in sensory-motor network (SMN), L postcentral gyrus in salience network (SN) and R cerebellum in the executive-control network (ECN). CRI subdomains analysis showed that higher social-CRI was correlated with lower RS-FC of L postcentral gyrus and R rolandic operculum in SMN, L postcentral gyrus in SN and R cerebellum in ECN. Higher physical-CRI was correlated with lower RS-FC of L postcentral gyrus in SMN, and R cerebellum in ECN. Higher cognitive-CRI was correlated with lower RS-FC of R medial cingulate gyrus and R insula in SMN, and L middle frontal gyrus in SN. Apart from physical-CRI, higher CRI scores in all domains were correlated with higher RS-FC of R cuneus in the default mode network.
Conclusion: Cognitive reserve in HC modulates RS-FC of the main brain functional networks.
Disclosure: Nothing to disclose

EPR3030

Quantitative evaluation of picture description may differentiate Alzheimer's disease from mild as well as from subjective cognitive impairment

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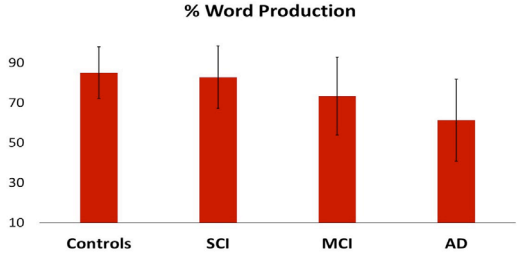
Background and aims: Progressive neurodegeneration in Alzheimer disease (AD) may not only affect memory, but also language, among other cognitive functions. We explored the utility of a quantitative template of a picture description task in the evaluation of patients with AD and the possible AD precursors, mild cognitive impairment (MCI) and subjective cognitive impairment (SCI).
Methods: Sixty-one patients with AD, 22 subjects with MCI, 17 subjects with SCI and 33 healthy controls from the German Frontotemporal Lobar Degeneration Consortium (www.ftld.de) were included. We used the Cookie Theft scene (Boston Diagnostic Aphasia Examination) to prepare a quantitative template containing fifteen words (ten nouns and 5 action words) associated with the objects, actors, and actions shown on the picture. All participants were asked to describe the picture and their results were compared according to their successful naming of the 15 items selected.
Results: One-way ANOVA showed a significant difference between groups ($p<0.001$): controls produced 85% of the required words while SCI, MCI and AD patients produced 83%, 73% and, 61%, respectively. Independent samples t-tests showed that patients with AD differed significantly from all three groups: controls ($p<0.001$), subjects with SCI ($p<0.001$) and with MCI ($p<0.005$), respectively. Naming scores also differed significantly between MCI and controls ($p<0.05$). SCI subjects scored in the range of both controls ($p=0.57$) and MCI ($p=0.11$).



Percentage of word production based on the quantitative template of the Cookie Theft picture

Conclusion: We propose that quantitative analysis of the Cookie Theft picture task may, at a group level, successfully differentiate AD patients from healthy individuals as well as from subjects with MCI or SCI, respectively.
Disclosure: Dr.Mustafa Seckin was supported by the Center for Advanced Studies at LMU Munich.

EPR3031

Cognitive functions one year after carotid endarterectomy – a prospective study

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Background and aims: The effect of carotid endarterectomy (CEA) on cognitive functions is debatable. Study aims to assess changes in cognitive functions after CEA.
Methods: Self-sufficient patients with carotid stenosis >70% indicated to CEA were included to the study. Physical, neurological and cognitive functions examinations including Addenbrooke's cognitive examination-revised (ACE-R), mini-mental state examination (MMSE), clock drawing test (CDT), speech fluency test (SFT) were performed prior to CEA, 24h, 30 days and 1 year after CEA. Brain magnetic resonance (MR) was performed prior to and 24h after CEA. Changes in cognitive tests 24h, 30 days, 1 year after CEA, influence of age, gender, side and degree of carotid stenosis, vascular risk factors, stroke or transient ischemic attack (TIA) prior to CEA, vascular complications (TIA, stroke, new brain infarction on control MR) on changes in cognitive functions were statistically evaluated.
Results: Totally 645 patients (448 males, mean age 69.0±7.7 years, 281 symptomatic stenoses) were included during 34 months. Stroke/TIA occurred in 32 (5%) patients within 30 days after CEA. New brain infarction on control MR was detected in 33 (14%) out of 235 patients. Improvement in cognitive tests after 30 days/1 year were 3.8/2.73 points in ACE-R, 0.8/0.6 points in MMSE, 0.2/0.2 points in CDT and 0.3/0.5 points in SFT ($p<0.05$ in all cases). Cognitive improvement was not dependent on age, gender, symptomatic stenosis, vascular risk factors, neither vascular complications after CEA.
Conclusion: CEA leads to improvement in cognitive functions 30 days and 1 year after surgery.
Supported by MHCR grants 16-29148A and 17-31016A.
Disclosure: Nothing to disclose

EPR3032

Is functional cognitive disorder characterised by disproportionate effort and exhausted attentional reserve?

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Background and aims: In a recent systematic review we concluded that the cognitive syndromes associated with fibromyalgia and chronic fatigue syndrome are associated with high symptom burden, high subjective effort, impaired sustained and divided attention but normal performance on other cognitive tests. We hypothesise that similar findings will be present in functional cognitive disorder (FCD), an emerging functional neurological disorder of increasing prevalence in cognitive clinics (ICD-11: 6B60.9 dissociative neurological symptom disorder, with cognitive symptoms).

Methods: We have developed an experimental paradigm to test effort, objective performance and physiological parameters during cognitive tasks that involve varying attentional demand.

Results: Pilot data suggest that individuals with FCD report large increases in subjective effort during cognitive tasks as demands on working memory and attention are increased. Further work will determine the extent to which test performance correlates with effort and is affected by increased attentional demand. We will determine whether attentional reserve in FCD is effectively "exhausted" leading to an inability to cope with non-complex tasks that require divided attention.

Conclusion: A defining feature of FCD is an incongruity between high levels of subjective symptoms and normal performance on tests of canonical cognitive domains such as memory and language. Our experiments will help determine whether FCD is a state of heightened effort, disordered attention or both. This will guide treatment paradigms towards reinterpreting "effort" and/or resetting basal levels of attention.

Disclosure: Nothing to disclose

Epilepsy 4

EPR3033

Changes in cardiac sympathetic index parameter before focal epileptic seizures

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Background and aims: To predict focal epileptic seizures in patients with temporal lobe epilepsy, we evaluated the heart rate variability that is generated by the fluctuating balance of sympathetic and parasympathetic nervous systems.
Methods: Scalp video EEG with simultaneous ECG (vEEG) was performed in 30 patients to obtain epileptic seizures recordings during presurgical evaluation. The ECG was recorded with electrodes placed on the chest (V1–V2 derivation). In all cases the registration time was up to several hours. The outcome from temporal lobe surgery with respect to seizures revealed that 22 patients (73%) were completely seizure-free or almost seizure-free (Engel class 1). Regarding the fact that heart rate variability (HRV) signals are nonstationary, our analysis focused on linear features in the time domain such as R-R interval (RRI), quantitative analyses of Poincaré plot features (SD1, SD2, and cardiac sympathetic index CSI=SD1/SD2).
Results: Table I presents calculated average CSI parameters characterizing recorded ECG signals. The calculations were made in minute intervals, starting from tenth minute before the clinical attack.
Conclusion: Significant changes of CSI parameter values were observed in the time intervals (10-9min, 8-7min, 7-6min, 6-5min, 5-4min, 4-3min, 3-2min, $p<0.005$) in relation to the first minute before the clinical attack 3.69±2.28. We can observe an increase in the CSI parameter-in the second and first minute before the clinical attack.
Thirty seizures - average CSI parameters.
Disclosure: Nothing to disclose

EPR3034

The predictors factors for acute and remote seizure in a cohort of Tunisian patients with cerebral venous and sinus thrombosis

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Background and aims: Epileptic seizures occur in around 40% of patients with cerebral venous thrombosis (CVST). Results vary concerning risk factors for seizures. We aimed to identify risk factors for acute (AS) and remote seizures (RS) in patients with CVTS.
Methods: In this retrospective study, we recruited 107 patients who were hospitalised in the National Institute of Neurology (Tunis,Tunisia). We compared clinical and paraclinical parameters between patients with and without seizures during acute (from clinical onset up to 2 weeks after confirmation of diagnosis) and remote (>2 weeks) phases after CVST. Variables with significant association in univariate analysis were entered in a logistic-regression analysis.
Results: A total of 44 (41.12%) patients had AS, 6 (5.6%) patients had RS. Twenty five (23.36%) patients had generalized seizures, 15 (14%) had partial seizures and 10 patients (9.34%) had generalized convulsive status epilepticus. On multivariate analysis, motor deficit (odds ratio (OR)=1.51;95% IC=0.19–11.99; p=0.009) and male gender (OR=1.48; 95% IC=0.12–1.00; p=0.001) were independently predictive of AS while presence of headache at presentation (OR=0.41; 95% IC =0.01–1.99; p=0.019) was negatively associated with seizures. The risk of RS, on multivariate analysis, was negatively associated with vomiting at presentation (OR=0.61; 95% IC=0.31-2.13; p=0.01).
Conclusion: Our results demonstrate that male gender and motor deficits are a significant factors for development of AS. Signs of intracranial hypertension (headache, vomiting) were found to be negatively associated with both AS and RS.
Disclosure: Nothing to disclose

EPR3035

Seizure patterns and trajectory in patients with epilepsy secondary to NMDA encephalitis

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Background and aims: The longer-term trajectory of seizures associated with anti-NMDA-R autoimmune encephalitis (AIE) is not clear. Recent data suggests that seizures manifest early in the disease course and are generally short lived. We characterised seizure semiology and associated prognosis in a cohort of patients with anti-NMDAR AIE.

Methods: Case note review of 14 patients with a "definite" diagnosis of anti-NMDAR AIE was undertaken. Patients were categorized as having seizures within one month of presentation (Group A) or no seizures. Seizures were classified as focal or generalised onset and patients were followed up for a mean duration of 2 years.

Results: Out of seven patients in group A, 3 patients (23%) had focal onset. Of the remaining 7 patients (group B), one developed a seizure disorder during relapse (18 months later). Four patients experienced persisting seizures at one year. Four patients were seizure free at 6 months whilst still prescribed AEDs. Four patients with a history of seizure didn't require AEDs at one year. Seizure semiology at presentation did not correlated with longer term seizure trajectory. Presence of inflammation on the MRI (2 patients) was not associated with seizure trajectory.

Conclusion: Seizures are a common presenting symptom in anti-NMDR AIE. Most patients in this cohort were seizure free at 6 months and did not require AEDs after 1 year. Those who were seizure free at presentation remained seizure free and those who had seizures at 6 months ended on AED at one year.

Disclosure: Nothing to disclose

EPR3036

Seizure patterns and trajectory in patients with epilepsy secondary to NMDA vs LGI1 auto-immune encephalitis

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Background and aims: Seizures pattern and trajectory during NMDA Vs LGI1 associated autoimmune encephalitis (AIE) have not previously been compared. Recent data in NMDA AIE suggests seizures manifest early and are generally short lived, but in LGI1 AIE they occur later and continue longer. We characterised seizure semiology and associated prognosis in two cohorts of AIE patients.

Methods: Case note review of 16 patients with a "definite" diagnosis of anti-NMDAR AIE and 14 patients with LGI1 AIE showed the latter to occur in older adults. Patients were categorized as having seizures within one month of presentation or no seizures. Semiology was classified as focal or generalised onset. We defined refractory seizures as seizures whilest on anti-epileptics, requiring a second agent, status epilepticus, and ITU admission at the initial presentation.

Results: In the NMDA group A, 3/7 patients (23%) had focal onset compared to 6/11 patients (55%) in the LGI1 group , with predominantly faciobrachial dystonic seizures. NMDA patients were more likely to be seizure-free at 6 months (9/12, 75%) and to have refractory seizures initially (6/9, 67%) compared to LGI1 patients (6/14, 43% and 4/11, 36% respectively). Similarly, fewer NMDAR patients remained on anti-epileptics at 1 year compared to LGI1 patients.

Conclusion: Seizures are common presenting symptoms in these AIE groups. More NMDA patients were seizure-free at 6 months and did not require AEDs after 1 year compared to the LGI1 patients. LGI1 patients represented a more susceptible group of AIE patients to epilepsy although seizures in this group were easier to be controlled.

Disclosure: Nothing to disclose

EPR3037

Ictal EEG at seizure-onset in mesial temporal lobe epilepsy due to hippocampal sclerosis

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Background and aims: Ictal electroencephalographic (EEG) activity may be helpful in understanding underlying ictogenic mechanisms. We aim to examine the ictal EEG at seizure onset (IESO) in mesial temporal lobe epilepsy related to hippocampal sclerosis (MTLE-HS).

Methods: We retrospectively analysed the scalp video-EEG monitoring of 282 patients with MTLE-HS, admitted for pre-surgical assessment in the epileptology unit. Seizure onset was defined as the first identifiable clinical or EEG sign. IESO was defined as the seizure onset EEG activity sustained for at least 3 seconds, ipsilateral to hippocampal sclerosis.

Results: A total of 871 seizures were analysed. For most patients, a single or predominant IESO was found. The following IESO were identified (see figures 1) focal low-voltage fast activity (46 seizures, 15 patients); 2) focal rhythmic theta/alpha activity (154 seizures, 53 patients); 3) focal rhythmic delta activity followed by faster rhythmic activity (81 seizures, 28 patients); 4) absence of initial visible EEG changes, or presence of flattening/attenuation of EEG background activity, followed by focal rhythmic activity (470 seizures, 186 patients); 5) bilateral IESO activity (105 seizures, 34 patients). Groups 4 and 5 were further classified into subgroups. Finally, for 15 seizures (7 patients) no ictal change was visible on surface EEG.

IESO Type 1 - focal recruiting low-voltage fast activity

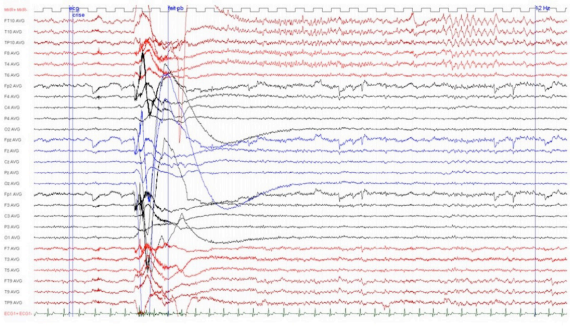

Figure 3

IESO Type 2 - focal rhythmic theta/alpha activity

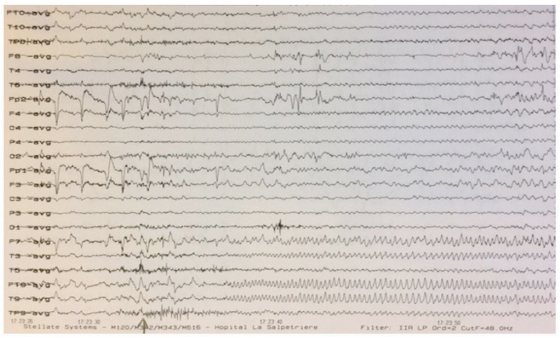

Figure 2

IESO Type 3 - focal rhythmic delta slowing followed by faster rhythmic activity

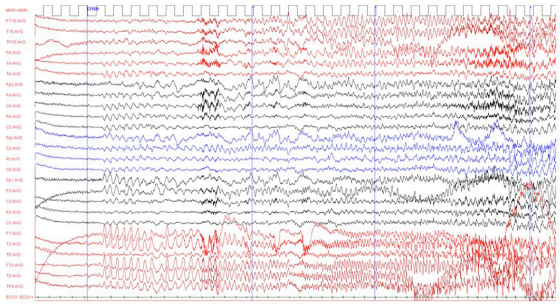

Figure 3

Conclusion: In our study, we found that scalp ictal EEG activities at seizure onset in MTLE-HS are varied and heterogeneous. This can be explained by different types of propagation of ictal hippocampal activities to the lateral neocortex. We will further examine IESO correlation with other variables, such as clinical, neuropsychological and histological features.

Disclosure: Nothing to disclose

EPR3038

Incidence and demographics of status epilepticus in French-speaking Valais canton in Switzerland

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Background and aims: Evaluation of the incidence of status epilepticus in the French-speaking Valais canton.
SE represents a medical emergency and prompt treatment is important. Data on the incidence, etiology, risk factors and outcomes are required for the decision-making process and for the allocation of resources by institutions and government agencies.
Methods: Prospective observational SE cohort in a single large community hospital. The center is the only one in the region with all available resources to treat SE (including neurologist available 24/7, EEG monitoring and ICU). Every adult patient with SE is included (except post-anoxic SE). All variables are collected prospectively. Population data were extracted from the official administration.
Results: 88 SE were identified (May 2015 – August 2018) for a referring population of 258,000 people. The incidence is 10/100,000 cases in each year of the study. The mean age of the cohort is 65. Males are preponderant in all the age groups, with the exception of 16-30 age group where we have 1 male for 4 females (see figure 1). Almost 70% of cases had a STESS score between 2 to 4 (see figure 2). Mortality rate is 12%.

Figure 1: Demographic data of the cohort (numbers are absolute values)

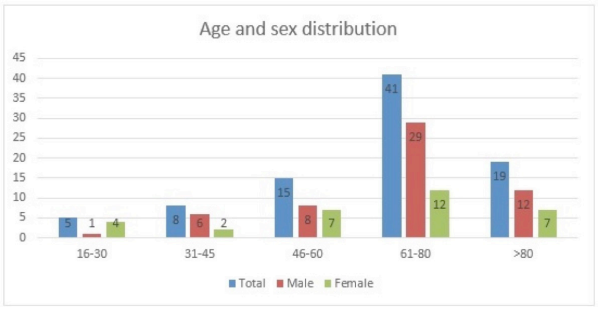

Figure 1: Demographic data of the cohort (numbers are absolute values)

Figure 2: SE severity according to the STESS (Status Epilepticus Severity Score)

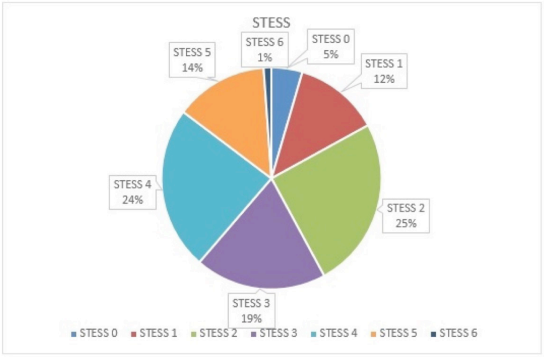

Figure 2: SE severity according to the STESS (Status Epilepticus Severity Score)

Conclusion: SE incidence in French-speaking Valais is 10/100,000/years. Being the only hospital capable of treating this condition in this area and the prospective design of the cohort ensure robust and reliable data. Also, we found very similar results than older studies in Europe: same incidence in Switzerland, 15/100,000 in Germany, 13/100,000 in Italy.
Disclosure: Nothing to disclose

Headache and pain 3

EPR3039

Evaluation of cardiovascular risks in adult patients with episodic or chronic migraine treated with galcanezumab: data from three phase 3, randomized, double-blind, placebo-controlled studies

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Background and aims: Calcitonin gene-related peptide (CGRP) is a potent microvascular vasodilator. Increased cardiovascular (CV) risks have been reported in patients with migraine. Cardiovascular events were evaluated in patients with episodic or chronic migraine treated with galcanezumab, a monoclonal antibody that binds to CGRP.
Methods: Data from two similarly designed 6-month episodic migraine studies, and one 3-month chronic migraine study were pooled. Patients were randomized 1:1:2 to receive subcutaneous injection of galcanezumab 120mg/month (following initial 240mg loading dose) or 240mg/month or placebo. The patients were grouped into CV disease risk "yes" or "no" subgroups based on reported medical history at baseline. Potential CV treatment-emergent adverse events (TEAE), and changes in blood pressure (BP), pulse, and electrocardiogram (ECG) were evaluated.
Results: At baseline, across all treatment groups, between 17% and 19% of patients were in the "yes" CV disease risk subgroup. Among treatment arms, the percentage of patients reporting ≥1 CV TEAE were low (<4%) and treatment-by-CV disease risk subgroup interactions were not significant. The same number of patients had CV related serious adverse events in the galcanezumab 240mg (n=3; acute myocardial infarction [MI], pulmonary embolism, and transient ischemic attack) and placebo (n=3; pulmonary embolism, deep vein thrombosis, and MI) groups, and the events were not considered treatment-related by the study investigator; none occurred in the galcanezumab 120mg group. Least-squares mean and categorical changes from baseline in BP, pulse, and QTcF were similar across treatment groups.
Conclusion: No clinically meaningful differences were observed for CV TEAEs, BP, pulse, or QTcF between patients treated with galcanezumab or placebo.
Disclosure: These studies were sponsored by Eli Lilly and Company, Indianapolis, Indiana, USA.

EPR3040

Red ear syndrome case report: a rational use of erenumab

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Background and aims: Red ear syndrome (RES) presents as ear redness and pain. It can be idiopathic, related to a primary headache disorder such as migraine, or due to a secondary cause such as cervical spondylosis. 1-3 angry back-firing C-nociceptor (ABC) syndrome has been described as a potential underlying mechanism in which non-noxious stimuli lead to antidromic discharges and release of peptides including calcitonin-gene related peptide (CGRP). These peptides lead to vasodilation, erythema, and pain.4-7 This case report describes a case of RES with response to erenumab, a CGRP receptor monoclonal antibody.
Methods: Case report.
Results: The patient is a 24-year-old man with a 10 year history of chronic migraine (daily headache with an average of 12 migraine days per month) who experienced the sequential onset of bilateral external ear pain involving the helix, antihelix, and auricular tubercle. The symptom complex evolved to include persistent burning and redness with 1-3 painful exacerbations per day each lasting 1-2h. Secondary causes were excluded. He failed multiple oral preventive medications. Erenumab led to complete resolution of migraine attacks and headache days, and significant (>75%) improvement of RES symptoms.
Conclusion: Erenumab may be effective for the treatment of RES, especially in those with a history of migraine. CGRP may be an important mediator of the erythema and pain in patients with RES. The effectiveness of anti-CGRP monoclonal antibodies in idiopathic and secondary RES awaits further support from other case reports. Whether ligand or receptor targeted anti-CGRP mAbs have differential efficacy is unknown at this time.
Disclosure: Nothing to disclose

EPR3041

Default mode network abnormalities predict the cutaneous allodynia in patients with episodic migraine without aura

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Background and aims: Two-thirds of patients with migraine without aura (MwoA) complain of cephalic allodynia (CA) during migraine attacks. CA is a clinical sign of central nociceptive pathway sensitization and independent predictor for migraine chronification.

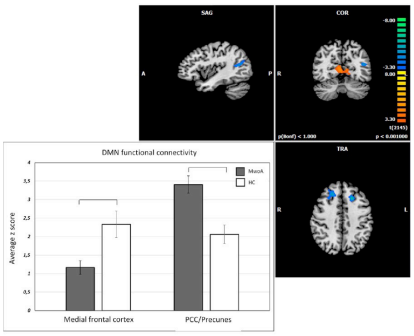
We aimed to investigate if abnormalities of default mode network (DMN) functional connectivity could predict the development of cutaneous allodynia in patients with MwoA.

Methods: 37 patients with MwoA were recruited between 2009 and 2015 and underwent whole-brain blood oxygen level–dependent (BOLD) fMRI. All these patients have been followed over a three years period and divided into 2 groups based on the development of cutaneous allodynia. We compared functional connectivity within the DMN in 20 patients with MwoA who have developed CA versus 17 patients with MwoA who have not developed CA and 19 sex- and age-matched healthy controls (HC). We assessed the correlation between functional connectivity within DMN and disease severity parameters.

Results: We observed a lower functional connectivity within posterior cingulate cortex (PPC)/precuneus in patients with MwoA who have developed CA when compared to patients with MwoA who have not developed CA and HC.

RESULTS-1

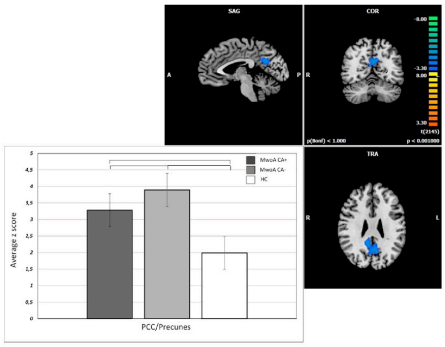
Patients with MwoA *vs* HC



T-map of statistically significant differences within the DMN between MwoA patients and HC groups (p<0.001, cluster-level corrected) overlaid on the standard "Colin-27" brain T1 template. Bar graphs of the averaged ICA z-scores for MwoA patients and HC groups regarding PCC/precuneus and MFC resulting from the whole brain analysis.

RESULTS-2

Patients with MwoA CA+ *vs* MwoA CA- *vs* HC



T-map of statistically significant differences within the DMN between MwoA CA+ and MwoA CA- groups (p<0.001, cluster-level corrected) overlaid on the standard "Colin-27" brain T1 template. Bar graphs of the averaged ICA z-scores for MwoA CA+, MwoA CA- and HC groups regarding PCC/precuneus resulting from the whole brain analysis.

Conclusion: PCC is a key hub of DMN with an antinociceptive functions, deactivated by experimental pain in HC but not in patients with chronic pain condition. An increased functional connectivity between the precuneus and the posterior cingulate cortex regions of the DMN has been observed in patients with MwoA.

We suggest that DMN abnormal functional connectivity could represent a prognostic imaging biomarker for the incipient development of CA in patients with episodic MwoA.

Disclosure: Nothing to disclose

EPR3042

Hyperresponsiveness of cerebellum and advanced visual network during trigeminal nociception in migraine with aura

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Background and aims: To investigate the functional response of neural pathways associated with trigeminal moderately painful stimulation in patients with migraine with aura (MwA).
Methods: Seventeen patients with MwA and eighteen patients with migraine without aura (MwoA) underwent whole-brain blood oxygen level–dependent (BOLD) fMRI during trigeminal heat stimulation (THS). The functional response of neural pathways to this stimulation in patients with MwA was compared with fifteen age- and sex-matched healthy controls (HC).
Results: We observed a robust cortical and subcortical pattern of BOLD signal changes in response to moderately painful THS across all participants. Patients with MwA showed a significantly increased activity of higher cortical areas, known to be part of an advanced visual network (AVN) and cerebellum when compared with both patients with MwoA and HC.

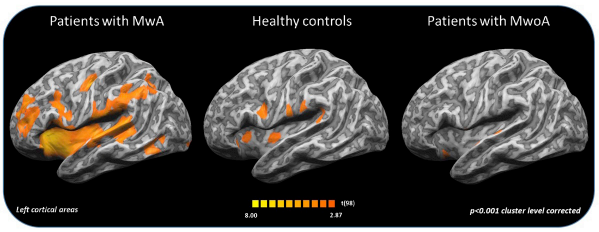

Figure 1
Group-level (main effects) BOLD-response of advanced visual network in patients with MwA, MwoA and HC during THS at 51° C. Statistical maps were obtained overlaying an inflated 3D brain surface from the 'Colin 27' atlas (p<0.001 cluster-level corrected).

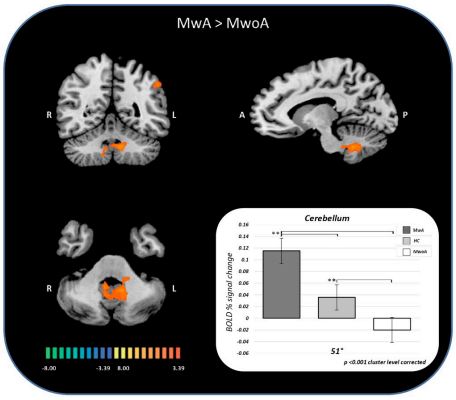

Figure 2

Percent of BOLD signal change (mean±SE) at 51°C from whole brain analysis in group comparisons between patients with MwA, patients with MwoA and HC. SE= standard error; MwA= migraine with aura; MwoA= migraine without aura; HC= healthy controls.

Conclusion: Our findings, characterized by abnormal visual pathway response to trigeminal noxious heat stimulation, support the role of a functional integration between visual and trigeminal pain networks in the pathophysiological mechanisms underlying MwA. Moreover, they expand the concept of "neurolimbic-pain network" as a model of MwoA including both limbic dysfunction and cortical dys-excitability. Indeed, our data suggest the model of "neurolimbic-visual-pain network" in patients with MwA, characterized by dysfunctional correlations between pain-modulating circuits not only with the cortical limbic areas but with advanced visual areas as well. Furthermore, the abnormal cerebellar response to trigeminal noxious heat stimulation may suggest a dysfunctional cerebellar inhibitory control on thalamic sensory gating, impinging on the advanced visual processing cortical areas in patients with MwA.

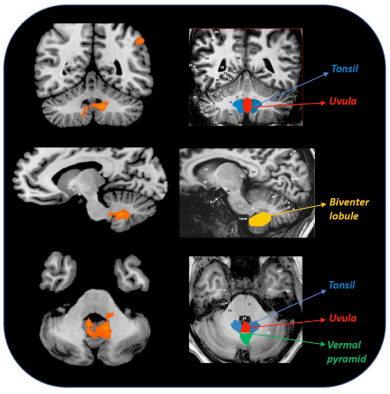

Figure 3
Correspondence of function and structure of midline and lower structures of the cerebellum showing interictal increased response to THS in MwA patients. The coloured areas highlight the uvula, the tonsils and the biventer lobule. (adapted from Duvernoy HM, 1995) THS: trigeminal heat stimulation; MwA= migraine with aura.

Disclosure: Nothing to disclose

EPR3043

Clinical picture of epicrania fugax: a prospective series of 87 cases with therapeutic results

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Background and aims: Epicrania fugax (EF) diagnostic criteria (Appendix of International Classification of Headache Disorders (ICHD-III) point out the appearance of brief pain paroxysms, describing a stable trajectory across the surface of one hemicranium, commencing and terminating in territories of different nerves. Pain radiation may be forward or backward. We aimed to analyse a large series of patients attended in an outpatient headache clinic.
Methods: We systematically included all patients fulfilling criteria from March 2008 to January 2019. We prospectively assessed clinical and demographic characteristics, therapeutic requirements and response.
Results: We included 87 patients (61 females, 26 males) out of 5980 attended during study period (1.45%). Age at onset was 45.3±16.8 years (16-84). 56 cases (64.4%) suffered a forward EF, 28 (32.2%) a backward EF, and in 3 (3.4%) paroxysms described both trajectories. Pain was strictly unilateral in 72 (82.7%) patients whilst in 11 (12.6%) shifted both sides and in 4 (4.6%) presented a sagittal trajectory. Pain quality was mainly described as electric (52, 59.7%), or stabbing (27. 31%) and intensity rated as 6.9±1.9 (3-10). In 28 cases (32%) autonomic features appeared (mainly lacrimation). Temporal pattern was heterogeneous, with spontaneous remissions in 27 cases (31%). 54 patients (62.1%) required a preventive therapy. The drugs that presented a better response were Gabapentin and Lamotrigin. 5 refractory cases were successfully managed with Lamotrigin.
Conclusion: EF is an infrequent but not exceptional syndrome in a headache clinic. Characteristics of forward and backward variants are comparable. When preventive therapy is required, the neuromodulator that reached the best responses was Lamotrigin.
Disclosure: Nothing to disclose

Infectious Diseases

EPR3044

Cognitive dysfunction in brain abscess patients is not attributable to beta-amyloid deposition

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Background and aims: Accumulation of beta-amyloid is an important aspect of Alzheimer's disease neuropathology, (1) but a physiological role for beta-amyloid has been difficult to establish. Recently, a role for beta-amyloid in the brain's antimicrobial response was forwarded. (2) Bacterial brain abscesses may entail cognitive dysfunction. (3) We asked if beta-amyloid accumulates after bacterial brain abscess and whether it may contribute to patients' cognitive sequelae.

1. Cohen AD.Mol Cell Neurosci. 2018 pii: S1044-7431(18)30370-1.
2. Kumar DK. Sci Transl Med. 2016;8:340ra72.
3. Visani P. Eur J Neurol. 2006;13:599-603.

Methods: Nine brain abscess patients (27-72-year-old) underwent 31F-flutemetamol positron emission tomography (PET) 1-24 months after brain abscess treatment. Eight patients underwent formal neuropsychological investigation 1-6 months prior to PET (Table 1).

Functions	Tests
Intellectual abilities	Wechsler Adult Intelligence Scale IV: Similarities, Vocabulary, Block design, Matrix reasoning
Motor functions	Halstead-Reitan Neuropsychological Test Battery: Grip strenght and Fingertapping test Kløve-Matthews' Steadiness Battery: Grooved pegboard
Psychomotor speed	Dehlis-Kaplan Executive Function System: Color-Word Interference Test 1 and 2 Halstead-Reitan Neuropsychological Test Battery: TMT A
Attention span and working memory	Wechsler Adult Intelligence Scale IV: Digit span Wechsler Memory Scale III: Spatial span
Executive functions	Halstead-Reitan Neuropsychological Test Battery: TMT B Dehlis-Kaplan Executive Function System: Color-Word Interference Test 3 and 4 and Verbal fluency trial 1
Memory	California Verbal Memory Test II Brief Visuospatial Memory Test Revised

Table 1. Neuropsychological indices and subtests

Results: Abscesses were localized in any of the cerebral lobes (volumes: 0.25-42cm^3); all affecting neocortex. Neuropsychological investigation revealed cognitive deficits in seven patients, defined as results ≤1.5 SD according to standardized norms on at least two tests in one cognitive domain. Deficits were both focal, revealing specific deficits in tests with higher load on language or visuospatial functioning, reflecting the location of the brain abscess (e.g left temporal and frontal lobes, occipital and parietal lobes), and non-specific, e.g. impairments in psychomotor speed, attention span, or executive functions.

In none of the patients did 31F-flutemetamol PET reveal increased beta-amyloid deposition focally or globally (Figs. 1 and 2). In some patients, a reduction in 31F-flutemetamol signal was observed in white matter in the abscess area (Fig. 1).

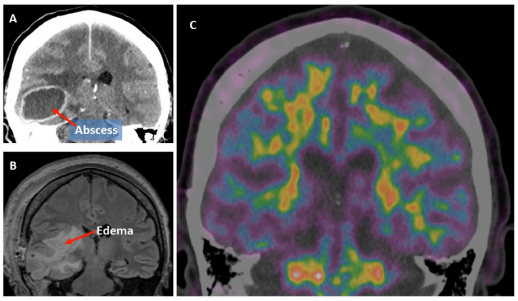

Fig. 1. Patient, 60 y, with a large abscess in the right temporal lobe as seen on CT (A). MRI two days after pus evacuation shows persistent edema (B). 31F-Flutemetamol PET seven months later shows no accumulation of beta-amyloid locally or globally, but rather a decreased signal in white matter in the region of the previous abscess (C).

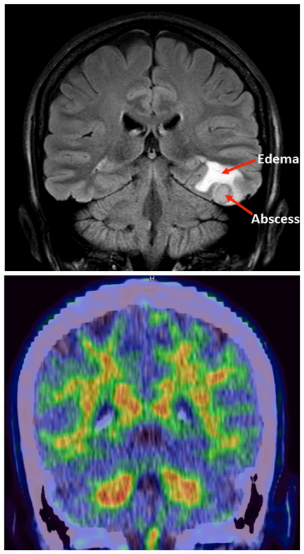

Fig.2. Patient, 40 y, with a small abscess in the left temporal lobe. At two months after neurosurgery there was persisting focal symptoms (auditory processing deficits) and mental fatigue, but no accumulation of beta-amyloid as could be seen with 31F-flutemetamol PET.

Conclusion: Beta-amyloid accumulation does not explain cognitive dysfunction in brain abscess patients.

Disclosure: Nothing to disclose

EPR3045

Group B streptococcus meningitis in infants and newborns: the clinical and molecular characteristics, risk factors and outcomes

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Background and aims: Group B streptococcus (GBS) is associated with high mortality and morbidity in infants and newborn, especially those with meningitis and neurological sequelae. We aimed to characterize the clinical features, molecular characteristics and outcomes of GBS meningitis in infants.
Methods: From 2003 to 2017, 51 infants with GBS meningitis were enrolled. The GBS isolates underwent serotyping, multilocus sequence typing (MLST) and antibiotic susceptibility testing. We compared these patients with GBS invasive diseases but without meningitis.
Results: Of the 51 patients with GBS meningitis, 14 (27.5%) were early-onset disease, 34 (66.7%) were late-onset disease and 3 (5.9%) were late late-onset disease (>90 days of age). Serotype III GBS strains accounted for 60.8%, followed by serotype Ia (25.5%) and Ib (11.8%). All GBS isolates were sensitive to ampicillin and all GBS invasive disease with meningitis were treated with appropriate antibiotics on time. Despite this, 30 (58.8%) had neurological complications, 6 (11.8%) died during hospitalization, and 15 (33.3%) of 45 survivals had long-term neurological sequelae at discharge. The correlation between serotype III and ST17 was evident (87.3% of all serotype III were ST17), and ST17 accounted for 47.1% of all these GBS isolates that caused meningitis. When compared with invasive GBS disease without meningitis, GBS meningitis in infants caused longer duration of hospitalization, higher rate of in-hospital mortality and was associated with long-term neurological sequelae.
Conclusion: Invasive GBS disease with meningitis still inevitably causes adverse outcomes. Further study to explore preventive strategies and development of serotype-based vaccines will be necessary in the future.
Disclosure: Nothing to disclose

EPR3046

Serotype replacement in adult pneumococcal meningitis in the Netherlands between 2014-2018

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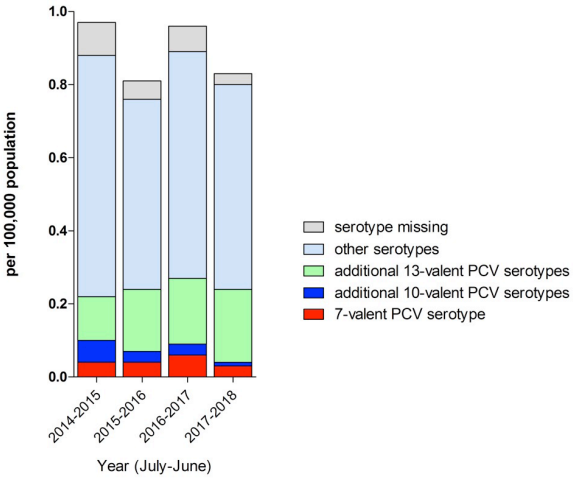
Background and aims: Streptococcus pneumoniae is the most common pathogen causing bacterial meningitis. The nationwide implementation of 7- and 10-valent pneumococcal vaccination (PCV) has resulted in a decline of pneumococcal meningitis incidence in The Netherlands. A nation-wide prospective bacterial meningitis cohort in the Netherlands did not show evidence for serotype replacement by non-PCV serotypes up to 2014, but this has been described in other invasive pneumoccocal disease.
Methods: National surveillance data from the Netherlands Reference Laboratory for Bacterial Meningitis were assessed for cases of culture-proven or PCR-positive pneumococcal meningitis identified between July 2014 and June 2018. Clinical data were obtained from patients included in a prospective nationwide cohort study. Nosocomial meningitis cases were excluded.
Results: A total of 500 pneumococcal meningitis cases (median age 63 (IQR 19), 243 female (49%)) were identified. Incidence was stable with a mean incidence of 0.89 cases per 100,000 population per year. Proportion of PCV10 serotypes declined during the study period (7% to 1%, p=0.02 [Figure 1]). However, proportion of PCV13 serotypes, which are not included in routine vaccination programs, concomitantly increased (13% to 24%, p=0.02). Increase of serotype 19A was most evident (2% to 10%, p<0.005). The rate of unfavorable outcome (Glasgow Outcome Scale score <5) was 153 of 347 patients (44%), and remained stable during the study period.

Incidence of pneumococcal meningitis in the Netherlands between 2014-2018.



Conclusion: The incidence of PCV10 serotype pneumococcal meningitis has further declined. However, the overall incidence of pneumococcal meningitis is still high due to serotype replacement, mainly by serotype 19A. Clinical outcome following pneumococcal meningitis remains poor.
Disclosure: Nothing to disclose

EPR3047

Progressive multifocal leukoencephalopathy in liver transplant recipients: a review of 21 cases

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Background and aims: To review the cases of progressive multifocal leukoencephalopathy (PML) in liver transplant recipients. To detect possible risk factors of PML in this group of patients.
Methods: PubMed and Cochrane data bases have been used to review the cases of PML after liver-transplantation. To statistical analysis, R package was used.
Results: In whole, 21 cases of PML in liver transplant recipients have been published (Table-1), 14 female and 7 male, 55 year-old mean. Viral chronic hepatitis was the most common cause of transplantation. The median time of PML onset following transplantation was 9 months (66.6% during the first 18 months). Only 3 cases developed PML more than 10 years after the transplant. All the cases but 2 were being treated with a combination of immunosuppressive drugs. Solely 2 had a single drug (mycophenolate mofetil in both) and developed the disease 9 and 11 years after the transplant, respectively. There seems to be an inversely relation between the total number of immusuppressants and the latency time (Figure 1). More than 50% of patients had previosuly needed an intensification of the immunosuppression regimen. Graft rejection after tapering of immunosuppression was reported in 2 cases. There is a mortality of 81%.

Case report	Gender	Age	Cause of transplantation	Immunosuppressive drugs	Need to intensify the immunosuppressive therapy	Latency time of PML onset following the transplant	Diagnosis of PML	Treatment of PML	Mortality: 81%	
									Survival time	Cause of death
Martinez and Abdel-Ilamada, 1993	Female	23	Not reported	Not reported	Yes: need to re-transplantation because of graft failure	7 months (postmortem diagnosis)	Postmortem brain biopsy	No	7 months y 2 weeks after the 2º transplantation	PML progression
Workhouse et al., 1994	Female	54	Hepatitis C virus cirrhosis	Cyclosporine A, azathioprine, and prednisolone, switched to tacrolimus and azathioprine	Yes: graft rejection	18 months (postmortem diagnosis)	Postmortem brain biopsy	No	18 months after transplantation	Other causes
Akram et al., 1995	Female	55	Cryptogenic cirrhosis	Cyclosporine A and prednisolone	Yes: need to re-transplantation because of graft failure	8 months (postmortem diagnosis)	Brain biopsy	No	8 months after transplantation	PML progression
Brunette et al., 1999	Male	51	Cryptogenic cirrhosis	Cyclosporine A, azathioprine and prednisolone	Yes: need to re-transplantation because of graft failure	2 months	Postmortem brain biopsy	-Ended immunosuppression regimen -Cytarabine	2 weeks after diagnosis, 17 weeks after transplantation	PML progression
Boulton-Jones et al., 2001	Female	60	Secondary biliary cirrhosis	Cyclosporine A and azathioprine switched to prednisolone, tacrolimus, add-on mycophenolate mofetil	Yes: graft rejection	11 months	JC Virus PCR on CSF	-Tapered and ended immunosuppression regimen -Cytarabine	Alive after 23 months after diagnosis	-
Lima et al., 2005	Female	39	Hepatitis C virus cirrhosis	Tacrolimus and prednisolone	No	8 months	JC Virus PCR on CSF	-Tapered immunosuppression regimen -Cytarabine	6 weeks after diagnosis, 9 months after transplantation	PML progression
Albert et al., 2006	Female	59	Hepatitis C virus cirrhosis	Prednisolone and tacrolimus	No	18 months	JC Virus PCR on CSF	-Tapered immunosuppression regimen -Cidofovir -PegIFN	5 months after diagnosis, 23 months after transplantation	PML progression
Yoka et al., 2009	Female	56	Hepatitis C virus cirrhosis	Mycophenolate mofetil	No	113 months	JC Virus PCR on CSF	-Tapered immunosuppression regimen	Not reported	PML progression
Verhelst et al., 2011	Female	72	Hepatitis C virus cirrhosis	Basiliximab, tacrolimus and mycophenolate mofetil	No	34 months	JC Virus PCR on CSF	-Tapered and ended immunosuppression regimen	4 months after diagnosis, 38 months after transplantation	PML progression
Mateos et al., 2011	Male	68	Hepatitis C virus cirrhosis alcohol	Not reported	Not reported	1 month	JC Virus PCR on CSF	Not reported	Alive 155 months after diagnosis	-
	Female	56	Cryptogenic	Not reported	Not reported	1 month	Postmortem brain biopsy	Not reported	8 months after diagnosis	Not reported
	Female	56	Cryptogenic	Not reported	Not reported	8 months	JC Virus PCR on CSF	Not reported	8 months after diagnosis	Not reported
	Female	42	Hepatitis C virus cirrhosis	Not reported	Not reported	116 months	JC Virus PCR on CSF	Not reported	124 months after diagnosis	Not reported
Mohanty et al. 2011	Female	45	Hepatitis C virus cirrhosis	Tacrolimus and prednisone	Yes: acute cellular rejection	6 weeks	JC Virus PCR on CSF and Postmortem brain biopsy	-Tapered immunosuppression regimen	Not reported	PML progression and multiorgan failure
Ocheni et al., 2015	Male	55	Hepatitis B virus cirrhosis. Re-transplantation due to hepatic artery thrombosis of the graft	Prednisolone, mycophenolate mofetil and tacrolimus	Yes: need to 2 re-transplantation because of graft failure	9 months	JC Virus PCR on CSF	-Ended immunosuppression regimen -Cytarabine	5 weeks after diagnosis, 10 months after transplantation	PML progression
Yoshida et al., 2015	Male	66	Hepatitis C virus cirrhosis and hepatic cell carcinoma	Tacrolimus and rapamycin	Yes: chronic graft-versus-host disease	48 months	JC Virus PCR on CSF	-Ended immunosuppression regimen -Mofetil	27 months after diagnosis	Liver failure
Dumoulin et al., 2016 (2 cases)	Female	48	Primary sclerosing cholangitis	Tacrolimus, mycophenolate mofetil, steroids	Yes: graft rejection	144 months	JC Virus PCR on CSF	-Tapered immunosuppression regimen	26 months after diagnosis	PML progression and Liver failure
	Male	54	Alcohol cirrhosis	Tacrolimus, steroids	Yes: pulmonary sarcoidosis	204 months	JC Virus PCR on CSF	-Tapered and ended of immunosuppression regimen	Alive 36 months after diagnosis	-
Moreno-Estébanez et al., 2017	Female	76	Hepatitis C virus cirrhosis and hepatic cell carcinoma	Mycophenolate mofetil	No	133 months	JC Virus PCR on CSF	-Tapered and ended immunosuppression regimen -Mitoxantrone	2 months and 14 days after clinical onset	PML progression
Arvesak et al., 2017	Male	65	Hepatitis C virus cirrhosis	Tacrolimus, mycophenolate mofetil and steroids	Not reported	4 months	JC Virus PCR on CSF	-Tapered immunosuppression regimen -Cidofovir -Mitoxantrone -Pegylated granulocyte colony-stimulating factor analog	Alive 4 months after diagnosis	-
Rastogi et al., 2017	Male	59	Hepatitis C virus cirrhosis and hepatic cell carcinoma	Tacrolimus, mycophenolate mofetil and steroids	No	2 months	Brain biopsy	-Tapered of immunosuppression regimen	3 weeks after diagnosis	PML progression

Cases of PML after liver transplantation. Table legend: PML, progressive multifocal leukoencephalopathy; PCR: Polymerase Chain Reaction; CSF: Cerebrospinal Fluid

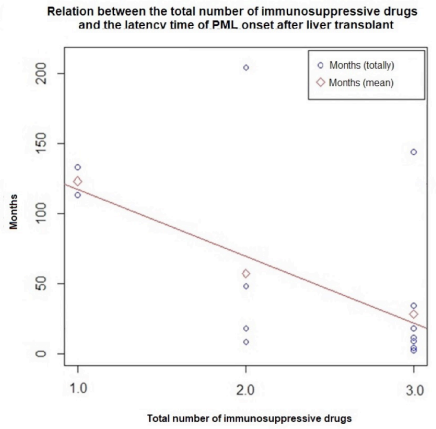

Figure: Regression line linking the mean of latency time of PML onset in months (y-axis) and the total number of immunosuppressants (x-axis): y=161,3 - 47,5 x, Pearson correlation: r= - 0,948, Determination coefficient: R= 0,89

Conclusion: PML is an uncommon but usually lethal complication of liver transplant linked to immunosuppressive drugs. Needing a higher number of immunosuppressants during a longer period of time or needing an intensification of immunosuppression may increase the risk of PML in liver transplant recipients. A greater diagnosis suspicion may be required in this subgroup of patients.
Disclosure: Nothing to disclose

EPR3048

Predictors of poor prognosis of Japanese encephalitis in adults

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Background and aims: Japanese encephalitis virus (JEV) causes encephalitis (JE), is a leading cause of viral encephalitis (JE) in North East India. It affects both adults and children mostly in rural areas and is associated with considerable mortality and morbidity.
Aims: We evaluate the predictors of poor prognosis in hospitalized adult patients with JE.
Materials and methods: Forty-seven patients with JE admitted in Assam Medical College, Dibrugarh, India were prospectively included during June 2017 to December 2018. Detailed clinical history and blood investigations were performed in all the patients. The diagnosis of JE was confirmed by detection of JEV specific IgM antibody in both CSF and serum. The poor prognosis was defined as either death at hospital or discharge against medical advice.
Results: Out of 47 patients, 55% were males. The mean age of the patients was 46.4 ±18.4 years. The most common presenting symptom was fever (100%) followed by altered sensorium (93.3%) and seizure (40.4%). Multiple infections were present in six cases (12.8%). Out of 47 patients, poor prognosis was observed in 48.9% of cases. Presence of diabetes mellitus, decreased CSF glucose level, decreased platelets counts, increased ALT and creatinine and presence of seizures were significantly associated with poor prognosis.
Conclusion: In JE, associated systemic disease and seizures predict poor outcome.
Disclosure: The work is supported by the Department of Biotechnology, Govt. of India.

EPR3049

Community-acquired bacterial meningitis due to cerebrospinal fluid leakage

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Background and aims: Cerebrospinal fluid (CSF) leakage is a risk factor for developing bacterial meningitis. Prospective studies evaluating CSF leakage associated bacterial meningitis are lacking.
Methods: We analyzed adult bacterial meningitis patients with CSF leakage from a prospective nationwide cohort study of community-acquired bacterial meningitis.
Results: We identified 65 episodes of CSF leak associated bacterial meningitis in 53 patients among 2022 episodes (3%) of community-acquired bacterial meningitis. The etiology of CSF leakage was identified in 49 episodes (75%), and mostly consisted of ear-nose-throat surgery in 19 (29%) episodes and remote head trauma in 15 (23%). The episode was a recurrence of meningitis in 38 (59%), 17 episodes (26%) were first episodes with a yet unrevealed CSF leakage, and 10 episodes (15%) were first episodes in patients with a previously identified CSF leak. Twenty recurrent episodes (53%) occurred despite surgery to close the CSF leak and 9 (14%) occurred after vaccination. Two patients were infected by serotype 7F pneumococci despite vaccination included this serotype. Liquorrhea was reported in 40 episodes (62%). The predominant causative agents were Streptococcus pneumoniae in 33 episodes (51%) and Haemophilus influenzae in 11 episodes (17%). The outcome was unfavorable (Glasgow outcome scale score <5) in 8 episodes (12%) and no patients died.
Conclusion: Patients with CSF leak associated bacterial meningitis have a high recurrence rate despite surgery to repair the leak or vaccination. Most patients have a mild disease course with a favorable outcome.
Disclosure: Nothing to disclose

EPR3050

Virus identification in cerebrospinal fluid of patients with CNS infections using Virus-Discovery-cDNA-AFLP and next generation sequencing (VIDISCA-NGS)

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Background and aims: Viral meningitis or encephalitis can be caused by various viruses. However, in about half of the patients with a clinical diagnosis of viral meningitis or encephalitis no pathogen is found during routine diagnostic work-up. With this study we aimed to validate a method to identify viruses, based on the cDNA amplified restriction fragment–length polymorphism technique (cDNA-AFLP), in cerebrospinal fluid (CSF) of patients with viral meningitis or encephalitis with and without identified causative pathogens.
Methods: Adult patients with a diagnosis of viral meningitis or encephalitis (based on clinical and/or laboratory results) were prospectively included. A selected panel of the most common causative viruses was tested in the CSF of these patients with quantitative polymerase chain reaction (qPCR). CSF specimens of all patients were then tested using the Virus-Discovery-cDNA-AFLP method, combined with Ion Torrent next generation sequencing (VIDISCA-NGS). Results from qPCR tests and VIDISCA-NGS were evaluated.
Results: From 2012 to 2015 we included 38 patients with viral meningitis or encephalitis. In 23 patients (60%) a causative pathogen was identified by qPCR. In ten of these patients the identified virus was also found by VIDISCA-NGS. In fifteen patients (40%) no virus could be identified by qPCR. In one of these patients, an enterovirus was discovered by VIDISCA-NGS.
Conclusion: In patients with a clinical diagnosis of viral meningitis or encephalitis but no identified causative virus by PCR in CSF, VIDISCA-NGS could be of additional diagnostic value. Studies in larger patient populations with suspected viral meningitis or encephalitis are necessary to determine diagnostic accuracy of VIDISCA-NGS in CSF.
Disclosure: Nothing to disclose

Miscellaneous

EPR3051

Spinal cord atrophy in neuromyelitis optica spectrum disorders is associated to spinal cord lesions and clinical disability

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Background and aims: Aim of this study is to characterize the spatial distribution of spinal cord atrophy in neuromyelitis optica spectrum disorder (NMOSD) patients, its relation with T1-hypointense lesions and their correlation with clinical disability.
Methods: Cord 3D-T1-weighted scans were acquired from 52 aquaporine4-positive NMOSD patients from two centers (Belgrade and Milan) and 28 age- and sex-matched healthy controls (HC). After identifying cord T1-hypointense lesions, binary lesion masks were produced. The active surface method was applied to calculate cross-sectional area of cervical and upper dorsal cord (until D3). A voxel-wise assessment of T1-weighted hypointense lesion probability maps (LPM) was performed and cord atrophy was compared between groups.
Results: Thirty-eight (73%) NMOSD patients had T1-hypointense cord lesions. LPM showed a predominant involvement of the upper cervical cord (C3-C4, 20%) and upper thoracic cord (D1, 20%), with a central distribution of lesions on the axial slices. In NMOSD, cord atrophy was in the anterior and posterior columns with a significant damage at C3-C4 ($p<0.001$) and D1 ($p<0.01$) segments, co-localized with focal cord lesions. Cervical cord lesions and atrophy correlated with Expanded Disability Status Scale (EDSS) ($p<0.01$). Pyramidal and sensitive EDSS subscores correlated with atrophy at lower cervical and upper thoracic levels ($p<0.01$). NMOSD patients without spinal cord lesions had no significant cord atrophy compared to HC.
Conclusion: NMOSD patients showed focal areas of spinal cord atrophy, corresponding to regions of higher lesional involvement. Such an evidence suggests the existence of a focal, inflammatory-driven mechanism of damage rather than a primary neurodegenerative and diffuse process.
Disclosure: Nothing to disclose

EPR3052

Seizures as an initial clinical presentation of reversible cerebral vasoconstriction syndrome due to cannabis overdose

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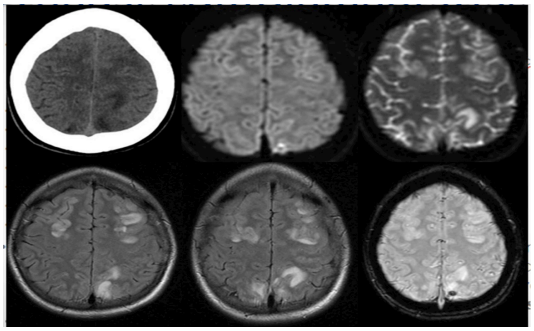
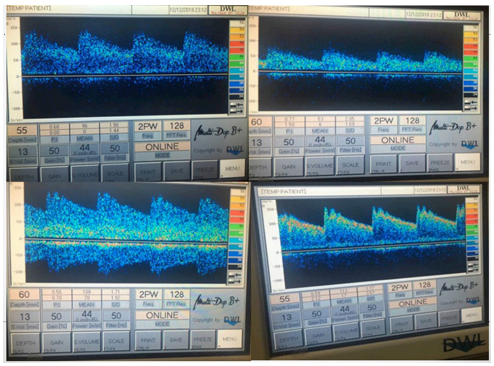
Background and aims: We report a case of a young woman with reversible cerebral vasoconstriction syndrome (RCVS) secondary to cannabis overdose with an uncommon clinical presentation of seizures and recurrent vomiting



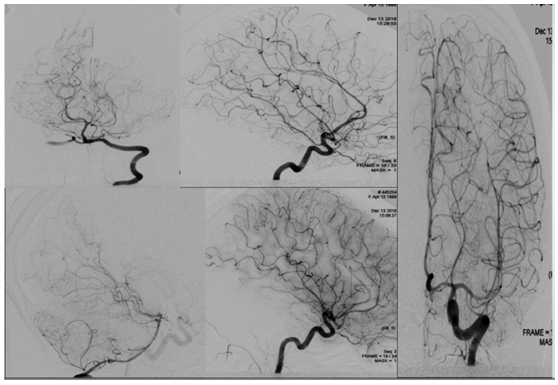
CT scan and cranial MRI were performed visualizing acute ischemic bilateral frontoparietal subcortical lesions with vasogenic edema, as well as chronic hemorrhagic deposits in both posteroparietal regions.

Methods: A 19-year-old female patient with episodes of recurrent vomitng presented a generalized tonic-clonic seizure followed by intense holocranial headache, with no other neurological focus on examination except high blood pressure. CT scan and cranial MRI were performed visualizing acute ischemic bilateral frontoparietal subcortical lesions with vasogenic edema, as well as chronic hemorrhagic deposits in both posteroparietal regions. Infectious, autoimmune, porphyria and vasculitic ethologies were excluded after exentesive studies in blood and CSF samples. A transcranial Doppler study showed datas compatible with segmental stenosis in both MCAs. In a new anamnesis the patient confessed that in the last days she has been consumming high dosis of cannabis during festival days (10 cigars per day).



Transcranial Doppler study showed datas compatible with segmental stenosis in both MCAs.

Results: Given the suspicion of RCVS, an intracraneal arteriorgraphy was done, showing multiple vasospasms in segmental distal territories of both ACA and left PCA, with lesser involvement of MCA. Toxic in urine was possitive for cannabis. Finally, she was discharged asymptomatic in the third week after treatment with metilprednisolone, analgesics and levetiracetam.



Intracraneal arteriorgraphy, showing multiple vasospasms in segmental distal territories of both ACA and left PCA, with lesser involvement of MCA.

Conclusion: The RCVS is characterized by intense headaches with or without other acute neurological symptoms accompanied by diffuse segmental vasoconstriction of the cerebral arteries that resolves spontaneously within three months. We highlight the unusual initial clinical presentation with vomiting and epileptic seizure after taking cannabis, a drug that is currently a major problem for our teenagers.
Disclosure: Nothing to disclose

EPR3053

Importance of heart rate variability analysis in post stroke cardiac autonomic dysfunction

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Background and aims: Assessment of cardiovascular autonomic activity is required for preventing life-threatening complications in stroke patients.
Our purpose was to evaluate cardiac autonomic activity in ischemic stroke patients using heart rate variability (HRV) analysis, illustrating the sympathovagal balance in different sympathetic and parasympathetic activation tests.
Methods: We analyzed the dynamics of the linear and non-linear HRV parameters in 40 right and 31 left middle cerebral artery ischemic stroke patients in resting state and during autonomic activation tests (Ewing tests). Data were compared with 30 age- and sex-matched healthy controls.
Results: Our results underlined a functional differentiation regarding the central autonomic modulation on HRV according to the hemispheric lateralization of the focal ischemic lesion. Left hemisphere stroke patients presented enhanced parasympathetic modulation of the heart rate (increased values for time and frequency domain parameters RMSSD, pNN50, HF, $p<0.05$) in resting state, in contrast to right hemisphere stroke patients, who presented a reduced cardiac parasympathetic control in resting state and during autonomic activation tests (hand grip and standing tests). Non-linear parameters DFA $\alpha 1$ and SD1 revealed a decrease of variability and complexity of the heart rate in right hemisphere stroke patients compared to controls and to left hemisphere stroke patients, later improved during vagal activation tests.
Conclusion: HRV analysis in resting state and during autonomic activation tests may reveal a sympathetic hyperactivation and a decrease of HRV in stroke patients. New therapeutic strategies for restoring sympathovagal balance in ischemic stroke patients may be developed based on autonomic nervous system modulation, by early pharmacologic or non-pharmacologic intervention.
Disclosure: Nothing to disclose

EPR3054

Para-infectious autonomic dysfunction following West Nile virus neuroinvasive disease

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Background and aims: West Nile virus (WNV) is a mosquito-borne neurotropic flavivirus which can manifest as a variety of clinical syndromes including meningo-encephalitis and acute flaccid paralysis. Autonomic dysfunction may be observed in this setting though little is known about autonomic impairment post-infection.
Methods: We present 3 cases of para-infectious autonomic dysfunction following West Nile Virus neuroinvasive disease.
Results: All 3 patients were diagnosed with WNV neuroinvasive disease based on clinical syndrome compatible with meningitis with positive WNV serologies or PCR testing. All had meningoencephalitis and Patient 1, the only immunocompromised one, had the most severe disease additionally with status epilepticus, anterior horn cell disease, and radiculitis. Autonomic reflex screens were completed in ambulatory setting months post-infection. Symptoms included fatigue and orthostatic intolerance. Patients 1 and 3 had excessive heart rate increment with tilt suggestive of postural tachycardia syndrome (POTS). Patient 1 additionally had hypertensive response with tilt and impaired postganglionic sympathetic sudomotor impairment, though latter potentially from medication effect. Patient 2 had evidence of cardiovascular adrenergic failure with borderline orthostatic hypotension (OH) with collapse in pulse pressure. Treatment included conservative measures for POTS and use of midodrine for OH. Patients 1 and 2 had full recovery from their autonomic disorder, whereas patient 3 continues to be symptomatic more than 2 years post-infection.
Conclusion: These cases highlight the presence and heterogeneity of autonomic dysfunction following West Nile Virus neuroinvasive disease. While direct infection of neurons has been implicated in autonomic dysfunction in acute WNV infection, relatively benign course suggests alternative mechanisms may contribute to autonomic perturbations.
Disclosure: Nothing to disclose

EPR3055

Should patients be told of their HIV-associated neurocognitive disorder Diagnosis?: a qualitative Analysis

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Background and aims: Between 30-50% of adults with HIV meet the clinical criteria for HIV-Associated Neurocognitive Disorder (HAND) when cognitively tested. Albeit, most people with HIV are unaware of HAND, much less whether they have it. Since there are no consensus-derived treatment guidelines, clinically is it not clear whether adults with HIV should be tested for HAND. This study examined participants' reactions to receiving news of a possible HAND diagnosis.
Methods: Participants (N=137) from a clinical trial investigating cognitive training in middle-aged adults (40+) with HIV were administered a cognitive battery; from this a HAND diagnosis was determined using the Frascati criteria. Upon being informed in a letter that they may have HAND, participants were later asked open-ended questions about their reactions to receiving news of this diagnosis.
Results: Participants' responses were coded into three major themes: negatively (n=49), indifference (n=93), and positively (n=132); each contained 3-4 subthemes. Negatively included denial (n=1), fear (n=23), surprise (n=18), and discontentment (n=7). Indifference included confusion (n=9), non-reactive responses (n=66), and apathy (n=18). Positively included responses of curiosity (n=18), desire for improvement (n=52), confirmation (n=34), and gratitude (n=28).
Conclusion: For many, the HAND diagnosis resulted in duress; however, this diagnosis seemed to benefit some participants by affirming perceived cognitive declines. Future research needs to investigate participants' health literacy concerning cognitive function and examine their attitudes towards possible therapies. This is especially important as nearly 50% of those with HIV are 50 and older and may experience accelerated age-related cognitive declines. Ethical implications of these findings are provided.
Disclosure: Nothing to disclose

Motor neurone diseases 3

EPR3056

Defining benign brachial monomelic amyotrophy: factors at presentation that differentiate from motor neurone disease

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Background and aims: Benign brachial monomelic amyotrophy (BMA) is a rare syndrome characterised by isolated lower motor neurone weakness of the upper-limbs, which can mimic motor neurone disease (MND) at onset. In contrast to MND, following a period of slow progression, the symptoms of BMA arrest. Differential diagnosis is challenging at first presentation. This study aims to determine the diagnostic value of clinical features and investigations at onset that differentiate BMA from MND.
Methods: Detailed phenotyping of baseline clinical profiles, biochemical, imaging and electrophysiological findings was performed in patients presenting with isolated upper-limb onset weakness to a tertiary neuroscience centre over 15 years. Diagnosis after >5 years of follow-up was recorded. Multivariate logistic regression was used to develop a predictive model.
Results: Compared to the MND group (n=45), patients with BMA (n=13) were significantly younger (median 39 years (20-50) vs 64 years (53-70), $p<0.0001$) and had a longer duration of symptoms (median 53 months (28-100) vs 18 months (10-47), $p=0.013$) at presentation. Clinically, BMA patients more frequently presented with unilateral onset ($p=0.016$), distal weakness ($p=0.024$), fewer clinical fasciculations ($p<0.0001$), sensory abnormalities ($p=0.038$), and less frequent electrophysiological denervation outside the cervical region ($p=0.0002$), compared to MND patients. The optimised predictive model, combining age at symptom onset with the presence of fasciculations in any region, correctly predicted 93.0% of BMA and MND diagnoses (sensitivity for diagnosis of BMA: 76.9%; specificity 97.7%).
Conclusion: Clinical and electrophysiological differences at presentation can help differentiate between upper-limb onset MND and BMA. The predictive model needs to be validated in an independent cohort.
Disclosure: Nothing to disclose

EPR3057

Comparative profiling of peripheral blood mononuclear cells proteome in patients with friedreich's ataxia

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Background and aims: Friedreich's ataxia (FRDA) is an autosomal recessive disorder caused by the intronic (GAA) repeat expansion in the FXN gene on chromosome 9q13. The expanded repeats acts as a transcriptional inhibitor, decreasing the expression of the protein frataxin, which leads to progressive cardio- and neurodegeneration
Aim: In this study we aim to identify differentially expressed peripheral blood mononuclear cells (PBMCs) proteins in FRDA patients for their diagnostic/prognostic applications.
Methods: Genetically confirmed homozygous FRDA patients (n=25) with FARS scores of 80±6 and age- and gender-matched healthy controls were included in this study. PBMC proteomics was done using two-dimensional difference in-gel electrophoresis and differentially expressed protein spots were selected (fold change ≥ 1.5; $P<0.05$) and identified by LC-MS/MS.
Results: Quantitative proteomic analysis revealed 11 differentially expressed protein spots. These proteins were found to be associated with various pathophysiological aspects of FRDA such as neuropathy and neurodegeneration (chloride intracellular channel protein 3; interferon inducible protein AIM2; GTPase activating Rap/Ran GAP domain like protein3; T complex protein 1), ataxia (apolipoprotein A-I;Annexin 1), oxidative stress (Caspase8), hypertrophic cardiomyopathy (Ca/calmodulin dependent protein kinase; actin α cardiac muscle 1; β-enolase), diabetes (mitogen activated protein kinase kinase), muscle spacity (T complex protein 1).
Conclusion: The identified PBMC proteins are suggestive of noble cellular biomarker pool and further investigations of these differentially expressed proteins can aid in identifying prognostic/diagnostic markers for FRDA.
Disclosure: Nothing to disclose

EPR3058

Prognostic value of high field MRI features in amyotrophic lateral sclerosis

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Background and aims: The natural history of amyotrophic lateral sclerosis (ALS) is extremely heterogeneous in terms of clinical presentation and survival. Conventional MRI can identify abnormalities associated with upper motor neuron (UMN) involvement, especially with high field scanners. We evaluated the prognostic contribution of 3T-MRI in ALS patients.

Methods: We retrospectively evaluated MRI from 81 ALS patients. 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 (CCT) T2/FLAIR hyperintensity, motor cortex (MC) T2*/SWI hypointensity and selective MC atrophy. The association of MRI features with death and clinical milestones (i.e. percutaneous endoscopic gastrostomy/parenteral nutrition and invasive/non-invasive ventilation) was analyzed using Cox proportional hazards models, adjusting for age at MRI, sex, and phenotype.

Results: Cox proportional hazards models showed that CCT T2/FLAIR hyperintensity (HR: 3.56, 95% CI: 1.34 to 9.49, p=0.011; figure 1), MC T2*/SWI hypointensity (HR: 2.17, 95% CI: 0.97 to 4.85, p=0.043; figure 2) and, to a greater extent, the combination of these two MRI features (HR: 4.41, 95% CI: 1.73 to 11.22, p=0.002; figure 3) predicted worst survival. CCT T2/FLAIR hyperintensity was also associated with less time to invasive/non-invasive ventilation (HR: 3.51, 95% CI: 1.35 to 9.12, p=0.01).

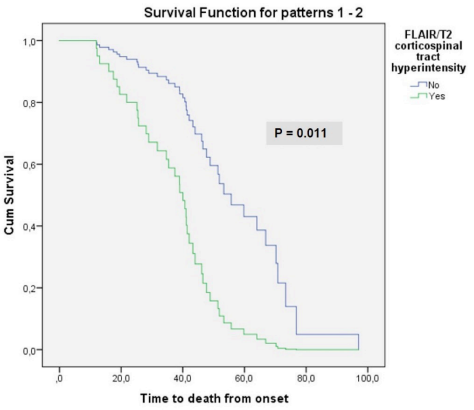

Figure 1

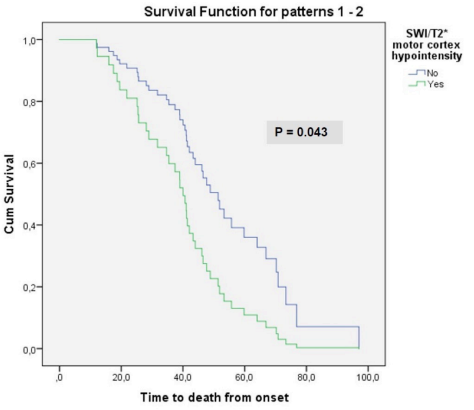

Figure 2

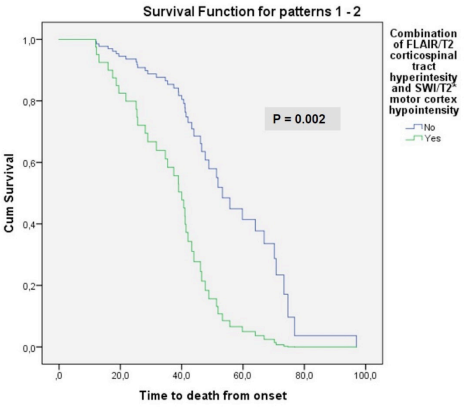

Figure 3

Conclusion: 3T-MRI is able to detect specific changes related to UMN involvement that are predictors of worst survival in ALS patients.

Disclosure: Nothing to disclose

EPR3059

Advance care planning in chronic progressive neurological disease: what we can learn from ALS

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Background: Advance care planning (ACP) is a systematically organized and ongoing communication process about patients' values, goals and preferences regarding medical care during serious illness, and aims to involve patients in decision-making before they become cognitively and communicatively incapable. In daily practice, however, it is underutilized except for specialty clinics.
Aim: To study ACP in the tertiary ALS centre Amsterdam and formulate recommendations for integration of ACP in the care of patients with other chronic progressive neurological diseases (CPNDs).
Methods: Non-participating observations of all medical appointments of patients with amyotrophic lateral sclerosis (ALS) or progressive muscular atrophy (PMA), in various stages of disease, during 6 consecutive months, followed by single in-depth interviews, and an inductive analysis.
Results: 28 Dutch patients participated, varying in age, gender, disease onset and severity of physical decline. ACP started directly when the diagnosis was given, by means of a general outlook on the future with progressive disability and immediate introduction to a customized multidisciplinary team. During follow-up ACP was realized by regular appointments in which monitoring of the patient's status and clear communication strategies formed the basis of tailor-made discussions on treatment options. Patients accepted this policy as careful professional guidance.
Conclusion: ACP is a professional communication process throughout the whole course of disease. It is feasible to integrate ACP in the follow-up of patients with ALS/PMA from diagnosis onwards. Supported by recent literature, we argue that such a well-structured approach would also enhance the quality of care and life of patients with other CPNDs.
Disclosure: The Netherlands Organization for Health Research and Development (ZonMw) funded this research project, but was not involved in any part of it.

EPR3060

Survival prediction models in motor neuron disease

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Background and aims: Motor neuron disease (MND) shows a highly heterogenous clinical progression. We aimed to assess the predictive value of multimodal brain magnetic resonance imaging (MRI) on survival in a large cohort of MND patients, in combination with clinical and cognitive features.
Methods: 200 MND patients were followed-up for a median of 4.13 years. At baseline, subjects underwent neurologic examination, cognitive assessment, and brain MRI. Grey matter (GM) volumes of cortical and subcortical structures and diffusion tensor (DT) MRI metrics of white matter tracts were obtained. A multivariable Royston-Parmar survival model was created using clinical and cognitive variables, assessing the increase of survival prediction accuracy provided by MRI variables.
Results: The multivariable clinical model included predominant upper or lower motor neuron presentations and diagnostic delay as significant prognostic predictors, reaching an AUC of 4-year survival prediction of 0.79. The combined clinical and MRI model including GM volumes of selected fronto-temporal regions and DT MRI metrics of the corticospinal and extra-motor tracts reached an AUC of 0.89. Considering amyotrophic lateral sclerosis (ALS) patients only, the multivariable clinical model including diagnostic delay and semantic fluency scores provided an AUC of 0.62, whereas the combined clinical and MRI model reached an AUC of 0.77.
Conclusion: Our study demonstrated that brain MRI measures of structural damage of the motor and extra-motor systems, when combined with clinical and cognitive features, are useful predictors of survival in patients with MND, particularly when a diagnosis of ALS is made.
Disclosure: Italian Ministry of Health (#RF-2010-2313220; #RF-2011-02351193).

EPR3061

A PET–based molecular study of microglia activation in SOD1 amyotrophic lateral sclerosis

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Background and aims: SOD1 mutations cause about 20% of familial amyotrophic lateral sclerosis (ALS). It has been suggested that SOD1 mutations might generate microglial activation triggering neurodegeneration. [11C]-PK11195 is the prototypical and most validated PET radiotracer to measure microglia activation, targeting the translocator protein (TSPO) which is overexpressed by activated microglia. Using [11C]-PK11195-PET, we in vivo investigated microglia activation in pre-symptomatic (preSOD1) and symptomatic (symSOD1) mutated carriers of familial ALS SOD1 mutation.

Methods: We studied N=4 preSOD1, neurologically normal, N=6 symSOD1 with probable ALS, and N=9 healthy controls (HC) for comparison. [11C]-PK11195 binding-potentials were estimated with a receptor parametric mapping procedure, a basis function implementation of the simplified reference tissue modeling method. Voxel-wise statistical comparisons were performed at group and single-subject level, thus estimating individual voxel-wise z-score maps for participants considering the HCs as reference.

Results: Both the symSOD1 and preSOD1 groups showed significant microglia activation peaking in the occipital lobe. At the individual level, there was a pattern variability, with subjects showing several clusters of activation across frontal, temporal, parietal and occipital regions, plus cerebellum, thalamus and medulla oblongata. The symSOD1 additionally showed consistent microglia activation in supplementary, primary motor and somatosensory regions.

Conclusion: SOD1 ALS is characterised by a significant but heterogeneous microglia activation since the earliest preclinical phase that seems to evolve during disease progression up to the involvement of structures implicated in motor control and execution. Further researches on the temporal and spatial dynamics of microglia activation and its relationship with neurodegeneration are necessary.

Disclosure: Nothing to disclose

EPR3062

FIREFISH Part 1: survival, ventilation and swallowing ability in infants with type 1 spinal muscular atrophy (SMA) treated with risdiplam (RG7916)

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Background and aims: Type 1 SMA is a debilitating neuromuscular disease, in which untreated infants require nutritional assistance, permanent ventilation, and typically die before 2 years of age. SMA is caused by reduced levels of the survival of motor neuron (SMN) protein from deletions and/or mutations in the SMN1 gene. SMN2 produces only low levels of functional SMN protein. Risdiplam (RG7916/RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing towards increasing SMN protein levels.

Methods: FIREFISH (NCT02913482) is an ongoing, multicentre, open-label, operationally seamless study of risdiplam in infants aged 1–7 months with Type 1 SMA and two SMN2 copies. Part 1 (N=21) assesses the safety, tolerability and PK/PD of different risdiplam dose levels (plus exploratory outcomes). Part 2 (N=40) is assessing the safety and efficacy of risdiplam.

Results: In a Part 1 interim anaylsis (data-cut, 07/09/18), survival rate was 90.5% (19/21) and no surviving infant required tracheostomy, reached permanent ventilation or lost the ability to swallow. Updated data on event-free survival rates, swallowing ability and exploratory outcome measures will be presented based on 1-year data from the trial.

Conclusion: In Part 1, event-free survival rates were improved in infants with Type 1 SMA receiving risdiplam compared with infants of the same age in natural history studies. Part 2 is ongoing worldwide.

Disclosure: Study sponsored by F. Hoffmann-La Roche AG, Basel, Switzerland. Writing and editorial assistance was provided by MediTech Media, UK, in accordance with Good Publication Practice (GPP3) guidelines.

Movement disorders 7

EPR3063

Intrinsic functional connectivity correlates of anxiety in cognitively unimpaired drug-naïve Parkinson's disease patients

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Background and aims: Anxiety symptoms are common in Parkinson's disease (PD) and have been proposed as a potential biomarker of future cognitive impairment. Using resting-state functional MRI, we investigated intrinsic brain networks connectivity correlates of anxiety in a cohort of cognitively unimpaired drug-naïve patients with PD.

Methods: 3T MRI images of 41 drug-naïve PD patients (with and without anxiety), and 20 matched healthy controls (HC) were acquired. Anxiety presence and severity was assessed by means of a clinical interview and the Parkinson's Disease Anxiety Scale (PAS). Single-subject and group-level independent component analysis was used to investigate intra and inter-network functional connectivity differences within the default mode (DMN), fronto-parietal (FPN), salience (SN) and executive control (ECN) networks between patients sub-groups and HC. Finally, linear regression analysis was used to investigate correlations between imaging and clinical data.

Results: Decreased connectivity within the DMN and the FPN as well as an increased connectivity within the SN and the ECN were detected in PD patients with anxiety compared with those without. Moreover, PD patients with anxiety showed a disrupted inter-network connectivity between FPN and SN. This imaging pattern was found to be correlated with both behavioral (i.e. PAS) and cognitive outcomes in PD patients.

Conclusion: Our findings demonstrated that an abnormal intrinsic brain connectivity within and between the major large-scale neurocognitive networks may represent a potential neural correlates of anxiety symptoms and severity in drug-naïve PD patients. These connectivity changes could be proposed as a potential biomarker of treatment response in clinical trial.

Disclosure: Nothing to disclose

EPR3064

Longitudinal evolution of white matter damage in Parkinson's disease

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

Methods: 152 PD patients underwent clinical assessment, cognitive evaluation and MRI scan (including T2-weighted and diffusion tensor [DT] MRI sequences) once a year over a follow-up of 36 months. White matter lesions (WML) were manually identified on T2-weighted scans and the total WML volume was calculated. Applying tract-based spatial statistics (TBSS), mean fractional anisotropy (FA), mean (MD), axial (axD) and radial (radD) diffusivity values of the total WM skeleton were extracted. Longitudinal regression models and Pearson correlation analyses between MRI and clinical/cognitive data were performed, adjusting for baseline motor impairment measured using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III).

Results: UPDRS-III score ($p<0.001$) and WML volume ($p<0.001$) showed significant progression over follow-up. Longitudinal trajectories of MD, axD, and radD values significantly correlated with UPDRS-III (r ranging 0.24/0.37, p ranging 0.01/0.04) and Addenbrooke Cognitive Examination total score (r ranging -0.27/-0.29, p ranging 0.01/0.02). WML volume did not correlate with longitudinal alterations of clinical variables.

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

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EPR3065

MR guided focused ultrasound thalamotomy for essential tremor: a 4 year single center experience

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Background and aims: MRI guided focused ultrasound (MRgFUS) is a new technology that enables VIM thalamotomy through an intact skull. Intracranial targeted tissue is warmed up gradually, while the patient is awake, for maximal efficacy and in order to avoid adverse events. We report our experience in treating patients with medication resistant Essential Tremor (ET) over a 4 years period.
Methods: 44 ET patients treated with unilateral MRgFUS VIM thalamotomy were assessed using the Clinical Rating Scale for Tremor (CRST) score and the Quality of Life in Essential Tremor Questionnaire (QUEST).
Results: Tremor was significantly improved immediately following MRgFUS in all patients and ceased completely in 24 patients. CRST scores significantly decreased from 45.3±13.3 to 19.9±11.1 at 1 year ($p<0.0001$). During a 4 year follow-up period, CRST scores remained significantly improved (19.5±16.2 at 2 years [$p<0.0001$], 23.6±18 at 3 years [$p=0.002$] and 22.5±25.9 [$p=0.01$] at 4 years, as compared with baseline). Significant return of tremor was seen in 5 patients. Quest scores showed significant improvement from 44.8±19.5 to 21.3±22.0 at 1 year ($p<0.0001$) and remained significantly lower during follow-up. Adverse events were mild and completely reversible in all but one patient who continues to suffer from mild gait ataxia.
Conclusion: MRgFUS for ET is an effective and safe procedure that provides long term tremor relief and improvement in quality of life in patients with medication resistant disabling tremor. Additional larger studies are needed to substantiate our results.
Disclosure: Nothing to disclose

EPR3066

Directional versus omnidirectional deep brain stimulation for Parkinson's disease: 3-month results of a prospective, blinded comparison, multi-center study

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Background and aims: To date, few studies have examined the clinical effects of directional deep brain stimulation (DBS). Directional leads have 4 ring electrodes, with the two middle rings divided into 3 segments. The Infinity DBS system (Abbott) is able to deliver conventional, omni-directional, stimulation to all 3 segments of the ring, or directional stimulation to only one or two segments. PROGRESS is the largest, prospective, directional lead study conducted to evaluate the safety and efficacy of the Infinity DBS system.
Methods: 229 Parkinson patients with bilateral STN DBS were enrolled in the PROGRESS study at 35 sites. The primary endpoint was the difference in therapeutic window between directional vs. omnidirectional stimulation, assessed during a follow-up visit after the first 3 months of omnidirectional stimulation. After identification of the optimal segment, subjects were then stimulated in directional mode for the following 3 months.
Results: Enrollment in PROGRESS ended on January 15, 2019, and all 3-month follow-up visits will be completed by May 2019. We will present the results of the blinded evaluation of the primary endpoint, the difference in therapeutic window between directional and omnidirectional stimulation, as well as data on safety, therapeutic current strength and total electrical energy delivered.
Conclusion: PROGRESS assessed the impact of directional DBS stimulation on therapeutic window using a blinded subject, blinded observer comparison. We will report the results of the largest study of DBS programming and the first multi-center experience with directional DBS.
Disclosure: Florence Defresne, Edward Karst and Binith Cheeran are Abbott employees.

EPR3067

Handicap as a measure of perceived health status in Parkinson's disease

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Background and aims: Handicap is a patient-centered outcome measure of health status encompassing the impact of social and physical environment on daily-living. It was previously assessed in advanced and late-stage Parkinson's disease (PD) patients, but there is no data concerning the rest of the disease spectrum.
We aim to characterize the handicap of a broad sample of PD patients.
Methods: Cross-sectional assessment of 405 PD patients during the MDS-UPDRS Portuguese validation study, using the MDS-UPDRS, unified dyskinesias rating scale, nonmotor symptoms questionnaire and PDQ-8. Handicap was measured using the London Handicap Scale (LHS) (maximum handicap=0; minimum handicap=1).
Results: Mean age 64.42 (±10.3) years, mean disease duration 11.30(±6.5) years and median Hoehn and Yahr (HY) 2 (IQR, 2-3). Mean LHS total score was 0.652 (±0.204). Mobility, occupation and physical independence were the most affected subdomains. Handicap was significantly correlated with disease duration (r=-0.35), motor experiences of daily living (EDL)(MDS-UPDRS-II) (r=-0.69), nonmotor EDL (MDS-UPDRS-I) (r=-0.51), motor disability (MDS-UPDRS-III) (r=-0.49), axial signs of MDS-UPDRS-III (r=-0.55), HY stage (r=-0.44), presence of nonmotor symptoms (r=-0.51) and PDQ-8 index (r=-0.64) (all $p<0.05$). Motor EDL, MDS-UPDRS-III and PDQ-8 independently predicted Handicap (adjusted R2=0.582; p=0.007).
Conclusion: The LHS was easily completed by patients and caregivers, independently of disease duration. Patients were mild to moderately handicapped and this was strongly determined by motor disability and its impact on EDL, and poor QoL. Despite strongly correlated, handicap and QoL might measure different perceived health status. Handicap seems to be a good measure of perceived-health status in PD.
Disclosure: Nothing to disclose

EPR3068

The impact of subthalamic deep brain stimulation on sleep and other non-motor symptoms in Parkinson's disease

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Background and aims: The non-motor symptoms (NMS) have a major impact on quality of life (QoL) in patients with Parkinson's disease (PD). We present results of the study on the impact of subthalamic deep brain stimulation (DBS-STN) on sleep and other NMS in PD patients.
Methods: 36 patients with advanced PD were assessed with NMS Scale (NMSS), PD Sleep Scale (PDSS), PD QoL questionnaire (PDQ-39), international RLS study group rating scale (IRLS), Beck depression inventory (BDI), before and at 6 and 12 months after surgery. Twenty four were evaluated with two-night polysomnography (PSG) before surgery and at 6 months after surgery.
Results: DBS-STN resulted in the deterioration of objective sleep parameters (total sleep time: 326 and 251 min, sleep efficiency: 68 and 52%, N1 sleep: 33 and 64 min, N2 sleep: 219 and 113 min, wakefulness after sleep onset: 136 and 199 min, sleep latency: 11 and 17 min, before and at 6 months after surgery, respectively). DBS-STN led to improvement in the subjective sleep scales, other NMS and QoL (PDSS: 81. 91 and 88, NMSS: 56.36 and 32, IRLS: 24. 18 and 19, PDQ39: 59. 42 and 48, before and at 6 and 12 months after surgery, respectively). Subjective improvement was most prominent in the first 6 months after DBS-STN and later significantly diminished in parallel to mood deterioration (as assessed by BDI).
Conclusion: DBS-STN deteriorated objective sleep parameters, whereas, improved subjective sleep disturbances, other NMS and QoL. Subjective improvement corresponded to changes in mood over time.
Disclosure: Nothing to disclose

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EPR3069

Drooling in Parkinson's disease: an [123I] FP-CIT SPECT study

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Background: Drooling is a common and troublesome symptom in Parkinson's disease (PD) patients, however the mechanisms underlying development of drooling remain unclear. This study used [123I]FP-CIT SPECT to evaluate the association between drooling and disease pathology (striatal dopamine uptake) and clinical progression (motor and cognitive symptoms).
Aims: To evaluate the association between drooling and striatal dopamine terminals and assess the hypothesis that drooling correlates with disease progression in de novo PD patients.
Methods: We included 389 de novo PD patients from the Parkinson's Progression Markers Initiative (PPMI) database. Using the MDS-UPDRS, PD patients were classified according to the presence (n=82) or absence (n=307) of drooling at baseline. PD patients had [123I]FP-CIT SPECT and structural MRI at baseline, and clinical assessments (motor, cognition and non-motor) at baseline and follow-up visits for 60 months. We investigated the association between drooling with the clinical and neuroimaging data.
Results: At baseline 21.1% of the PD patients reported some degree of drooling. Drooling in PD patients was associated with higher motor scores ($P<0.001$) and lower dopamine transporter binding in the putamen ($P<0.01$). Bradykinesia ($r=0.286$; $P<0.001$) and rigidity ($r=0.149$; $P=0.003$) correlated with the specific binding ratio (SBR) of putamen ($r=-0.132$; $P=0.009$). Cox survival analysis showed that the presence of drooling was associated with faster cognitive decline (HR=1.823; P=0.007; 95% CI=1.176-2.827).
Conclusion: PD patients with drooling show prominent dopaminergic pathology compared to those without drooling and the severity of drooling is associated with cognitive decline.
Disclosure: Data was obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). PPMI is sponsored by the Michael J. Fox Foundation for Parkinson's Research (MJFF) and is co-funded by MJFF, Abbvie, Avid Radiopharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Covance, Eli Lilly & Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Merck, MesoScale, Piramal, Pfizer and UCB. Industry partners contribute through financial and in-kind donations and provide feedback on study parameters through the Industry Scientific Advisory Board, which is positioned to inform the selection and review of potential progression markers that could be used in clinical testing.

EPR3070

Structural connectivity changes in prodromal Parkinson's disease patients: a multimodal MRI study

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Background and aims: There is wide consensus that prolonged prodromal phase precedes the onset of motor symptoms in Parkinson's disease (PD). We hypothesised that changes in the brain structure and connectivity would be present at this stage.
Methods: We included T1- and DTI-MRI data of 21 prodromal subjects, with anosmia or idiopathic rapid eye movement sleep behaviour disorder (RBD), to assess structural changes in grey (GM) and white matter (WM) in comparison with 60 age- and gender- matched healthy controls. Voxel-based morphometry (VBM) was used to quantify GM changes and tract-based spatial statistics to quantify WM fractional anisotropy (FA) and mean diffusivity (MD).
Results: Prodromal PD subjects had greater RBD symptoms and olfactory dysfunction, and greater global non-motor burden (MDS-UPDRS I) and autonomic dysfunction (SCOPA-AUT) compared to healthy controls ($P<0.05$). Prodromal subjects showed structural and microstructural changes in the hypothalamus, with decreased VBM-GM ($P<0.05$) and WM-FA ($P<0.001$), and increased WM-MD values ($P<0.001$). Lower VBM-GM in the hypothalamus correlated with greater non-motor burden ($r=-0.664$, $P=0.004$) and autonomic dysfunction ($r=-0.740$, $P=0.001$). Prodromal PD patients also showed increased WM-MD in the substantia nigra ($P<0.001$), globus pallidus ($P<0.05$) and ventral striatum ($P<0.05$) and increased WM-FA in the substantia nigra ($P<0.001$), thalamus ($P<0.001$), and putamen ($P<0.001$) compared to healthy controls.
Conclusion: Prodromal PD patients possess a unique set of structural and microstructural volumetric alterations that distinguish them from healthy subjects. Our findings demonstrate that MRI changes are present in the premotor stages of PD.
Disclosure: Data was obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). PPMI is sponsored by the Michael J. Fox Foundation for Parkinson's Research (MJFF) and is co-funded by MJFF, Abbvie, Avid Radiopharmaceuticals, Biogen Idec, Bristol-Myers Squibb, Covance, Eli Lilly & Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genentech, GlaxoSmithKline, Lundbeck, Merck, MesoScale, Piramal, Pfizer and UCB. Industry partners contribute through financial and in-kind donations and provide feedback on study parameters through the Industry Scientific Advisory Board, which is positioned to inform the selection and review of potential progression markers that could be used in clinical testing.

EPR3071

The neuromodulatory impact of subthalamic nucleus deep brain stimulation on natural history of Parkinson's disease – a prospective case controlled study

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Background and aims: STN-DBS has been claimed to change progression symptoms in animal models of PD, but there are lacking information about the possible neuromodulatory role of STN-DBS in humans. The aim of this prospective controlled study was to evaluate the long-term impact of STN-DBS on motor disabilities and cognitive impairment in PD patients in comparison to best-medical-therapy (BMT) and long-term-post-operative (POP) group.
Methods: Patients were divided into 3 groups: BMT-group consisted of 20 patients treated only with pharmacotherapy, DBS-group consisted of 20 PD patients who underwent bilateral STN-DBS (examined pre- and postoperatively) and POP-group consisted of 14 long-term postoperative patients in median 30 month-time after DBS. UPDRS III scale was measured during 3visits in 9±2months periods (V1,V2,V3) in total-OFF phase. Cognitive assessment was performed during each visit in total-ON phase.
Results: The comparable UPDRS III OFF gain was observed in both BMT-group and POP-group evaluations ($p<0.05$). UPDRS III OFF results in DBS-group revealed significant UPDRS III OFF increase in V2-V1 assessment ($p<0.05$) with no significant UPDRS III OFF alteration in V3-V2 DBS-group evaluation ($p>0.05$). Cognitive assessment revealed significant alterations between DBS-group and BMT-group in working memory, executive functions and learning abilities ($p<0.05$).
Conclusion: The impact of STN-DBS on UPDRS III OFF score and cognitive alterations can suggest its neuromodulatory role, mainly during first 9-18 months after surgery.
Disclosure: Nothing to disclose

EPR3072

The quality of life burden in advanced Parkinson's disease applying "5-2-1" diagnosing criteria: subgroup analyses of the JAQPAD (Japanese QOL survey of Parkinson's disease) study

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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 been proposed for identifying advanced Parkinson's disease (APD) (Antonini, A. et al., Curr.Med.Res.Opin. 2018). This study was aimed to describe the burden of APD patients who meet the APD criteria.
Methods: The PD patients meeting a single criterium of "5-2-1" from JAQPAD study were analyzed as a post-hoc subgroup analysis. JAQPAD was a cross-sectional survey of large population (n=3,457) assessing the impact of PD on QOL of patients belonging to the Japan Parkinson's Disease Association. The survey included QOL questionnaires PDQ-8 and other disease related questions of PD.
Results: Of the 3,457 study patients, 1,958 patients (56.6%) met one of the "5-2-1" criteria. Of these APD patients, mean times oral levodopa intake/day was 5.1±2.4 times, mean duration of OFF/day was 4.73±3.72 hours, and mean duration of TSD/day was 1.91±3.28 hours. Only 11.8% of APD patients were treated with Device Aided Therapy (DBS 10.4%; LCIG 1.4%). Mean PDQ-8 score was 38.99±20.53 in APD and 27.24±18.98 in non-APD patients.
Conclusion: By applying "5-2-1" APD diagnosis criteria, this study identified more than half patients fulfilled the APD criteria and they were facing worse QOL level than non-APD patients, suggesting the needs of earlier detection, diagnosis, and optimizing treatments to improve their QOL for APD patients.
Disclosure: This work was funded by AbbVie GK. AbbVie participated in the study design, research, data collection, analysis and interpretation of data, writing, reviewing, and approving the publication.

EPR3073

The role of synaptic vesicle protein 2A (SV2A) in patients with Parkinson's disease dementia and dementia with Lewy bodies: an in vivo [11C]UCB-J PET study

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Background and aims: Synaptic vesicle glycoprotein 2A (SV2A) is a transmembrane protein expressed ubiquitously in secretory vesicles, within the brain, which is critical for synaptic and mitochondrial function. We aimed to investigate the role of SV2A in Parkinson's disease dementia (PDD) and Dementia with Lewy bodies (DLB) using [11C]UCB-J PET.

Methods: [11C]UCB-J PET corrected with arterial input function, was used to assess SV2A levels in 9 PDD and 9 DLB patients compared to 12 healthy controls (HCs); HC [11C]UCB-J PET data was used from the MINDMAPS Consortium. Regionalvolume of distribution (VT) was calculated using the one-tissue compartmental model with MIAKATTM.

Results: PDD and DLB patients showed global loss of [11C]UCB-J VT compared to HCs, with greatest reductions in DLB. PDD patients had reduced [11C]UCB-J VT in the precentral gyrus, superior temporal gyrus, supramarginal gyrus, angular gyrus, superior parietal gyrus and the caudate, putamen, pallidum and substantia nigra ($P<0.05$) compared to HCs. DLB patients had reduced [11C]UCB-J VT in the frontal, temporal, parietal, insula and occipital cortex, as well as the caudate, thalamus and brainstem ($P<0.05$). In PDD and DLB patients loss of [11C]UCB-J VT was associated with global cognitive impairment (MMSE; $P<0.05$), reduced cognitive stability (PD-CRS sustained attention task; $P<0.05$), deficits in instrumental cortical functions (PD-CRS confrontation naming task; $P<0.05$) and with deficits in executive function (SCOPA-COG executive task; $P<0.05$).

Conclusion: Our findings demonstrate cortical and subcortical synaptic loss in patients with PDD and more prominently in patients with DLB that is associated with cognitive decline.

Disclosure: Healthy control [11C]UCB-J PET data was used from the MINDMAPS Consortium: Karl Schmidt, Celgene Corp; Laigao Chen, Pfizer Worldwide Research and Development; Adam Schwarz, Takeda Pharmaceutical; Laurent Martarello, Biogen; Paul Matthews, Imperial College London; Jonathan Rohrer, University College London. Marios Politis research is supported by Parkinson's UK, Lily and Edmond J. Safra Foundation, Cure Huntington's Disease Initiative (CHDI) Foundation, Michael J Fox Foundation (MJFF) for Parkinson's research, and KCL's NIHR Biomedical Research Unit.

EPR3074

Evaluation of imidazoline 2 binding sites reflecting astroglia pathology in Huntington's disease: an in vivo [11C] BU99008 PET study

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Background and aims: Preclinical studies provide evidence for the critical and pathogenic role of mutant huntingtin in glial cell function suggesting that glial dysfunction may contribute to neuronal cell death in Huntington's disease (HD). The imidazoline 2 binding sites (I2BS) are expressed on activated astrocytes; by measuring I2BS levels we can indirectly evaluate astrogliosis in HD gene expansion carriers (HDGECs). We aimed to evaluate the role of astroglial activation in HDGECs using [11C]BU99008 PET, a novel radioligand with selectivity for I2BS.

Methods: 12 HDGECs, 5 symptomatic and 7 premanifest HDGECs, and 12 healthy controls (HCs) underwent MRI and [11C]BU9908 PET corrected with arterial input function. Regional volume of distribution (VT) was calculated using the two-tissue compartment model with MIAKATTM.

Results: In premanifest HDGECs, increased [11C] BU99008 VTuptake was observed in frontal, temporal, parietal, insular and occipital cortex regions ($P<0.05$). No differences were observed in the caudate, putamen, thalamus and brainstem. In the group of manifest HDGECs, [11C]BU99008 VTuptake was in line with HCs, showing trends towards decreased binding but not reaching significance. In premanifest HDGECs, increased [11C] BU99008 VTin the anterior ($r=0.893$; $P=0.007$) and medial ($r=0.786$; $P=0.036$) frontal gyrus, fusiform gyrus ($r=0.786$; $P=0.036$), and the insula anterior short ($r=0.778$; $P=0.036$) and inferior ($r=0.821$; $P=0.023$) cortex correlated with higher probability to symptomatic conversion.

Conclusion: Our findings demonstrate that astrogliosis is an early event in the pathophysiological mechanisms underlying HD and highlights the potential use of [11C] BU99008 PET as a marker to predict symptomatic onset in premanifest HDGECs.

Disclosure: Marios Politis research is supported by Parkinson's UK, Lily and Edmond J. Safra Foundation, Cure Huntington's Disease Initiative (CHDI) Foundation, Michael J Fox Foundation (MJFF) for Parkinson's research, and KCL's NIHR Biomedical Research Unit.

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EPR3075

Total macular volume in multiple sclerosis patients treated with fingolimod: a two years longitudinal OCT study

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Background and aims: Optical coherence tomography (OCT) is a noninvasive technique for measuring retinal thickness and is increasingly being utilized as a marker of axonal loss in multiple sclerosis (MS) treatment trials. Fingolimod has been associated with the development of cystoid macular edema in a small subset of patients, but little is known about how the drug generally affects retinal tissue volume in patients with MS. Our aim is to determine whether fingolimod treatment leads to changes of retinal tissue volume in MS patients.
Methods: In this longitudinal, multicenter, observational study, we compared changes in macular volume on spectral-domain OCT in 64 consecutive MS patients enrolled in 3 different centers (Naples, Catania, Milan) who started fingolimod treatment. Changes in macular volume after 3-6 months and 2 years of fingolimod treatment were analyzed using a paired t test.
Results: Macular volume did not significantly change over a two years follow-up time (two time points: 3-6 months and 24 months) in MS patients treated with fingolimod (mean change after 24 months -0.03 mm3, p=0.06). Moreover, our cohort exhibited a not significant increase in macular volume after 3-6 months of treatment with fingolimod (mean change +0.01 mm3, p=0.67). No one of our MS patients showed cystoid macular edema over the two years follow-up time.
Conclusion: Initiation of fingolimod in MS is associated with a modest, not significant increase in macular volume followed by no further significant changes over two years, highlighting the good safety profile of such treatment in MS.
Disclosure: Nothing to disclose

EPR3076

Distinguishing neurosarcoidosis from multiple sclerosis based on cerebrospinal fluid analysis: a retrospective cohort study

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Background and aims: Neurosarcoidosis is an aggressive manifestation of sarcoidosis, and its distinction from several disorders, particularly MS, can be troublesome. This study characterises a cohort of neurosarcoidosis patients with a focus on CSF analysis and whether this could help distinguish these two conditions.
Methods: This study enrolled 80 patients with a diagnosis of neurosarcoidosis based on stringent diagnostic criteria. The CSF protein, white cell count, and angiotensin converting enzyme levels were measured. The CSF and serum oligoclonal IgG patterns were compared.
Results: 80 patients had a probable or definitive diagnosis of neurosarcoidosis, with a mean age at time of diagnosis of 48 years. The commonest neurological symptoms included limb weakness, headaches, and sensory disturbance. Frequent findings on MRI were leptomeningeal enhancement (35%) and white matter and spinal cord involvement (30% and 23%). PET had a low sensitivity (16%). CSF analysis frequently showed lymphocytosis (57%) and elevated protein (56%), but oligoclonal bands were rare (3% in CSF alone, and 11% matched in the serum). Serum ACE levels were elevated in 51% of patients, but in only 14% of those with isolated neurosarcoidosis.

CSF findings in patients with neurosarcoidosis

Total patients	80
Intrathecal OCB synthesis	
With OCB synthesis	10/70
No OCB synthesis	60/70
% OCB synthesis	14%
Total protein	
Total protein ≥0.8g/L	40/72
% Total protein ≥0.8g/L	56%
White cell count	
White cell count ≥50/μL	41/72
% White cell count ≥50/μL	57%
CSF ACE	
CSF ACE elevation	0/27
% CSF ACE	0%

Figure 1

Baseline characteristics

Characteristics	n/N (%)	Characteristics	n/N (%)
Age at NS diagnosis	48 (19-74)		
Male sex	37/80 (46%)	*Neurological Involvement*	
Sarcoidosis known at onset of NS	30/80 (38%)	Pain	5/80 (6%)
		n. III	8/80 (10%)
		n. V	10/80 (13%)
		n. VII	13/80 (16%)
		Optic	10/80 (13%)
Systemic involvement		Limb weakness	31/80 (39%)
Pulmonary	59/80 (74%)	Sensory disturbance	16/80 (20%)
Cutaneous	10/80 (13%)	Headache	28/80 (35%)
Cardiac	2/80 (3%)	Drowsiness	4/80 (5%)
Lymph	13/80 (16%)	Vertigo	3/80 (4%)
Ocular	11/80 (14%)	Hearing	5/80 (6%)
Sialadens	4/80 (5%)	Seizure	6/80 (8%)
Bone	1/80 (1%)	Cognitive decline	9/80 (11%)
Joints	5/80 (6%)	Urinary	5/80 (6%)
Spleen	2/80 (3%)	Ataxia	16/80 (20%)
Kidney	2/80 (3%)	Pituitary	2/80 (3%)
Liver	2/80 (3%)	Vomiting	2/80 (3%)
Fatigue	1/80 (1%)	Transverse Myelitis	1/80 (1%)
Fever	2/80 (3%)	Stroke	1/80 (1%)

Figure 2

Comparison of CSF results with previously reported average values for MS

	Neurosarcoidosis	Multiple sclerosis
Intrathecal synthesis of oligoclonal IgG	10/70 (14%)	95-98%
Total protein ≥ 0.8g/L	40/72 (56%)	34% (*≥ 1g/L very rare*)
White cell count ≥50/µL	41/72 (57%)	very rare
Angiotensin converting enzyme	0/27 (0%)	<0.1%

Figure 3

Conclusion: Large elevations in CSF protein, WCC and ACE occur in neurosarcoidosis, but are rare in MS. The diagnostic use of these tests is limited, however, since minimal changes may occur in both conditions. In contrast, intrathecal synthesis of oligoclonal IgG is a powerful discriminator as it is rare in neurosarcoidosis whilst occurring in 95-98% cases of MS. We suggest caution in making a diagnosis of neurosarcoidosis when intrathecal oligoclonal IgG synthesis is found.
Disclosure: Nothing to disclose

EPR3077

Alemtuzumab reduces brain atrophy in patients with neither relapses nor mri disease activity: a pooled CARE-MS I and II analysis

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Background and aims: In treatment-naive RRMS patients (CARE-MS I; NCT00530348) or those with inadequate response to prior therapy (CARE-MS II; NCT00548405), alemtuzumab (12 mg/day: 5 days; 12 months later: 3 days) significantly improved clinical/MRI outcomes over 2 years (y) versus SC IFNB-1a. Adverse events (AEs) included infusion-associated reactions, infections, and autoimmune AEs. The effects of alemtuzumab versus SC IFNB-1a on brain atrophy in patients without relapses/MRI disease activity were examined.
Methods: Analysis populations included pooled CARE-MS patients with no disease activity between baseline and Y1 or baseline and Y2. Absence of disease activity was defined as no baseline gadolinium (Gd)-enhancing T1 lesions and no clinical relapses or MRI disease activity (new Gd-enhancing or new/enlarging T2 lesions) from Y0-1 or Y0-2. A second definition had the additional criterion of no relapse within 60 days before baseline. Brain atrophy was measured by brain parenchymal fraction (BPF); annualised percent brain volume change (PBVC) was assessed using ranked ANCOVA adjusted for geographic region and baseline BPF.
Results: Alemtuzumab reduced median PBVC versus SC IFNB-1a in patients free of disease activity in Y0-1 (alemtuzumab: -0.37% vs SC IFNB-1a: -0.61%; P=0.006) and Y0-2 (alemtuzumab: -0.54% vs SC IFNB-1a: -0.87%; P=0.014). Alemtuzumab reduced median PBVC versus SC IFNB-1a in patients who met the second definition of no disease activity in Y0-1 (alemtuzumab: -0.37% vs SC IFNB-1a: -0.53%; P=0.024) and Y0-2 (alemtuzumab: -0.56% vs SC IFNB-1a: -0.81%; P=0.045).
Conclusion: Alemtuzumab significantly reduced brain atrophy in absence of relapse/MRI disease activity versus SC IFNB-1a, possibly suggesting an effect on neurodegeneration.
Disclosure: STUDY SUPPORT: Sanofi and Bayer HealthCare Pharmaceuticals.

EPR3078

Variation in time to first DMT among people with MS in the United States, United Kingdom and Germany

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Background and aims: The number of disease-modifying therapy (DMT) options in multiple sclerosis (MS) has increased over time. Recent EAN/ECTRIMS guidelines highlighted the need for early introduction of DMT. We aimed to investigate the time to first DMT after diagnosis in three large MS registry populations (NARCOMS, United Kingdom (UKMSR) and Germany (GMSR)).

Methods: Each registry captures demographics, disability status (categorized as mild, moderate or severe) and treatment status. Inclusion criteria were a relapsing disease course, diagnosis in 2014 or later and provided data on DMT and disability status. The overall and age-, gender- and disability-specific times to first DMT after diagnosis were summarized. Kaplan Meier curves were used to examine time to first DMT (in years). Comparisons between countries were evaluated in a meta-analytic approach using Cochran's Q-test.

Results: 2,506 participants (NARCOMS:325, UKMSR:453, GMSR:1,728) fulfilled the inclusion criteria. Of those that started a DMT (table 1) (N=2065, 82.4%) the overall mean time to first DMT was shortest in Germany followed by the UK and NARCOMS (p<0.001). 4.5 years after diagnosis, a vast majority (93.5%) of NARCOMS participants received a DMT where as in Germany 16.4% and more than 29% in the UK have not received a DMT at that point (figure 1).Time to first DMT was shortest for mild disability levels in Germany, moderate in the UK and severe in NARCOMS.

Country		Germany	United Kingdom	NARCOMS
		N=1444	*N=317*	*N=304*
Overall		0.4 (0.83)	0.52 (0.54)	0.86 (1.2)
Gender	Male	0.39 (0.82)	0.53 (0.58)	0.72 (1.25)
	Female	0.40 (0.84)	0.51 (0.52)	0.89 (1.18)
Disabillity	Mild	0.39 (0.79)	0.51 (0.56)	0.83 (1.20)
	Moderate	0.42 (1.28)	0.49 (0.43)	0.93 (1.24)
	Severe	0.99 (1.04)	0.60 (0.51)	0.77 (0.98)
Age-band	<=20	0.27 (0.58)	0.12 (0.04)	0.10 (0.22)
	21-30	0.40 (0.77)	0.51 (0.60)	0.46 (0.79)
	31-40	0.43 (0.90)	0.51 (0.49)	0.88 (1.22)
	41-50	0.40 (0.93)	0.52 (0.60)	0.87 (1.20)
	51-60	0.38 (0.65)	0.59 (0.49)	1.09 (1.33)
	>=61	0.65 (0.84)	0.52 (0.23)	1.54 (1.46)

Mean and standard deviation within those patients that did receive DMT

Table 1

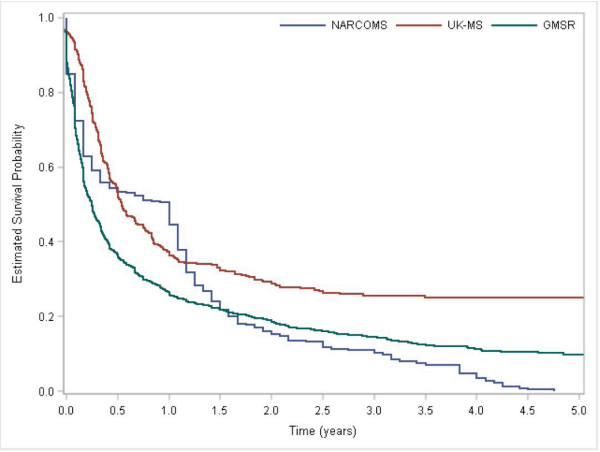

Figure 1

Conclusion: Time to first DMT varied strongly across countries, however, a larger proportion of PwMS in NARCOMS received a DMT within 5 years of diagnosis than Germany and the UK.

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EPR3079

K index is a reliable marker of intrathecal synthesis, and an alternative to IgG index in multiple sclerosis diagnostic work up

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Background and aims: Although recent evidence suggested kappa free light chains (KFLC) as a reliable marker of multiple sclerosis (MS) intrathecal synthesis, the 2017 McDonald criteria suggested to "interpret with caution positive immunoglobulin (Ig) type G index when testing for oligoclonal bands (OB) is negative or not performed". We aimed to evaluate the role of KFLC (or K) index performances in comparison to IgG (or Link) index and OB in a large cohort of Italian patients.
Methods: We enrolled 385 patients (127 MS, 117 other neurological inflammatory diseases or ID, 141 neurological non-inflammatory diseases or NID). All had cerebrospinal fluid (CSF) analysis performed in the diagnostic work up of a neurological disorder for whom the clinician requested isoelectrofocusing (IEF) to detect OB. Albumin, IgG and FLC were measured by nephelometry to calculate IgG and KFLC indexes.
Results: K index resulted a relevant marker in identifying intrathecal synthesis strongly relating to OB and MS diagnosis. Despite we confirmed a correlation between IgG and KFLC indexes ($r=0.75$, $r2=0.55$, $p<0.0001$), the latter showed higher sensitivities not only in detecting OB (96.5 versus 48.0) but also in relation to MS diagnosis (96.1 versus 49.6).
Conclusion: OB, IgG and KFLC indexes showed similar accuracy in diagnosing MS. The great sensitivity of K index supported it as first-line marker instead of Link index, and followed by IEF. These data confirm that use of a "sequential testing" in MS is an optimal procedure with accurate performance.
Disclosure: Nothing to disclose

EPR3080

Reduction in 48-Week confirmed disability progression after 5.5 years of ocrelizumab treatment in patients with primary progressive multiple sclerosis

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Background and aims: In the double-blind period (DBP) of the ORATORIO Phase III trial (NCT01194570) in primary progressive multiple sclerosis, risk of 24-week confirmed disability progression (CDP) was reduced by 25% for ocrelizumab versus placebo ($p=0.037$). After 5.5 years' (264 weeks) follow-up, 12-week/24-week CDP outcomes favoured earlier and continuous ocrelizumab, compared with delayed initiation. We examine the efficacy of ocrelizumab on 48-week CDP (CDP48) in the extended controlled treatment (ECT) period, and long-term outcomes in patients switching to or maintaining ocrelizumab therapy in the ORATORIO open-label extension (OLE).
Methods: At the end of the DBP, patients remained on randomised blinded treatment until the trial outcome was evaluated (ECT period). At the start of the OLE, patients continued ocrelizumab or switched from placebo to ocrelizumab. Time to onset of CDP48 was analysed for the ECT/OLE periods through week 264.
Results: In the ECT period, ocrelizumab reduced the risk of CDP48 by 34% ($p=0.001$) versus placebo. Overall, 72% of patients entered the OLE. The proportion of patients with CDP48 was lower in the continuous ocrelizumab versus placebo-ocrelizumab group at week 168 (30.5% vs 44.4%; $\Delta=13.9\%$; $p<0.001$), week 192 (34.8% vs 48.5%; $\Delta=13.7$; $p<0.001$) and Week 264 (43.7% vs 53.1%; $\Delta=9.4$; $p=0.03$). Analysis of other CDP endpoints will be presented.
Conclusion: The effect of ocrelizumab on CDP48 was greater than on 12-/24-week CDP, potentially due to higher specificity for permanent disability accumulation. In accordance with previous analyses, CDP48 data demonstrate consistent and sustained benefit with ocrelizumab treatment, and advantages for accrued disability for patients starting earlier on continuous ocrelizumab.
Disclosure: Sponsored by F. Hoffmann-La Roche Ltd; writing and editorial assistance was provided by Articulate Science, UK.

EPR3081

Switching to oral first-line DMTs due to long-term intolerance to injectables in RR-MS patients: efficacy and adherence analysis in a 5 years follow-up study

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Background and aims: Switching to oral first-line disease modifying therapies (DMTs), namely Teriflunomide (TERI) and Dimethyl-fumarate (DMF), is an opportunity for multiple sclerosis (MS) patients not tolerating injectables. Real-world long-term studies evaluating injective to oral switch are limited. We compared disease activity and treatment adherence in patients switching to oral therapy because of long-term tolerability issues, versus patients continuing injectables.

Methods: We enrolled RR-MS patients undergoing injectable DMTs from at least 24 months who switched to oral DMTs after May 2013 due to tolerability issues (switchers). Control group were patients continuing injectables (stayers). Clinical and brain MRI data were retrospectively analyzed. We compared time to first relapse, time to first evidence of disease activity and time to DMTs discontinuation. We used propensity-score (PS) matching and multivariate cox-regression analysis with on-treatment (OT) and intention-to-treat (ITT) design.

Results: We included 121 PS-matched patients in each cohort. Baseline characteristics were comparable. Mean follow-up was 47.5±10.5 months (up to 5.5 years). In OT analysis switchers had lower risk of experiencing relapses (HR 0.43,p=0.048) or any disease activity (HR 0.55, p=0.035). NEDA-3 was reached in 73.7% of switchers and 56.2% of stayers. Subgroups analysis suggests that stronger relapse risk reduction in switchers was provided by DMF (HR 0.12, p=0.014), while TERI effect was comparable to injectables. ITT results were similar. Discontinuation for intolerance was higher in switchers (HR 0.33, p=0.017).

Conclusion: Switching to first-line oral DMTs due to injectable intolerance is associated with a reduction of disease activity, especially in DMF treated patients, in a 5 years duration follow-up study.

Disclosure: Nothing to disclose

Muscle and neuromuscular junction disease 2

EPR3082

Longitudinal reliability of clinical outcome measures and quantitative muscle MRI in ambulant patients with Duchenne muscular dystrophy

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Background and aims: The definition of reliable outcome measures has won increasing interest with the expanding number of clinical trials performed in patients with Duchenne muscular dystrophy. Outcome measures need to be reproducible and sensitive enough to show even small changes in clinical progression. In this retrospective study we analysed the longitudinal reliability of commonly used clinical and radiological endpoints in 29 ambulant patients with Duchenne muscular dystrophy.
Methods: Clinical outcome measures included motor function measure and timed function tests, whilst quantitative MRI data were based on mean fat fraction and T2 relaxation time of thigh muscles. Statistical analysis using standardized effect sizes, sample sizes, and correlations was based on 3, 6, and 12-month follow-up data.
Results: MFM total score and its D1 domain showed the highest sensitivity to detect clinical decline for a longitudinal observation time of up to 12 months. The superiority of 6MWT could not be confirmed in this analysis, moreover, 6MWT was shown to be inferior to the D1 domain of MFM. Quantitative muscle MRI using the mean fat fraction was the most powerful tool to detect disease progression. Longer follow-up duration and inclusion of a homogeneous patient population with more stable motor function increased the power of outcome measures.
Conclusion: In our analysis, the D1 domain of MFM and mean fat fraction of the thigh extensors were the most powerful outcome measures, underlining their application as primary endpoints in clinical trials. Prolonged observation increased the power of outcome measures, supporting clinical trial duration of at least 12 months.
Disclosure: We would like to thank the Lorenzo-Piaggio Foundation, Switzerland, for supporting the DMD00-Study, and the Swiss National Science Fundation (SNF) for their financial contribution in the DMD02-Study. The sponsors had no influence on study design, data evaluation or publication.

EPR3083

Efficacy and safety of eculizumab in patients with anti-acetylcholine receptor antibody positive generalized refractory myasthenia gravis previously treated with rituximab

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Background and aims: The phase 3 REGAIN study and its open-label extension (OLE) evaluated efficacy and safety of eculizumab in patients with anti-acetylcholine receptor antibody positive refractory generalized myasthenia gravis (gMG). Although not approved for MG, rituximab has been used to treat such patients. The goal of this retrospective analysis was to assess response to eculizumab in individuals with refractory gMG previously treated with rituximab.
Methods: This retrospective analysis of REGAIN compared baseline disease characteristics, safety and response to eculizumab in patients who had previously received rituximab (prior-rituximab group) and those who had not. Rituximab was not permitted within 6 months of screening or during REGAIN/OLE.
Results: Of 125 patients in REGAIN, 14 had previously received rituximab (placebo, n=7; eculizumab, n=7). Patients with and without prior rituximab exposure had comparable mean baseline MG Activities of Daily Living (MG-ADL) total scores (10.6 vs 10.1) (Table). A higher proportion of patients in the prior-rituximab group had used ≥4 immunosuppressants (57.1% vs 16.2%) (Table). Patients who had received rituximab and were treated with eculizumab for 18 months (26 weeks REGAIN, 52 weeks OLE; n=6) experienced similar clinical improvements to those who had not (n=43) (mean [standard deviation] change in MG-ADL total score from REGAIN baseline to OLE week 52, –3.8 [3.54] and –5.3 [3.49], respectively). Eculizumab safety was consistent with its known profile.

	Prior rituximab (n = 14)	No prior rituximab (n = 111)
Sex, n (%)		
Female	12 (85.7)	70 (63.1)
Male	2 (14.3)	41 (36.9)
MG history		
Age at MG diagnosis, years, mean (SD)	27.6 (14.8)	39.4 (18.7)
Duration of MG, years, mean (SD)	13.9 (10.5)	9.0 (7.8)
Time to gMG if first clinical presentation was oMG, months, mean (SD)	5.1 (6.6)	16.3 (31.6)
Treatment history		
Used only two ISTs, n (%)	1 (7.1)	57 (51.4)
Used only three ISTs, n (%)	5 (35.7)	34 (30.6)
Used at least four ISTs, n (%)	8 (57.1)	18 (16.2)
Used IVIg, n (%)	14 (100.0)	85 (76.6)
Used PLEX, n (%)	9 (64.3)	51 (45.9)
Baseline MG-ADL total score, mean (SD)	10.6 (3.48)	10.1 (2.76)

gMG, generalized myasthenia gravis; IST, immunosuppressive therapy; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; oMG, ocular myasthenia gravis; PLEX, plasma exchange; SD, standard deviation.

Table. Patient sex, disease history, treatment history and MG-ADL total scores at REGAIN baseline.

Conclusion: Patients in the prior-rituximab group with refractory disease, experienced similar long-term clinical improvement with eculizumab to those in the no prior-rituximab group (NCT01997229, NCT02301624).
Disclosure: Research funding for this study was provided by Alexion Pharmaceuticals. Dr Patti has received speaker's fees from and is an advisory board member for Almirall, Bayer, Biogen, Merck, Novartis, Roche, Sanofi and TEVA. Dr Mozaffar has served as a consultant and site investigator for Alexion. Drs O'Brien and Yountz are employees of Alexion Pharmaceuticals and own Alexion stocks. Dr Siddiqi has received unrestricted educational grants from CSL Behring, Grifols and Sanofi Genzyme, and is an advisory board member for Alexion.

EPR3084

Self-report questionnaire vs. clinical evaluation form in the French National Registry on facioscapulohumeral dystrophy: a statistical comparison

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Background and aims: FSHD, one of the most prevalent neuromuscular dystrophies (NMD), has no treatment. The physiopathological mechanism must be further characterized in view of future clinical trials. To this end, national registries on FSHD have been set up. Data are gathered mostly through medical evaluation, which relies on the willing participation of physicians; some databanks are fed with data provided by patients themselves, the reliability of which has never been investigated. To help increase inclusions and data quality, the French registry was designed to combine both a clinical evaluation form (CEF), and a self-report questionnaire (SRQ), thereby allowing for an evaluation of data accuracy.
Methods: Statistical comparison between CEF/SRQ pairs collected at close time points was made for 281 patients (131 women/150 men; average age 59.5±16.0 years). Kappa or ICC values were calculated to determine the correlation between answers provided in both forms.
Results: Quantitative or objective content such as the Brooke scale show the best agreement (kappa/ICC $\geq$0.6). Discordance is observed in questions involving symptoms, interpretation or medical technicalities. Errors may originate from either party, but it is safe to assume that patients better answer symptom-related questions, while more technical items are best left to physicians.
Conclusion: Patient answers to questions involving easily understandable objective criteria should be trusted, allowing physicians to focus on items requiring medical expertise. Our results form the basis for tailoring an optimized collection form, addressing questions to either rater. Once online, such questionnaires will facilitate telemedicine care of FSHD.
Disclosure: This work was supported by AFM-Téléthon.

EPR3085

NEO1 and NEO-EXT studies: pharmacodynamic and exploratory biomarker assessments following repeat avalglucosidase alfa dosing for up to 4.5 years in patients with late-onset Pompe disease

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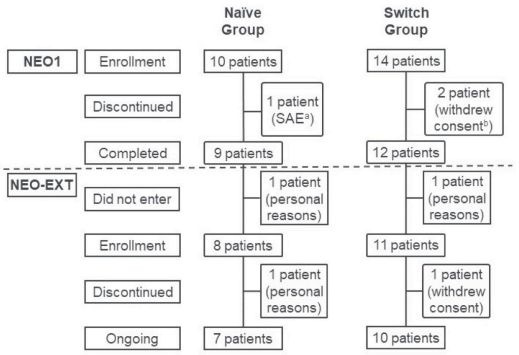
Background and aims: In NEO1 (NCT01898364;Eudra CT:2012-004167-42), safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of repeat avalglucosidase alfa dosing (5, 10, or 20 mg/kg qow) for 6 months were evaluated in late-onset Pompe disease patients, either treatment-naïve (Naïve) or having received alglucosidase alfa for ≥9 months (Switch). In the ongoing NEO-EXT study (NCT02032524; EudraCT: 2013-003321-28), long-term safety and pharmacokinetics of repeat avalglucosidase alfa dosing will be monitored for ≤6 years following NEO1. Pharmacodynamic/exploratory biomarker data after ≤4.5 years of avalglucosidase alfa exposure are reported.

Methods: NEO1 began in July 2013. After NEO1, patients could enter NEO-EXT, receiving the same avalglucosidase alfa dose, all NEO-EXT patients then switched to 20 mg/kg qow during 2016. CK, Hex4, AST, and ALT were assessed as secondary endpoints at baseline and every 6 months.

Results: 24 patients entered NEO1; 19 entered NEO-EXT with 17 currently participating (Figure 1). At NEO1 enrolment, patients' mean (SD) age was Naïve: 44.8(20.3) years; Switch: 46.7(14.1) years. Mean (SD, range) avalglucosidase alfa exposure durations were Naïve: 1025(611,109-1572) days; Switch: 1179(570, 102-1658) days. Table 1 shows NEO1 Baseline Hex4, CK, ALT, and AST levels; all groups demonstrated reductions from Baseline to Week 208 in these biomarkers (Table 2). During NEO1/NEO-EXT, no deaths/life-threatening serious adverse events (SAEs) were reported; 1 Switch patient discontinued NEO1 for a treatment-related SAE (respiratory distress/chest discomfort).



[a]Serious (SAE) respiratory distress and chest discomfort during the 9th avalglucosidase alfa infusion; considered to be infusion-associated reactions.
[b]Non adverse event-related reasons following 8th and last avalglucosidase alfa infusions, respectively.

Figure 1. Patient disposition

Parameter	Group		Avalglucosidase alfa (initial dose*) 5 mg/kg qow	10 mg/kg qow	20 mg/kg qow
Patients, n	Naive		4	3	3
	Switch		4	4	6
Urinary Hex4, mmol/mol	Naive	Mean (SD)	7.0 (3.9)	13.0 (4.8)	5.4 (4.3)
		Median (min, max)	6.8 (2.9, 11.5)	15.1 (7.6, 16.4)	3.1 (2.8, 10.4)
	Switch	Mean (SD)	7.0 (3.8)	3.9 (1.9)	7.5 (8.3)
		Median (min, max)	6.5 (3.4, 11.7)	3.7 (1.9, 6.4)	3.8 (1.7, 23.6)
Plasma CK, IU/L	Naive	Mean (SD)	308 (188)	1014 (404)	600 (309)
		Median (min, max)	310 (83, 528)	1147 (560, 1334)	745 (245, 809)
	Switch	Mean (SD)	272 (167)	459 (212)	501 (189)
		Median (min, max)	236 (127, 490)	375 (316, 769)	460 (259, 816)
Plasma ALT, IU/L	Naive	Mean (SD)	44.3 (18.2)	116.3 (59.5)	55.0 (21.6)
		Median (min, max)	48.0 (20.0, 61.0)	101.0 (66.0, 182.0)	61.0 (31.0, 73.0)
	Switch	Mean (SD)	43.5 (20.5)	35.5 (17.4)	36.5 (8.9)
		Median (min, max)	42.0 (23.0, 67.0)	33.0 (19.0, 57.0)	38.0 (25.0, 46.0)
Plasma AST, IU/L	Naive	Mean (SD)	47.0 (17.0)	136.3 (77.6)	62.0 (28.5)
		Median (min, max)	45.5 (32.0, 65.0)	140.0 (57.0, 212.0)	56.0 (37.0, 93.0)
	Switch	Mean (SD)	40.5 (17.9)	35.8 (9.8)	40.5 (8.7)
		Median (min, max)	37.5 (23.0, 64.0)	33.5 (27.0, 49.0)	44.5 (29.0, 49.0)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; Hex4, glucose tetrasaccharide; qow, every other week; SD, standard deviation.
*All patients transitioned to 20 mg/kg qow in 2016 and have received this dose for at least 2 years.

Table 1. NEO1 Baseline biomarker levels

Parameter	Group	Avalglucosidase alfa (initial dose*) 5 mg/kg qow	10 mg/kg qow	20 mg/kg qow
Patients, n	Naive	3	1	3
	Switch	3	3	4
Urinary Hex4	Naive	–44.1 (15.7)	–39. 9 (NC)	–40.4 (40.6)
	Switch	–38.4 (33.4)	–38.8 (19.9)	–41.0 (25.8)
Plasma CK	Naive	–44.3 (13.7)	–34.1 (NC)	–37.0 (10.9)
	Switch	–54.9 (27.3)	–40.6 (30.6)	–24.0 (22.4)
Plasma ALT	Naive	–28.6 (24.5)	–39.0 (NC)	–30.2 (26.3)
	Switch	–37.9 (7.4)	–23.7 (43.4)	–20.6 (15.2)
Plasma AST	Naive	–25.1 (27.7)	–28.8 (NC)	–38.7 (21.2)
	Switch	–36.7 (9.2)	–31.0 (31.7)	–29.0 (12.7)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; Hex4, glucose tetrasaccharide; NC, not calculable; qow, every other week; SD, standard deviation.
*All patients transitioned to 20 mg/kg qow in 2016 and have received this dose for at least 2 years.

Table 2. Mean (SD)% changes from Baseline to Week 208

Conclusion: Avalglucosidase alfa treatment in NEO1 and NEO-EXT for up to 4.5 years resulted in persistent improvements in muscle (CK), disease substrate (Hex4), liver/muscle (AST), and heart/liver/muscle (ALT) biomarkers from baseline and consistent safety profile.

Disclosure: Funding received from Sanofi Genzyme.

EPR3086

VRK1 pathogenic variants in two Portuguese patients with early-onset ALS

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Background and aims: Advances in genetics has improved the diagnosis of hereditary forms of motor neuron disease. VRK1 encodes a serine-kinase with a role in embryonic cortical neuronal proliferation/migration.
Methods: Pathogenic variants have been related to different phenotypes. We describe novel VRK1 pathogenic variants in two unrelated patients with similar phenotypes.
Results: Patient 1 presented with progressive bilateral distal weakness in lower limbs, foot-drop and frequent falls, beginning at 10 years old. Neurodevelopment was normal. By the age of 25, clinical examination revealed a severe symmetric distal muscular wasting and weakness, brisk reflexes and bilaterally positive Hoffman sign. EMG and Transcranial Magnetic Stimulation confirmed lower and upper motor neuron dysfunction. Whole exome sequencing based NGS, identified two variants in VRK1: c.265C>T,p.(Arg89*), classified as pathogenic, and c.769G>A,p.(Gly257Ser), of uncertain significance.
Patient 2 developed gait difficulties due to bilateral distal weakness in lower limbs at the age of 6, with otherwise normal neurodevelopment. Hand muscles became weak. On examination, jaw brisk reflex and bilateral positive Hoffmann were disclosd. The EMG disclosed predominant loss of motor units and signs of chronic reinnervation in distal segments. Brain MRI was normal. Whole exome sequencing revealed two pathogenic variants in VRK1: c.710.14T>C (p.7), and c.721C>T (p.(Arg241Cys).
Conclusion: We present two patients displaying a slowly progressive upper and lower motor neuron degeneration beginning in childhood, consistent with clinically probable ALS. They were compound heterozygous for VRK1 novel variants. These cases support that VRK1 pathogenic variants can be related to early-onset ALS.
Disclosure: Nothing to disclose

EPR3087

The Givinostat trial cohort: functional, histopathological and muscle MRI features in Becker muscular dystrophy

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Background and aims: Becker muscular dystrophy (BMD) is an X-linked disorder caused by non truncating DMD mutations, leading to altered, but still detectable dystrophin expression in muscle fibers. Givinostat, a histone deacetylase inhibitor, is currently being tested in a phase II clinical trial in BMD patients. Aim of this study is to describe clinico-pathological, functional and muscle MRI features of a cohort of adult BMD patients with in order to better define the natural history of the disease and to improve design of clinical trials.
Methods: Patients need to be able to perform 6MWT at screening with a minimum distance of 200 m and maximum distance of 450 m and to have a left ventricular ejection fraction ≥50%. We screened a population of ~80 molecularly diagnosed BMD patients. More than half of the patients did not meet the inclusion criteria due to cardiac involvement, ambulatory status, age or concomitant diseases. We performed functional assessments, muscle biopsy and muscle magnetic resonance imaging (MRI) of the enrolled patients at screening and after 48 weeks of treatment.
Results: Clinical presentation of patients ranged from milder to more severe cases and showed different age of disease onset and different rate of progression, partly related to the underlying mutations. MRI study showed specific pattern and helped selecting more useful muscles for patient's follow-up.
Conclusion: We characterized a population of BMD adult patients with functional measures, muscle biopsy and muscle MRI. These data expand our knowledge of BMD natural history and can be useful in the setting and evaluation of clinical trials.
Disclosure: Nothing to disclose

EPR3088

TDP43 gene variants in patients with autosomal dominant degenerative myopathy

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Background and aims: TDP43 gene variants are associated with a familial form of amyotrophic lateral sclerosis (ALS). Other hereditary and the more common sporadic forms of ALS also display TDP43 aggregates in motor neurons. In addition, TDP43-positive deposits are detectable in the skeletal muscle of patients with inclusion body myositis. We have examined whether TDP43 variants can cause hereditary degenerative myopathies.
Methods: DNA samples from patients with suspected hereditary myopathies were analysed by exome and Sanger sequencing. The effects of identified TDP43 variants were investigated in cell culture models.
Results: We identified TDP43 sequence alterations in two families with autosomal dominant inheritance and a single sporadic patient. These variants affected highly conserved amino acid residues and were undetectable in databases of human genome variation. All patients had degenerative distal myopathy. Histology revealed autophagic vacuoles and cytoplasmic inclusions. In transfected cells, TDP43-positive aggregates could be observed.
Conclusion: The identification of TDP43 variants in patients with degenerative myopathy implies a primary role of TDP43 in the pathophysiology of skeletal muscle. In order to understand the underlying mechanisms, functional studies are currently being carried out in zebrafish embryos.
Disclosure: Nothing to disclose

Neuroepidemiology

EPR3089

The burden of brain disorders in Norway

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Background and aims: Comparable data on the burden of different disorders are crucial for planning of health-care and resource allocation. The Global burden of diseases, injuries, and risk factors (GBD) study provides information that allows comparisons between all disorders. The aim of this study was to compare the burden of the different brain disorders (neurological and mental) in Norway, with other major disease groups by extracting GBD 2016 estimates.

Methods: Disease burden is measured in time units, as years of life lost (YLLs), years lived with disability (YLDs), and the sum of these (disability adjusted life years, DALYs). YLD is the average number of years lived with the disorder multiplied with a disability weight for the same disorder. The prevalence and years lost to premature death are estimated by collecting all available data on prevalence, incidence, average duration and mortality, and also taking into consideration comorbidities. Estimates are made for both sexes and all age groups in each country.

Results: Brain disorders constituted a major disease burden in Norway for 2016, causing 30.9% of all YLDs, 23.1% of YLLs and 27.2% of all DALYs (Table 1, Figure 1). Migraine, anxiety and depression were the leading three causes of YLD counts among brain diseases.

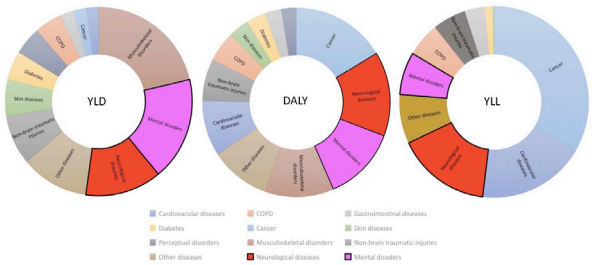

Figure 1. Years lived with disability (YLDs). disability adjusted life years (DALYs) and years of life lost YLL given as% of total all disorders.

	YLDs % of total	95 % UI	DALYs % of total	95 % UI	YLL % of total	95 % UI
Alzheimer	1.32	1.06-1.62	3.46	3.10-3.86	6.08	5.86-6.27
Stroke	2.37	1.91-2.84	3.84	4.23-3.41	5.63	4.43-5.95
Migraine	6.36	4.59-8.51	3.49	2.43-3.49	0	
Cancer in the nervous system	0.07	0.06-0.09	0.76	0.63-0.94	1.60	1.40-1.94
Epilepsy	0.67	0.34-1.17	0.57	0.39-0.83	0.44	0.40-0.48
Tension type headache	0.81	0.51-1.17	0.44	0.27-0.67	0	
Parkinson	0.18	0.12-0.24	0.49	0.39-0.56	0.87	0.64-0.95
Multiple sclerosis	0.36	0.28-0.44	0.38	0.31-0.43	0.41	0.26-0.46
Motorneuron disease	0.02	0.01-0.02	0.22	0.19-0.26	0.47	0.45-0.50
Traumatic brain injury	0.68		0.38		0	
Traumatic spinal injury	0.21		0.12		0	
Other neurological diseases	0.18	0.12-0.26	0.29	0.25-0.35	0.43	0.40-0.47
Anxiety	5.05	4.09-6.21	2.78	2.19-3.42	0	
Depression (MDD)	4.56	3.75-5.58	2.51	1.98-3.14	0	
Schizophrenia	1.08	0.80-1.37	0.59	0.46-0.71	0	
Bipolar disorders	1.25	0.85-1.76	0.69	0.47-0.97	0	
Autism spectrum disorder	0.56	0.47-0.66	0.31	0.24-0.38	0	
ADHD	0.05	0.03-0.07	0.03	0.02-0.04	0	
Eating disorders	0.72	0.55-0.92	0.40	0.29-0.53	0.01	0.01-0.01
Drug addiction	1.24	0.98-1.53	1.56	1.37-1.74	1.95	1.82-2.03
Alcohol use disorders	1.01	0.82-1.22	1.13	1.02-1.26	1.28	1.21-1.42
Behavioural disorders	0.81	0.54-1.15	0.25	0.17-0.37	0	
Idiopathic intellectual disability	0.05	0.03-0.07	0.03	0.02-0.06	0	
Self-harm	0.08	0.06-0.09	1.82	1.56-2.11	3.96	3.79-4.19
Other psychiatric disorders	1.22	0.93-1.55	0.67	0.49-0.87	0	
Cardiovascular diseases	2.14		9.43		18.34	
COPD	4.77	4.12-5.51	5.22	4.81-5.65	5.79	5.64-5.95
Gastrointestinal diseases	2.33	2.03-2.70	2.81	2.60-3.03	3.40	3.16-3.57
Diabetes	4.96	4.20-5.77	3.36	2.83-3.93	1.41	1.36-1.46
Cancer	2.28		16.30		33.40	
Skin disorders	6.25	5.06-7.71	3.54	2.75-4.51	0.23	0.09-0.28
Perceptual disorders	4.78	3.86-5.95	2.63	2.00-3.41	0	
Musculoskeletal disorders	21.28	19.17-23.66	11.88	10.04-14.00	0.40	0.37-0.42
Non-brain traumatic injuries	8.51		7.23		5.62	
Other diseases	11.79		10.39		8.28	
Sum neurological disorders	13.23		14.44		15.93	
Sum mental disorders	17.68		12.77		7.2	
Sum non-brain disorders	69.09		72.79		76.87	
Sum all	100		100		100	

Table 1. Years lived with disability (YLDs). disability adjusted life years (DALYs) and years of life lost YLL given as% of total in brain disorders and other disorders with 95% uncertainty interval (UI).

Conclusion: Brain disorders are important causes of disability and death. The number of patients who needs treatment and follow-up by clinicians with expertise in brain disorders are tremendous. Policy makers and health-care providers should be aware of these large numbers to provide adequate services.

Disclosure: Nothing to disclose

EPR3090

Breastfeeding and risk of developing multiple sclerosis

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Background and aims: Early life factors are reported to modulate the risk of developing multiple sclerosis (MS) among adults. The association between breastfeeding and the risk of developing MS is controversial. The aim is to determine whether the duration of breastfeeding is associated with risk of MS.

Methods: We linked a large Norwegian community-based survey on health status (CONOR) to the nation-wide Medical Birth Registry of Norway and the Norwegian MS Registry. Information on breastfeeding was available for 95,891 subjects born between 1922 and 1986 and collected prior to the current study. Information on the onset of MS was collected through 2016. Perinatal factors were recorded on more than 60% of subjects. Breastfeeding was categorized (≥4 months vs. <4). Adjustments for the year of birth, demographic, perinatal factors and mother's lifestyle were applied.

Results: Overall 63% of subjects were breastfed. Those that were breastfed were more likely to have a mother who was highly educated and a non-smoker. Among the whole cohort, 215 subjects developed MS.

Cox multivariable regression analysis showed no statistically significant association between breastfeeding and MS (Table 1). Similar results were obtained considering different breastfeeding durations. A sub-analysis including perinatal factors (mode of delivery, parity, birth-weight, gestational age) showed similar results.

Factor	HR (95% CI)	p
BF at least 4 months	0.9 (0.7-1.2)	0.5
Gender (male)	0.4 (0.3-0.5)	<0.001
Mother's smoking habit (ever)	1.00 (0.7-1.3)	0.8
Mother's education		
Mandatory	1.0 (Ref.)	
High school	0.8 (0.4-1.6)	0.3
College	1.2 (0.9-1.8)	0.2
Missing information	0.9 (0.6-1.4)	0.6

Table 1. Multivariable Cox regression analysis to evaluate the association of breastfeeding for at least 4 months and risk of development of MS. Also adjusted for year of birth (categorized by 5 years).

Table 1

Conclusion: Our study could not confirm previous findings of an association between breastfeeding and risk of MS. Breastfeeding information was less likely to be biased by knowledge of disease compared to case-control studies.

Disclosure: Nothing to disclose

EPR3091

Long-term exposure to air pollution and the risk of dementia: the role of cardiovascular diseases

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Background and aims: Air pollution might negatively affect cognition, but little is known concerning its relationship with dementia, and no studies have examined the role of cardiovascular diseases (CVD) in this association. We aim to investigate the association between long-term air pollution and cognitive decline and dementia, and to clarify the role of CVD on the studied association.

Methods: We examined 3,150 dementia-free 60+ year-olds in the Swedish National study on aging and care in Kungsholmen for up to 13 years. Two major air pollutants were assessed yearly, using dispersion models for particulate matter (≤2.5μm in diameter, PM2.5), and nitrogen oxides (NOX). Mixed-effect linear regression models were used to quantify the association between air pollution and cognitive decline (with the mini mental state examination). The risk of dementia, in keeping with the Diagnostic and Statistical Manual of Mental Disorders IV edition, was estimated using competing-risks models, considering death as competing event. Stratified analyses by CVD were also performed.

Results: During the follow-up, 363 people developed dementia. Higher levels of air pollution were associated with the steepest cognitive decline over the follow-up period. After controlling for potential confounders, higher levels of PM2.5 and NOx were associated with up to 50% increased risk of dementia (HR:1.13;95%CI:1.05-1.22 for NOx; HR:1.52;95%CI:1.37-1.67 for PM2.5). The stratified analyses showed that the presence of CVD enhanced the negative effect of air pollution on dementia.

Conclusion: Long-term exposure to air pollution is associated with a higher risk of dementia. CVD might play a role in such association.

Disclosure: Nothing to disclose

EPR3092

Small area demographic associations with multiple sclerosis incidence in Scotland: latitude, a small-town effect, and overcrowding

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Background and aims: Scotland has been reported to have the highest incidence of multiple sclerosis (MS) in the world, but previous work, which we have recently replicated – using different methods in a separate patient cohort – shows that there is statistically significant variability – up to three-fold – in rates between Health Board regions. Analysis of association of MS risk with local demographic factors is possible in Scotland using publically-available, well-characterized aggregate units of small-area geography combined with a national, prospective incidence register.
Methods: We analysed rates and counts of cases from the Scottish Multiple Sclerosis Register (1/1/2010 to 31/12/2017) using multivariable linear and Poisson regression models to explore the demographic areal predictive factors at the level of intermediate zone (n~4,000 persons) and data zone (n~760 persons).
Results: By analysing all 3,726 incident cases in Scotland over this period we show that there persists a definite latitude effect in Scotland at small-area resolution. There is also an apparent small town effect with rates higher in close-knit communities than in large-urban centres or remote-rural regions. We find that when adjusting for latitude, there is no effect of socioeconomic status or access to health care services. However, a small but significant association with overcrowding of housing is detected. We hypothesize this to be a result of earlier-life infection with Epstein Barr virus, for which overcrowding is a known predictor.
Conclusion: In this study we have confirmed some previously described demographic factors and identify some novel factors associated with MS risk. These findings may have aetiological implications.
Disclosure: Nothing to disclose

EPR3093

Incidence and prevalence of Parkinson's disease (PD) in Wales

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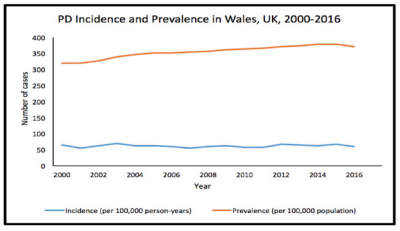
Background and aims: Previous epidemiological studies in the UK have suggested a decline in the incidence of Parkinson's disease (PD) in recent years, accompanied by a relatively stable prevalence rate. Globally, there seems to be variation in the trend of PD incidence and prevalence over time. A Welsh population-based study is required to estimate the incidence and prevalence of PD in comparison to previous studies.
Methods: Using the Secure Anonymised Information Linkage (SAIL) Databank, we conducted a population-based study of residents in Wales, UK, aged 40 years or older between 2000 and 2016. The annual prevalence and incidence of PD were estimated using the Read codes for PD diagnosis. Poisson regression was used to estimate the incidence rate ratio (IRR) and prevalence risk ratio (PRR) across the study period.

Read codes that define the PD diagnosis	
Read code	Definition
F12..00	Parkinson's disease
F120.00	Paralysis agitans
F12z.00	Parkinson's disease not otherwise specified
147F.00	History of Parkinson's disease

Read codes used to define Parkinson's disease (PD)

Results: We analysed 16,693,205 person-years during 2000-2016. The incidence rate ranged from 54.74 to 68.04 per 100,000 person-years across the study period. The incidence rate did not differ significantly between the reference year (calendar year of 2000) and the majority of years of the study period (in 2016 the IRR was 1.05 95% CI 0.93–1.18). However, the overall prevalence rate increased significantly from 319.40 to 370.05 per 100,000 population between 2000 and 2016 (in 2016 the PRR was 1.16 95% CI 1.11–1.21).



PD incidence and prevalence in Wales, UK, 2000-2016

Conclusion: In Wales, the prevalence of PD has increased in the period between 2000 and 2016 with a relatively stable incidence rate. This could be due to increasing population aging.
Disclosure: This research was funded by a scholarship from King Khalid University (KKU) in Saudi Arabia supporting Khalid Orayj to undertake a PhD at Cardiff University, UK

EPR3094

Cardiovascular risk and atherosclerosis progression in hypertensive participants treated to blood pressure targets

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Background and aims: Arterial hypertension promotes atherosclerosis and cardiovascular events. In the population-based Heinz Nixdorf Recall, we evaluated how cardiovascular risk and atherosclerosis progression are associated with blood pressure, antihypertensive treatment, and treatment efficacy.

Methods: In 3,373 participants without previous cardiovascular disease, we evaluated the association of baseline antihypertensive treatment efficacy (normotension without treatment, treatment to normotension, untreated hypertension, hypertension despite treatment, based on 140/90 mmHg cutoffs) with incident coronary artery calcification (CAC) and CAC progression during 5-year-follow-up and with incident cardiovascular events during median 13.5-year-follow-up. We further evaluated the association of incident arterial hypertension and efficacy of new antihypertensive treatment at the 5-year-follow-up with subsequent cardiovascular events.

Results: At baseline, 1,636 participants had normotension without treatment, 528 hypertension treated to normotension, 739 untreated hypertension, and 470 hypertension despite treatment. 647 participants experienced rapid CAC progression; 107, 132, and 249 experienced incident stroke, coronary, and cardiovascular events, respectively. Compared with normotensive participants without treatment, participants treated to normotension had an elevated risk of stroke (hazard ratio 2.33, 95% confidence interval 1.19–4.55), coronary (2.04, 1.20–3.45) and cardiovascular events (2.23, 1.48–3.36), but not rapid CAC progression (1.19, 0.91–1.48). Participants without hypertension at baseline, who were newly hypertensive but treated to normotension at the 5-year-follow-up, again exhibited an elevated stroke (4.80, 1.38–16.70) and cardiovascular event risk (2.99, 1.25–7.16), whereas the effect for coronary events did not reach statistical significance (2.24, 0.70–7.18).

Conclusion: Cardiovascular risk is elevated in participants treated to normotension despite modest CAC progression.

Disclosure: Nothing to disclose

Neurogenetics 4

EPR3095

Chronic progressive external ophthalmoplegia resulting from a rare de novo m.12334G>A MT-TL2 pathogenic variant

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Background and aims: To describe a patient with chronic progressive external ophthalmoplegia due to a rare mitochondrial genetic variant.
Methods: Case report. Family members were assessed clinically and neurophysiologically and samples of urine, buccal mucosa and serum were analysed for the variant. One sibling also had a muscle biopsy. Single fibre segregation analysis was performed in the proband's muscle biopsy.
Results: A 47-year-old male with a history of migraine and glucose intolerance presented with ptosis which was noticed incidentally in his twenties. He suffered from painful cramps in his leg muscles at the end of the day. He reported four family members with ptosis. The pedigree suggested autosomal dominant inheritance. Neurological examination revealed ptosis and ophthalmoplegia. Genetic testing for common mitochondrial DNA variants and mitochondrial DNA maintenance genes was negative. Muscle biopsy revealed numerous cytochrome c oxidase (COX)-deficient fibres, prompting sequencing of the entire mitochondrial genome in muscle, revealing a m.12334G>A variant in the mitochondrial transfer RNA leucine 2 (MT-TL2) gene. Testing of family members proved this to be a de novo mutation event. Single muscle fibre analysis revealed that the mutation segregated with the COX histochemical defect, proving pathogenicity.
Conclusion: This rare pathogenic mitochondrial DNA variant has been reported only once before. Our case highlights the importance of assessing family members and of pursuing molecular genetic analysis in affected tissues when mitochondrial disease is suspected.
Disclosure: Nothing to disclose

EPR3096

Determinants of age-at-onset in a Portuguese cohort of autosomal dominant spastic paraplegia

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Background and aims: Hereditary spastic paraplegias (HSP) are characterized by progressive spasticity and lower limb weakness due to corticospinal degeneration. A high variability of age-at-onset has been described in some series and genetic modifiers were recently reported. Our objective was to identify the determinants of age-at-onset in autosomal dominant HSP (AD-HSP).
Methods: Analysis of families identified in the Portuguese nationwide systematic population-based survey of hereditary ataxias and spastic paraplegias (1993-2004). Patients were examined by the same team of neurologists and all families were genetically tested.
Results: We included 239 patients from 89 families with a mean age of 50.7 years. Age-at-onset followed a bimodal distribution. Average age-at-onset was 38.2-year-old in the first generation, 32.3-year-old in the second and 17.5-year-old in the third, with a significant decrease between generations ($p<0.001$). This decrease was observed in 78.9% of families with more than one generation. We also observed a significant lower age-at-onset in patients with missense versus truncating mutations ($p=0.015$). In multivariate linear regression model, the independent effects of generation and missense mutations in a lower age-at-onset were confirmed ($p<0.001$), adjusting for family and genotype. No independent effect of sex was identified.
Conclusion: Notwithstanding some possible subjectivity in the verification of age-at-onset, our results are consistent with the presence of an anticipation phenomenon in AD-HSP. This effect may be related to environmental or epigenetic factors not yet identified. This study also confirms the recently reported effect of mutation type in age-at-onset.
Disclosure: Nothing to disclose

EPR3097

Evaluation of next generation sequencing panels in adult-onset hereditary neurological disorders

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Background and aims: Next-generation sequencing (NGS) panels are increasingly used in neurological practice. The aim of this study was to evaluate their effectiveness in reaching a genetic diagnosis in a tertiary neurogenetics clinic.
Methods: We performed a retrospective review of 157 patients seen in the Oxford Neurogenetics Clinic between 2011 and 2018. Demographic data, presenting symptoms, family history, laboratory and genetic test results were obtained from clinical notes.
Results: 39 patients were referred with a known genetic diagnosis. The remaining 117 patients without a diagnosis were referred with the following symptoms alone or in combination: ataxia (81), spasticity (26), extrapyramidal symptoms (13) and neuropathy (4). Male:female ratio was 3:2. Mean symptom onset was at age 39 (0-74) and mean age at presentation was 53 (16-86). Time to referral from symptom onset was 15 years (0-54).A new genetic diagnosis was made in 30 patients (25%). The overall diagnostic yield from NGS panels was 17% with the following positive results per subgroups divided according to the predominant phenotype: Ataxia Panel (9/81-11%), HSP panel (8/20-40%) and PD-dystonia panel (1/4-25%). SPG7 (9), CACNA1A (2) and KIF5A (2) were the most common causative genes. The remaining 11 (9%) patients were diagnosed by targeted genetic testing based on their phenotype (7) or a known mutation in the family (4). A further 22 patients (19%) received a definitive clinical diagnosis, most commonly MSA (5), CANVAS (4) and ALS (2).
Conclusion: NGS panels in well-phenotyped patients offer a cost-effective means of obtaining a positive genetic test in otherwise undiagnosed hereditary neurological conditions.
Disclosure: Nothing to disclose

EPR3098

Amyotrophic lateral sclerosis-like phenotype in patients with mutations in ATP13A2 (PARK9) gene

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Background and aims: Amyotrophic lateral sclerosis (ALS) is a genetically neurodegenerative disorder, characterized by degeneration of upper and lower motoneurons. To date mutations/expansions of C9orf 72, SOD1, FUS and TARDBP genes account for most genetically positive cases. Here we describe two juvenile-onset ALS patients carrying mutations of the ATP13A2 gene.
Methods: Two juvenile-onset ALS patients of Italian and French ancestry were identified who were negative for mutations in any of the known ALS-causative genes. Whole-exome sequencing analysis was performed on the genomic sample of the Italian case. Candidate de novo changes or variants segregating in an AR manner were confirmed by Sanger sequencing. Then, a survey on ALS datasets was performed to search for additional ATP13A2 variants, which led to identification of a second patient. Finally, we performed Zebrafish assays to evaluate the impact of the ATP13A2 mutations found in the two ALS-like patients on motoneuron and cerebellar development.
Results: Starting with the index case, a patient of Italian origin, we performed whole-exome sequencing and identified candidate pathogenic mutations in 35 genes. We next parsed all candidates against a cohort of 3,641 ALS cases; only ATP13A2 was found to harbor recessive changes, in a patient clinically similar to the index case. In vivo complementation of ATP13A2 using zebrafish model that focused on motoneuron morphology and cerebellar integrity confirmed the role of this gene in nervous system maintenance.
Conclusion: We here expand the phenotypic spectrum associated with genetic variants in ATP13A2 that comprise Kufor-Rakeb syndrome, SPG78, and neuronal ceroid lipofuscinosis type 12, to also include juvenile-onset ALS.
Disclosure: Nothing to disclose

EPR3099

A novel heterozygous SCL52A3 mutation in a case of Brown-Vialetto-Van Laere syndrome with an unusual slowly progressive course

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Background and aims: Brown-Vialetto-Van Laere syndrome (BVVLS) is a neurodegenerative disorder causing ponto-bulbar palsy and bilateral sensorineural deafness. Homozygous and compound heterozygous mutations of SLC52A2 and SCL52A3 genes are causative although dominant pathogenic mutations are emerging. We describe a novel heterozygous frameshift mutation in the SLC52A3 gene, identified in an unusually slowly progressive case.

Methods: A 23-year-old female patient, with familial history of deafness and unsteadiness in her father and one sibling, presented with bulbar signs, severe bilateral deafness, gait unsteadiness and facial diparesis since the age of 20, which very slowly progressed during a 50-years follow-up. An extensive laboratory and instrumental diagnostic protocol was performed, as well as a detailed genetic and segregation study.

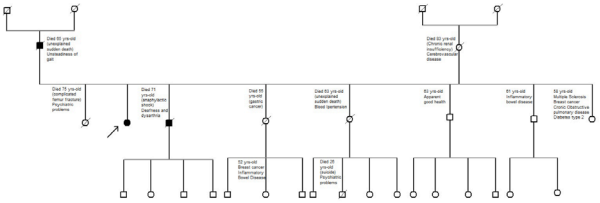

Fig. 1. Proband's pedigree. Genetic investigation in the symptomatic father of proband was not possible, because he died before extending the genetic study

Results: Blood laboratory screening was not contributive, whereas brain MRI showed severe leukoencephalopathy and mild ponto-bulbar atrophy. Electrophysiological assessment and tonal audiometry confirmed the clinical suspicion. Genetic analysis displayed the novel dominant variant c.481_484dupTCCG; p.(Gly162ValfsTer11) in the exon 2 of SLC52A3 gene. Segregation study confirmed the mutation in affected but not in healthy siblings. Quantitative Real-Time PCR assay excluded other exon or deep intronic mutations on both alleles of the gene and showed a reduction of mRNA expression levels of about 50%.

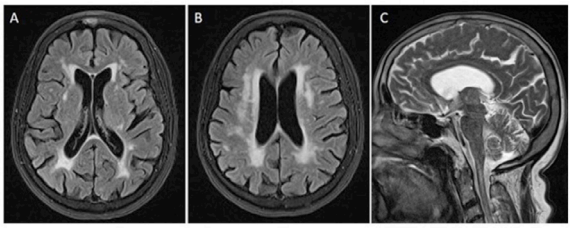

Fig.2. Brain MRI. Axial T2 FLAIR sequences showing severe ischemic leukoencephalopathy (A-B); Sagittal T2 sequence displaying mild ponto-bulbar atrophy (C).

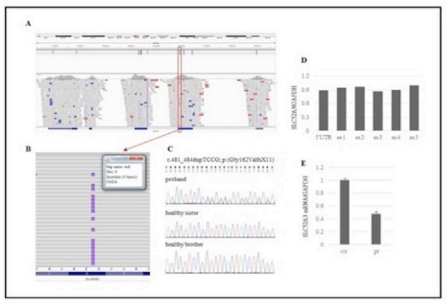

Fig. 3. Characterization of the SLC52A3 heterozygous mutation. A, B. Integrative Genomics Viewer (IGV) showing the coverage of all exons of SLC52A3 gene. Red rectangle indicates the position of the pathogenic SLC52A3 mutation (c.481_484dupTCCG). C. Sanger sequencing of the pathogenic mutation in the proband and his healthy mother. D. SLC52A3 exon dosage in the proband shows the absence of intragenic dosage imbalance. E. Measurement of SLC52A3 mRNA expression levels shows a reduction of about 50% in the proband compared with normal control.

Conclusion: We reported an unusual slowly progressive case of BVVLS, carrying a newly described dominant mutation in SLC52A3 gene. As confirmed through in vitro analysis, this four-nucleotide insertion adds a new stop codon, resulting in degradation of mutated transcript. We hypothesize that a preserved residual riboflavin metabolism due to the non-mutated allele could justify our patient's mild phenotype.

Disclosure: Nothing to disclose

EPR3100

An AARS mutation as the likely cause of Swedish type HDLS

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Background and aims: The Swedish type HDLS is a severe adult-onset leukoencephalopathy with hallmark of neuraxonal degeneration with spheroids and a dominant segregation. The initial stage is dominated by frontal lobe symptoms with rapidly advancing encephalopathy. Pathogenic mutations in CSF1R were reported, but the cause of HDLS-S has been illusive. The aim was to elucidate the gene mutation.

Methods: We collected and reexamined the clinical, MRI and DNA from all of the family members in this large original Swedish family. To identify the genetic cause of disease in this HDLS-S family we performed exome sequencing and followed up the results with Sanger sequencing. Twenty-five family members participated in this study (2 were affected and 23 were healthy).

Results: Exome sequencing analysis revealed that both patients carried novel variants, heterozygous, and predicted as deleterious in two genes related with the nervous system: AARS: c.455G>T p.(Cys152Phe) and ESRP2: c.728T>G p.(Val243Gly), and these were absent in the two healthy relatives. After segregation analysis to validate the association of the variants with the disease, only p.Cys152Phe in AARS remained absent in the healthy family members.

Conclusion: Here we update the original findings associated with HDLS-S by reporting a p.Cys152Phe mutation in the alanyl tRNA sythetase (AARS) gene as the potential cause of this disease. The mutation affects an evolutionarily conserved amino acid located in the aminoacylation domain of the protein and we have indirect support for a gain-of-function mechanism.

Our results point to AARS as a candidate gene for rapidly progressing adult-onset CSF1R-negative leucoencephalopathies.

Disclosure: Nothing to disclose

Neuroimaging 2

EPR3101

Incidental findings identified on MRI of the head for investigation of early onset dementia – a retrospective six-year review from a regional cognitive disorders clinic

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Background and aims: To determine the prevalence, nature, and management implications of incidental findings on MRI of the head in patients presenting with cognitive symptoms, and to quantify and describe unexpected MRI abnormalities that are of unclear relevance to the patient's cognitive symptoms

Methods: A single-centre retrospective review of patients attending a regional early-onset cognitive disorders clinic between March 2012 and October 2018. Medical records of consecutive patients who underwent MRI of the head were reviewed. Unexpected MRI findings were classified according to their severity and likelihood of being incidental. Markers of small vessel disease and cerebral atrophy were excluded.

Results: Records of 694 patients were reviewed (median age 60 years, 49.9% female), of whom 514 (74.1%) underwent MRI of the head. 53% of patients received a diagnosis of a neurodegenerative disorder. Overall 111 incidental findings were identified in 100 patients. Of these, 18 patients (3.5%, 95%CI 2.2%, 5.6%) had 18 incidental findings classified as requiring additional medical evaluation. 82 patients (16%, 95%CI 13.0%, 19.5%) had 93 incidental findings without clearly defined diagnostic consequences. 17 patients (3.3%) underwent further investigations, 14 patients (2.7%) were referred to another specialist clinic and three patients (0.6%) were treated surgically. Two patients had MRI findings of unclear relevance to their cognitive symptoms, necessitating prolonged clinic follow-up.

Word cloud diagram of incidental findings classified as reportable. Size of words does not correspond to prevalence.

Table 1. Prevalence and type of category II/reportable incidental findings

	N (%)	95% CIs	Likelihood finding is incidental	Referred (n)	Further Investigated (n)	Treated (n)
Vascular abnormalities (total)						
Cerebral ancurysm (berry/fusiform)	2/1 (0.58)	0.15, 1.8	A	1	1	1
Cavernomas (multiple, no haemorrhage)	1 (0.19)	0.01, 1.3	A		1	
Cysts						
Rathke's cleft cyst	1 (0.19)	0.01, 1.3	A	1	1	
Neoplasms						
Low grade glioma	1 (0.19)	0.01, 1.3	B	1	1	
Meningioma*	1 (0.19)	0.01, 1.3	A	1	1	
Vestibular Schwannoma	1 (0.19)	0.01, 1.3	A	1	1	
Dysembryoplastic neuroepithelial tumour (DNET)	1 (0.19)	0.01, 1.3	A	**	1	
Pituitary abnormality (haemorrhagic adenoma or haemorrhagic cyst)	1 (0.19)	0.01, 1.3	A	1	1	
Retro-orbital mass	1 (0.19)	0.01, 1.3	A	1		
Warthin's tumour	1 (0.19)	0.01, 1.3	A	1	1	
Other intracranial abnormalities						
Possible demyelination	2 (0.39)	0.07, 1.6	A, B		2	
Encephalomalacia (initially unable to exclude DNET)	1 (0.19)	0.01, 1.3	A		1	
Cerebellar abnormality***	1 (0.19)	0.01, 1.3	A		1	
Extracranial						
Periapical cyst	1 (0.19)	0.01, 1.3	A			
Mixed solid and cystic thyroid cyst	1 (0.19)	0.01, 1.3	A	1	1	1
Total	**18 (3.5)**	**2.2, 5.6**		**9**	**13**	**2**

*Table 3. Prevalence and type of category II reportable incidental findings. *A further patient had a meningioma which was heavily calcified and therefore classified as category I/non-reportable. **Already under regular Neurology follow- up. ***Peripheral symmetrical band of T2 and FLAIR hyperintensity of unclear aetiology*

Type and prevalence of incidental findings classified as reportable

Conclusion: Incidental findings are common in patients with cognitive impairment from this large clinic-based series; however, few required additional medical evaluation. These data help inform discussions between clinicians and people with cognitive symptoms regarding the risks of incidental imaging findings.

Disclosure: Nothing to disclose

EPR3102

Greater preserved baseline functional MRI connectivity in zolpidem responders compared to non-responders in patients with disorders of consciousness

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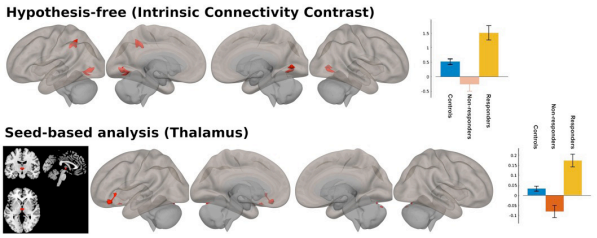
Background and aims: Zolpidem is commonly used as sleep inducer but it is one of the few available pharmacological treatments for patients with disorders of consciousness (DOC). Some DOC patients have exhibited paradoxical improvements with zolpidem treatment but the neurological profile of responders remains unclear. No fMRI study has ever been conducted in a group of DOC patients. We investigated the baseline functional brain connectivity in DOC patients responding to zolpidem compared to non-responding patients.

Methods: Eleven patients in minimally conscious state and 5 who emerged received a 10 mg single dose of zolpidem. Patients were considered responders if a new behaviour was observed using the coma recovery scale-revised after zolpidem administration. All patients underwent resting-state fMRI (without zolpidem). Hypothesis-free and seed-based region (thalamus) analyses were conducted with age and gender covariates regressed out, comparing patients with 36 healthy volunteers.

Results: Seven patients qualified as responders (5 sedated, 2 non-sedated) and 9 as non-responders (6 sedated, 3 non-sedated). Hypothesis-free analyses in the sedated group revealed significantly increased intrinsic connectivity among responders in the occipital, occipito-temporal and parieto-occipital areas compared to non-responders. Seed-based analyses showed significantly more preserved positive connectivity of the fronto-insular network in responders compared to non-responders. No significant differences were found between responders and non-responders in the non-sedated condition, possibly due to smaller sample size.



Difference between sedated zolpidem responders compared to non-responders. Upper row: hypothesis-free analysis (intrinsic connectivity contrast). Lower row: seed-based analysis using thalamus (4mm radius spheres at [-4 -12 0] and [4 -12 0], left corner). Significance threshold: non-parametric permutation voxel-wise $p<0.001$, cluster-mass FWE $p<0.05$.

Conclusion: Our findings suggest a greater preservation of global and local connectivity in zolpidem responders at baseline. Targeting more accurately potential responders to zolpidem can improve the clinical management of DOC patients.

Disclosure: We thank the University and University Hospital of Liège, the Belgian National Funds for Scientific Research (F.R.S-FNRS), NeuroHealing Pharmaceuticals Inc., the European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 785907, the Luminous project (EU-H2020-fetopenga686764), the Center-TBI project (FP7-HEALTH- 602150) and the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 778234; LS and SKL are research fellows and SL is research director at F.R.S-FNRS; we thank Eurogenerics and Britannia Pharmaceuticals Ltd. for providing clinical trial materials.

EPR3103

withdrawn

EPR3104

Probabilistic tractography study of the nigrostriatal pathway in Parkinson's disease

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Background and aims: Loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which projects to the dorsal striatum, is the main pathological feature of Parkinson's disease (PD). Probabilistic tractography, that analyses in vivo white matter trajectories can be employed to study the connectivity between brain regions.
Objectives: To investigate changes in connectivity of the nigrostriatal and striatonigral pathways in PD and association with clinical symptoms.
Methods: Probabilistic tractography was performed in 24 PD patients and 16 healthy controls (HCs) to measure the nigrostriatal connectivity using as a seed the SNpc manually delineated on neuromelanin sensitive MRI and the striatonigral connectivity using as a seed the dorsal striatum manually delineated on T1 MRI. Neuromelanin-sensitive MRI allows the identification of dopaminergic neurons within the SNpc to differentiate the SNpc from SN reticulata.
Results: Mean nigrostriatal ($P<0.001$; -79%) and striatonigral ($P<0.01$; -52%) streamline number was lower in PD compared to HCs. Moreover, in PD the number of streamlines of the nigrostriatal tract correlated positively with the neuromelanin area ($r=0.435$; $P<0.05$) and negatively with UPDRS-III scores ($r=-0.431$; $P=<0.05$).
Conclusion: Abnormal tractography characteristics in both the nigrostriatal and striatonigral pathways suggest loss of integrity of the motor control circuitry in PD. Degradation of the nigrostriatal tract in PD is associated with the severity of motor symptoms. The loss of pigmented neurons inside the SNpc is correlated with the loss of microstructural integrity inside the motor circuitry. Our results suggest that probabilistic tractography and neuromelanin-sensitive MRI are a potential diagnostic marker of the disease.
Disclosure: Nothing to disclose

EPR3105

Machine learning system for stroke risk stratification: conventional vs. integrated approach

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Background and aims: Stroke risk startification (SRS) using machine learning (ML) algorithms is gaining grounds amoung neurological research community. Despite vital role of some carotid ultrasound image phenotypes (CUSIP) in stroke prediction, the ML-based SRS has been only tried by using convetional risk factors (CRF) including blood biomarkers and patient's demographics. Therefore we evaluated the performance of ML-based algorithms using CUSIP alongside the CRF (integrated model) against the stand-alone CRF-based ML system.
Methods: 202 Japanese patient's left/right common carotid arteries were examined to obtain 404 ultrasound scans. Support vector machine (SVM)-based system was trained and tested to provide SRS in these patients using 13 CRF (age, gender, hemoglobinA1c, fasting blood sugar, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), ratio TC/ HDL, hypertension, smoking, familty history, tryglycerides plaque score). Then we trained and tested the SVM system using the integrated model with 36 covariates (13 CRF, 6 current CUSIP, 6 types of 10-year values of CUSIP, 10 quadratic terms derived from the current, 10-year CUSIP) and one carotid plaque morphology-based age-adjusted grayscale median. Lastly, performance of both the systems (conventional vs.

integrated) were evaluated using receiver operating characteristics and risk startification accuracy.
Results: The SVM-based integrated ML system showed higher SRS mean accuracy (92.15%) compared to the conventional-based ML system (67.64%). Area-under-the-curve (AUC=0.89) was higher in the SVM-based integrated ML system compared to the CRF-based ML system (AUC=0.54).
Conclusion: Integrated risk factor-based ML algorithms provide better SRS compared to CRF-based ML system thus they could improve the future preventive stroke risk assessment.
Disclosure: Nothing to disclose

EPR3106

Specific cerebral multiple sclerosis lesions are associated with sympathetic cardiovascular activation

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Background and aims: Autonomic dysfunction is common in multiple sclerosis (MS) and might be related to cerebral MS-lesion-sites. Using voxel-based lesion-symptom mapping (VLSM) we determined associations between cardiovascular autonomic dysfunction and cerebral MS-related lesion-sites.
Methods: In 74 MS-patients (mean age 37.0±10.5 years), we recorded electrocardiographic RR-intervals and systolic and diastolic blood pressure. We assessed low (0.04–0.15 Hz) and high (0.15-0.5 Hz) frequency RR-interval- and blood pressure-oscillations and determined parasympathetically-mediated RR-interval–high-frequency modulation, mainly sympathetically-mediated RR-interval–low-frequency modulation, sympathetically-mediated blood pressure-low-frequency modulation, and the ratios of sympathetic and parasympathetic RR-interval-modulation reflecting sympathetic-parasympathetic balance. We analyzed cerebral MS-lesions using magnetic resonance imaging scans and performed a VLSM-analysis correlating parameters of autonomic dysfunction with cerebral MS-lesion sites. Autonomic parameters were correlated with potential confounding factors of autonomic modulation age, disease-duration and -severity, and total cerebral lesion-volume (Spearman-rank-correlation; significance: $p<0.05$).
Results: The VLSM-analysis showed associations between increased RR-interval low-frequency-high frequency ratios and lesions in the left insular, hippocampal, and right frontal inferior-opercular region, and a smaller lesion-cluster in the right middle cerebellar peduncle. Increased blood pressure-low-frequency powers were associated with lesions primarily in the right posterior parietal white-matter and again left insular region. RR-interval low-frequency/high-frequency ratios and systolic blood pressure-low-frequency powers did not correlate with potential confounding factors.
Conclusion: Our data indicate associations between a shift of cardiovascular sympathetic-parasympathetic balance towards increased sympathetic modulation and left insular and hippocampal lesions, areas that normally modulate parasympathetic function. The VLSM-analysis differentiated between right inferior-fronto-opercular lesions disinhibiting cardiac sympathetic activation and right posterior-parietal lesions increasing sympathetic blood pressure-modulation.
Disclosure: Nothing to disclose

Neuroimmunology 2

EPR3107

Immunoglobulin deficiency in multiple sclerosis – prevalence and association with disease-modifying therapy and disease course

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Background and aims: In multiple sclerosis (MS), the frequency of immunoglobulin (Ig) deficiency is unknown. Therefore, we aim to evaluate the frequency of Ig deficiency (IgG, IgM, IgA) and its association with immunotherapy and disease course in two independent MS cohorts.

Methods: In our retrospective cross-sectional study, MS patients from the following two centers were included: Bern University Hospital (Bern, Switzerland) and Eginition University Hospital (Athens, Greece). The definition of Ig deficiency followed international recommendations (IgG <7.0g/L, IgM <0.4g/L, IgA <0.7g/L). The Mann-Whitney test, the ANOVA test, and the multiple linear regression analysis were employed.

Results: In total, 327 patients were retrospectively identified (Bern/Athens: n=226/101). Ig deficiency was frequently observed in both cohorts (Bern/Athens: IgG: 15.5%/14.9%, IgM: 16.9%/7.0%, IgA: 3.9%/2.0%), even when considering only untreated MS patients (Bern/Athens: IgG: 7.9%/8.6%, IgM: 12.5%/5.2%, IgA: 0%/1.7%). Independently of age, secondary-progressive MS patients had lower serum IgG concentrations than relapsing-remitting and primary-progressive MS patients (both: $p \leq 0.01$). After adjusting for sex, age, and MS disease course, IgG concentrations were lower in patients treated with rituximab (p=0.001; n=42/327), intravenous corticosteroids administered ≤4 weeks before blood sampling (p<0.001; n=16/327), natalizumab (p<0.001; n=48/327), and fingolimod (p=0.003; n=6/327) compared to patients without immunotherapy.

Conclusion: Our study demonstrated high prevalence rates of Ig deficiency in MS patients with and without disease-modifying treatments. Rituximab, intravenous corticosteroids, natalizumab, and fingolimod were associated with lower IgG concentrations. Our findings are clinically important because Ig deficiency may predispose to treatment complications such as infections and interfere with standard serological testing, e.g. antibodies against John-Cunningham or Varicella-Zoster virus.

Disclosure: Nothing to disclose

EPR3108

FDG-PET signature of refractory epilepsy with GAD antibodies

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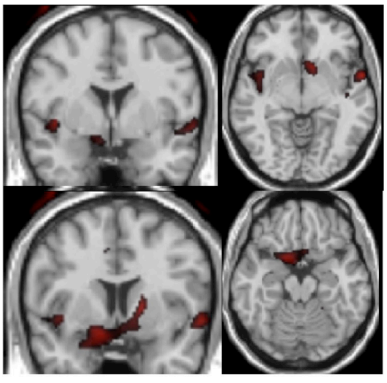
Background and aims: Antibodies to glutamic acid decarboxylase (GAD-Ab) are found in patients with chronic epilepsy without an acute debut. These patients may present as epilepsy with classical temporal lobe features, being difficult to recognize them. Our aim is to describe specific metabolic changes that could help to differentiate GAD-Ab patients from those with typical temporal lobe epilepsy with hippocampal sclerosis (TLE-HS).

Methods: A retrospective study, which included all patients with epilepsy and GAD-Ab who underwent a brain 18-FDG-PET, and we compared them to patients and with TLE-HS.

All studies were performed on a Discovery ST (GE Healthcare, Milwaukee, WI) PET/CT system. Patients were injected with 148 MBq (4 mCi). Images were reconstructed with an iterative method with corrections for attenuation and scatter based on CT scan (47 transaxial tomographic slices of 4.25 mm, matrix size=128x128). All images were normalised to SPM 8 template. Comparisons voxel to voxel were done using two-tailed t-test.

Results: We included 30 patients, 18 women. 11 had GAD-Ab positive chronic epilepsy, and 19 TLE-HS (9 left HS, 5 right HS and 5 bilateral HS). On visual analysis, both groups had reduced metabolism in medial temporal lobe areas, being bilateral in 7/11 (63%) of GAD-ab and 5/19 (26%) in TLE-HS, insular hypometabolism was observed in 5/11 (45%) of GAD-ab patients. When comparing both groups, GAD-Ab patients had significant statistically reduced metabolism in both insulae and medial inferior frontal – hypothalamus area ($p<0.001$).



Hypometabolism in both insulae and hypothalamus

Conclusion: Epilepsy with GAD-Ab presented a specific FDG-PET pattern being hypometabolism in the insulae and hypothalamus distinctive.

Disclosure: Nothing to disclose

EPR3109

Corneal immune cell infiltration in corneal confocal microscopy confirm as biomarker for disease activity in autoimmune inflammatory neuropathies

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Background and aims: Novel, non-invasive imaging techniques like corneal confocal microscopy (CCM) aim to predict the treatment response in patients with autoimmune inflammatory neuropathy (AIN) and especially the subtypes of chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP). In a pilot study of seventeen patient with CIDP, examined prospectively using CCM every nine months over a period of eighteen months, quantify corneal immune cell infiltration (CICI) (≥30 total corneal cells/mm2) identified patients with clinical progression and need of therapy escalation (Pitarokoili et al. in revision).
Methods: In the present follow-up study further 61 patients with AIN (mean age 55.24 years ±12,34) were prospectively examined every six to nine months using CCM to validate our results of CICI as robust biomarker for disease activity.
Results: A corneal cell value of ≥30/mm2 in CCM identified patients with clinical progression in INCAT/ODSS (p=0.004), as well as the need of therapy escalation (p=0.006) in a broad disease spectrum of patients with CIDP and AIN. Classical CCM parameters like corneal nerve fiber density (CNFD) and length (CNFL) (signs for axonal impairment) remained low and stable over the study period and did not work as robust short-time biomarker of disease activity in our cohort.
Conclusion: CICI seems to be suitebale for application as an early biomarker for clinical progression in AIN, thus having the potential to identify at-risk patients and may have impact in treatment decisions. Axonal loss or regeneration, displayed by classical CCM-markers like CNFL/CNFD, should investigated in further prospective long-term studies.
Disclosure: Nothing to disclose

EPR3110

FcRn inhibition ameliorates disease course and visual outcome in an antibody-driven experimental model mimicking neuromyelitis optica spectrum disorder

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Background and aims: Treatment options of neuromyelitis-optica-spectrum-disorders (NMOSD) are limited. The neonatal Fc-receptor (FcRn) stabilizes immunoglobulin (Ig) G in vivo. Blockade of FcRn results in a reduction of IgG serum concentration and may represent a treatment target for antibody-mediated disorders. We investigated a monoclonal anti-FcRn antibody in a murine model.
Methods: Myelin-oligodendrocyte-glycoprotein (MOG33-55) experimental autoimmune encephalomyelitis (EAE) was actively induced and exacerbated by i.v. administration of a monoclonal anti-MOG antibody (8-18C5, 10mg/kg) at day 10 after immunization. Treatment was performed with a murine IgG1 monoclonal anti-FcRn antibody (4470) or IgG1 isotype control (30mg/kg i.p.) on days 7, 10 and 13.
Disease scoring (10-point-scale) and spinal cord histology were performed. Visual function was longitudinally measured (optokinetic reflex, OKR).
Results: Disease course was ameliorated in anti-FcRn-treated animals versus controls (final mean scores: anti-FcRn (n=27): 4.6 (SEM 0.3); control (n=24): 7.0 (SEM 0.2), n=3 independent experiments, Mann-Whitney-test, p=0.03). Spinal cord histology corroborated these findings. Controls experienced deterioration of visual function (mean visual acuity, baseline: 0.51 c/d (SEM 0.01) vs. day 19-20: 0.44 (SEM 0.02), Wilcoxon's signed-rank-test, p=0.024); visual function was preserved in anti-FcRn-treated mice (baseline: 0.50 (SEM 0.01) vs. day 19-20: 0.52 (SEM 0.01), p=n.s.) with a difference of visual acuity between control and anti-FcRn groups (Mann-Whitney-test, p=0.005).
Conclusion: Anti-FcRn treatment resulted in significant amelioration of functional parameters in an antibody-driven model of NMOSD. FcRn inhibition might be a treatment option in antibody-mediated CNS disorders. A phase 1 study demonstrated sustained dose-dependent reduction of serum IgG levels after administration of the FcRn inhibitor rozanolixizumab.
Disclosure: Funded by UCB Pharma.

EPR3111

Paraneoplastic neurological syndromes epidemiology: a population-based study

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Background and aims: Epidemiology of paraneoplastic neurological syndromes (PNS) remains to be defined. We present the first population-based incidence study and report the clinical spectrum and antibody profile of PNS in a large area in northeastern Italy.
Methods: We performed a 9-year (2009-2017) population-based study of incidence of PNS in the provinces of Udine, Pordenone and Gorizia, in the Friuli-Venezia Giulia region (983,190 people as of January 1, 2017). PNS diagnosis and subgroups were defined by 2004 diagnostic criteria, while the 2016 criteria were adopted for classification of autoimmune encephalitis (AE) cases. Age- and sex-adjusted incidence rates were calculated.
Results: We identified 91 patients with a diagnosis of definite PNS. Median age was 68 years (range: 26-91), 52.7% were female. The incidence of PNS was 0.91/100,000 person-years (95% confidence interval [CI]: 0.72-1.10). PNS incidence rates increased over time from 0.62/100,000 person-years (2009-2011), 0.84/100,000 person-years (2012-2014) to 1.25/100,000 person-years (2015-2017), attributable to increased awareness and improved detection techniques. Most common PNS were: limbic encephalitis (31.9%), cerebellar degeneration (27.5%) and encephalomyelitis (20.9%). Among antibody (Ab)-positive cases, most frequent specificities included: Yo (28%), Hu (24%), Ma2 (20%), while the most frequent associated tumors were breast and lung cancer (16.5% each), followed by gastrointestinal tract cancer (9.9%). Statistically significant association were observed between cancer type and Ab-specificity ($P<0.05$), and between neurological syndrome and Ab-specificity ($P<0.05$).
Conclusion: This first population-based study found an incidence of PNS that approximates 1/100,000 person-years, and the detection of PNS is increasing over time.
Disclosure: Nothing to disclose

Sleep disorders 2

EPR3112

Multiple sleep latency test cut offs for pediatric narcolepsy type 1 diagnosis

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Background and aims: A sleep latency <8 minutes with ≥2 sleep onset REM periods (SOREMPs) at the multiple sleep latency test (MSLT) are polysomnographic markers for narcolepsy type 1 (NT1) in adults. We aimed at validating MSLT criteria for NT1 in children, against cerebrospinal hypocretin-1 (CSF hcrt-1) deficiency and presence of cataplexy, the biological and clinical pathognomonic features.
Methods: Clinical, neurophysiological and, when available, biological data (HLA-DQB1*06:02 positivity, CSF hcrt-1 levels) of 357 consecutive children below 18 years of age evaluated for suspected narcolepsy were collected. Best MSLT cut-offs were obtained by ROC curve analysis by contrasting among patients with available CSF hcrt-1 assay (n=228) those with versus without CSF hcrt-1 deficiency, and further validated in patients without available CSF hcrt-1, against cataplexy (n=129).
Results: Patients with CSF hcrt-1 deficiency were best categorized using a mean MSLT sleep latency ≤ 8.2 minutes, or by at least 2 SOREMPs at the MSLT (cut offs identified in a randomly selected group of 150 subjects and validated in a second group of 78 subjects). The combination of MSLT sleep latency and SOREMPs counts did not improve diagnostic accuracy, and the cut offs correctly categorized patients with cataplexy in the third clinical group. Age or sex also did not significantly influence these results in our pediatric population.
Conclusion: At least 2 SOREMPs or a mean sleep latency ≤ 8.2 minutes at the MSLT are valid and reliable markers for pediatric NT1 diagnosis, a result contrasting with adult NT1 criteria.
Disclosure: Nothing to disclose

EPR3113

Cerebral metabolism (FDG-PET) in DNMT1 mutations

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Background and aims: Autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN) and Hereditary sensory and autonomic neuropathy with dementia and hearing loss type IE (HSAN IE) are two rare neurodegenerative diseases, linked to DNMT1 gene mutations (respectively of exon 21 and exon 20) sharing several overlapping features. Here, we aimed at investigating the anatomical clinical correlated of these discrete entities, by means of functional brain imaging.
Methods: Data collection included comprehensive clinical and neurophysiological evaluations, 18F-fludeoxyglucose positron emission tomography (PET) obtained in seven subjects carrying mutations in DNMT1 gene [4 females and 3 males, mean age 44.85 years (36-62 years); 2 ADCADN phenotype, 3 HSN1E phenotype, 2 exon 20 mutation asymptomatic carriers. A qualitative (visual) and semiquantitave (SPM 8 software) analysis was carried out. A voxel-based comparison between FDG metabolism patterns of DNMT1 mutations carriers, and healthy controls was made.
Results: Compared with heathy controls, patients showed hypometabolism in cerebellar vermis and hemispheres, callosum corpus, caudate nucleus, thalamus, hypothalamus, superior temporal circumvolution (Fig.1, 2). These findings however did not correlate with disease duration and severity. The two asymptomatic carriers showed absence of abnormalities.

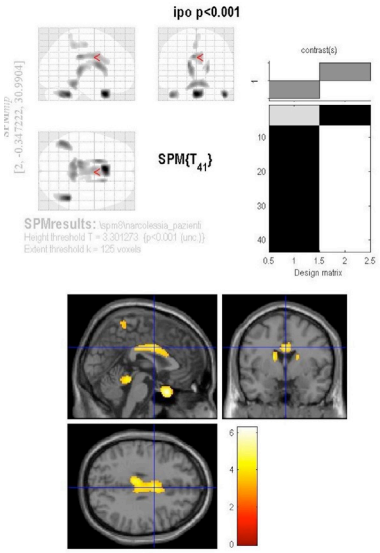

Fig.1- Comparative analysis patients vs healthy controls. In yellow are represented hypomethabolic areas in DNMT1 mutations carriers in confront of controls. The cursor, in particular, points callosum corpus

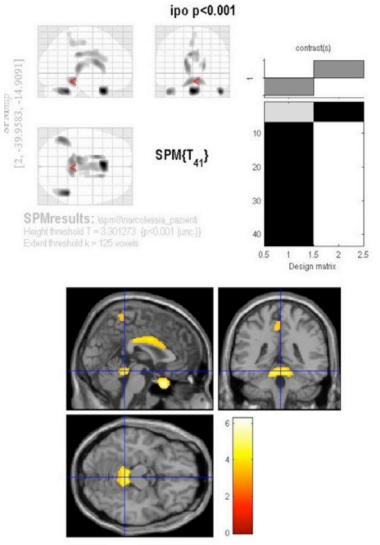

Fig.2- Comparative analysis patients vs healthy controls. In yellow are represented hypomethabolic areas in DNMT1 mutations carriers in confront of controls. The cursor, in particular, points cerebellar vermis.

Conclusion: The wide spectrum of functional abnormalities mirrored the severe and broad clinical features, with different pathophysiological systems likely affected by the neurodegenerative process, as shown also in previous neuroradiological and neuropathological studies. To enlarge the cohort will be the second step, aiming at defining a possible discrete metabolic pattern of the two phenotypes.
Disclosure: Nothing to disclose

EPR3114

Microsleep episodes in the borderland between wakefulness and sleep

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Background and aims: The wake-sleep transition zone represents a poorly defined borderland between wakefulness and sleep, containing e.g. microsleep episodes (MSEs), which are of potential relevance for diagnosis and consequences while driving. Yet, the scoring guidelines of the American Academy of Sleep Medicine (AASM) completely neglect it. We aimed to explore the borderland between wakefulness and sleep by developing the Bern continuous and high-resolution wake-sleep (BERN) criteria for the visual scoring of the wake-sleep transition zone, focusing on MSEs visible in the electroencephalogram (EEG).
Methods: Maintenance of wakefulness test trials of 76 randomly selected patients were retrospectively scored according to both the AASM and the newly developed BERN scoring criteria. The scoring was compared with quantitative EEG analysis.
Results: The quantitative EEG analysis enabled a reliable objectification of the visually scored MSEs. For less distinct episodes within the borderland, either ambiguous or no quantitative patterns were found. Defining sleep according to the AASM criteria, the latency to the first MSE was significantly shorter in comparison to the sleep latency. In certain cases, a large difference between the two latencies was observed, and a great number of MSEs occurred between the first MSE and sleep. Series of MSEs were more frequent in patients with shorter sleep latencies, while isolated MSEs were more frequent in patients who did not reach sleep.
Conclusion: The BERN criteria extend the AASM criteria and represent a valuable tool for in-depth analysis of the wake-sleep transition zone, particularly important in the maintenance of wakefulness test.
Disclosure: This work was supported by the Swiss National Science Foundation (grant 32003B_176323) and the Commission of Technology and Innovation (CTI) of the Swiss Government (grant 17864.1 PFLS-LS).

EPR3115

Association of restless legs syndrome with presence of surgical interventions in medical history

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Background and aims: Restless legs syndrome (RLS) is a common sleep disorder both idiopathic and secondary. Surgical interventions (SI) are considered probable iatrogenic factors for iron deficiency, thus also for RLS. Our aim was to investigate the prevalence of SI in history of RLS.

Methods: Patients from a sleep clinic population were involved. Based on international diagnostic criteria participants were divided into RLS(+) and RLS(-) groups. Detailed SI history was obtained including, total number of SI, with 2 and more defined as multiple SI (MSI), and anesthesia type. Mann-Whitney U and Chi-square tests were utilized for statistics.

Results: We included 230 adult patients (F=51.3%, mean age=39.4), with RLS diagnosed in 30.9% (71), and subgroups (Table): RLS(+) (mean age=47.6) and RLS(-) (mean age=35.7). Prevalence of any SI in RLS(+) was 78.8% (56), while in RLS(-) was 64.8% (103) ($p<0.05$). In RLS(+) prevalence of MSI was 40.9% (29) versus 23,3% (37) in RLS(-) ($p<0.05$). The total SI number means in RLS(+) and RLS(-) were 1.493/0.956 respectively ($p<0.001$). The SI with general anesthesia (GA) in RLS(+) and RLS(-) was 67.6% (48) and 45.1% (73) respectively ($p<0.01$).

Group	RLS(+)	RLS(-)	P
Sample	30.9% (71)	69.1% (159)	-
Mean age	47.6	35.7	-
Prevalence of SI	78.8 (56)	64.8% (103)	<0.05
Prevalence of MSI	40.9% (29)	23,3% (37)	<0.05
Total number of SI (means)	1.493	0.956	<0.001
SI with general anesthesia	67.6% (48)	45.1% (73)	<0.01

Table. Sample characteristics and comparison of SI by history in RLS vs. non-RLS

Conclusion: RLS patients report significantly more SI and MSI in history. Difference in mean age could be a confounding factor, but presence of independent correlation is not excluded. Interestingly, GA is more prevalent in RLS and could also be a risk factor for RLS. To the best of our knowledge this is the first study to correlate RLS and SI by history.

Disclosure: Nothing to disclose

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A possible role of palmitoylethanolamide combined with luteoline in frontotemporal dementia treatment: a clinical and neurophysiological study

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Background and aims: Frontotemporal dementia (FTD) is a frequent cause of presenile neurodegenerative dementia and there is no effective pharmacological treatment to slow its progression. A link has been proposed between neuroinflammation and specific forms of FTD, suggesting that neuroinflammation is an important component of the disease since the early phases. We aim to investigate efficacy and safety of palmitoylethanolamide combined with luteoline (PEA-LUT) in a sample of FTD patients to reduce behavioral disturbances.

Methods: We enrolled ten patients with a diagnosis of probable FTD. We performed cognitive and neurophysiological evaluations at baseline (T0) and after 4 weeks (T1) treatment with PEA-LUT 700 mgx2/day.To evaluate the cognitive effects of PEA-LUT administration we used a battery of tests including the MMSE, the frontal assessment battery (FAB), the neuropsychiatric inventory (NPI) and the screening for aphasia in neurodegeneration (SAND). We measured change on synaptic transmission using SICI-ICF, LICI and SAI paired-pulse TMS protocols over the primary motor cortex. We used iTBS protocol to measure changes in cortical plasticity. We used combined TMS/EEG methods to evaluate changes in DLPFC cortical oscillatory activity

Results: We observed an improvement in NPI mean score ($p=0.018$) and FAB score ($p=0.038$). Neurophysiological evaluation showed a restoration of LICI ($p=0.040$), in particular at ISI 100ms (post-hoc $p=0.035$), suggesting a modulation of GABA(B) activity. We observed an increase of LTP-like cortical plasticity ($p=0.079$) and of DLPFC oscillatory activity in beta/gamma range.

Conclusion: PEA-LUT could reduce behavioural disturbances and improve executive function in FTD patients through the modulation of cortical excitability and GABAergic transmission.

Disclosure: Nothing to disclose.