Oral Presentations

Motor Neurone Disease 1

OPR-001

Neural correlates of motor imagery of gait in amyotrophic lateral sclerosis

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Background and aims: Gait impairment is understudied and poorly characterised in Amyotrophic Lateral Sclerosis (ALS), despite increasing evidence of considerable extrapyramidal and cerebellar dysfunction. Gait impairment adds to the considerable motor disability of ALS patients and requires target multidisciplinary interventions. The objective of this study is to assess gait imagery specific-networks and functional adaptation in ALS.

Methods: 17 ALS patients with lower motor neuron predominant (LMNp) disability, fourteen patients with upper motor neurons predominant (UMNp) disease and fourteen healthy controls performed a dual motor imagery task on fMRI; normal and precision. The Movement Imagery Questionnaire – Revised Second Version (MIQ-rs) was used to appraise movement imagery in each participant. Study-group specific activation patterns were evaluated during motor imagery of gait. Additional generalized psychophysiological interaction analyses were carried out using the supplementary motor area, caudate, cerebellum, and superior parietal lobule as seed regions.

Results: Our data revealed a significant increase in imagery time in UMNp patients compared to controls and LMNp during imagined gait. UMNp patients exhibited decreased SMA, DLPFC and superior parietal lobule activation and increased orbitofrontal, parietal and cerebellar signal during imagined locomotion. Increased effective connectivity of the striato and parieto-cerebellar circuits was also demonstrated. Additional activation was detected in the insula and cingulate cortex.

Conclusion: Our results suggest functional reorganisation in ALS. Enhanced striato- and parieto-cerebellar networks in UMNp ALS patients are likely to represent a compensatory response to impaired postural control. Activation of insular and cingulate regions suggest that fear of falling is a an implication of gait disturbance in ALS

Disclosure: All authors have approved the abstract and agree with submission

OPR-002

Impaired recognition of disgust is related to subcortical volume loss in amyotrophic lateral sclerosis

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Background and aims: The impairment in detecting disgust in Amyotrophic Lateral Sclerosis (ALS) has been hypothesized to be related with the integrity of subcortical structures. However, this has not been demonstrated yet and was the aim of the study.

Methods: 20 ALS patients without cognitive/behavioural symptoms and 52 matched healthy controls (HC) underwent a brain MRI scan and a neuropsychological assessment including the Comprehensive Affect Testing System (CATS) investigating emotion recognition. Composite scores were calculated by summing up the correct answers for each emotion. Gray matter (GM) volumes of the subcortical structures were obtained using FIRST in FSL. Sociodemographic, cognitive and MRI data were compared between groups. In ALS patients, CATS significant findings were correlated with the subcortical volumes, ECAS performances, patients' mood and behaviour.

Results: ALS patients performed significantly worse than HC at the CATS, and they were significantly less able to recognize disgust. No GM volume differences were observed between groups. In ALS patients, a low performance in disgust recognition was related with a reduced volume of the left pallidum and with low performances at the ECAS.

Conclusion: In a sample of cognitively/behaviourally unimpaired ALS, we demonstrated an altered ability to correctly recognize disgust and a potential role of basal ganglia in the altered processing of this emotion. These findings, together with the relationship between the altered disgust recognition with lower ECAS performances in patients, suggest that disgust could be the first emotion to be hit in ALS cognitive decline. These findings offer new potential markers for monitoring extra-motor progression in ALS.

Disclosure: Italian Ministry of Health (GR-2013-02357415); European Research Council (StG-2016_714388_NeuroTRACK).

OPR-003

### Human spinal cord organoids to model C9orf72 ALS and test new therapies in vitro.

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Background and aims: Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease. Underlying genetic pathomechanisms include the C9orf72 repeat expansion, the most frequent genetic cause of ALS (C9ALS) in Europe and North America. Despite recent progress in unraveling C9ALS pathogenesis, reliable disease models and disease-modifying therapies still lack. Here, we aim to model C9ALS in vitro using 3D human spinal cord organoids (SCOs).

Methods: We differentiated C9ALS induced pluripotent stem cells (iPSCs) and isogenic controls using a free-floating 3D-culture method. We generated SCOs with a modified Lancaster's protocol promoting neural caudalization and ventralization. Then, we treated C9ALS SCOs with morpholino antisense oligonucleotides (MO) against C9Orf72 repeat expansion. Finally, we assessed the differentiation of organoids at different time points with immunohistochemical and qPCR analysis.

Results: We obtained isogenic and C9ALS SCOs displaying different co-existing neuronal subpopulations. SCOs expressed neural progenitor, pan-neuronal, astrocyte, motor neuron, and rostrocaudal markers, including markers of cervicobrachial spinal cells. Compared to controls, C9ALS organoids exhibited increased dipeptide repeat proteins (DPRs) levels, DNA damage markers associated with C9orf72 expansion, and cytoplasmic inclusions of translocated TDP-43, C9ALS-specific disease hallmarks. Gene expression analysis using qPCR reported differential expression of genes associated with DNA damage and motor neurons in MO treated C9ALS organoids.
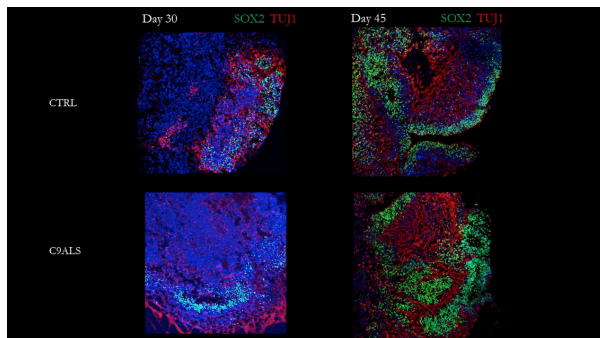
Confocal microscopy imaging showing markers of neural precursors (SOX2) and early proliferating neurons (TUJ1) in C9ALS spinal cord organoids and isogenic controls at day 30 and day 45.
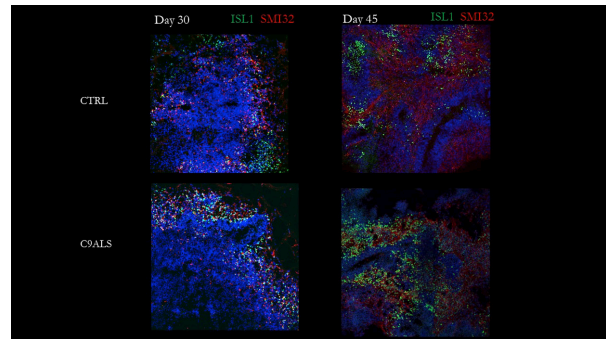
Confocal microscopy imaging showing motor neuron markers (Islet and Smi32) in C9ALS spinal cord organoids and isogenic controls at day 30 and day 45.
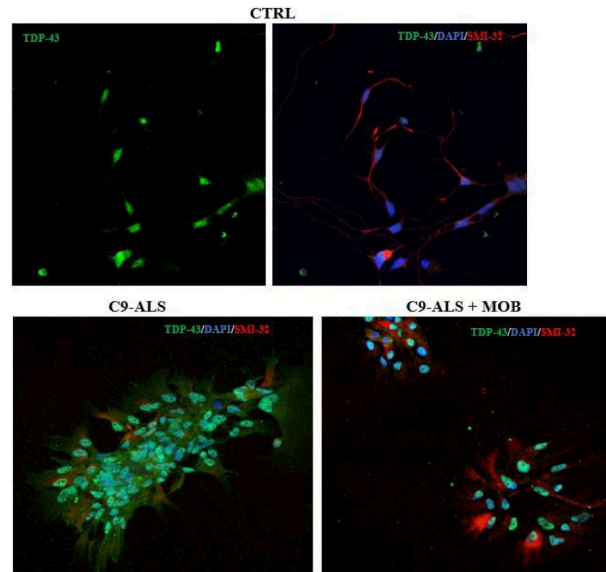
Confocal microscopy imaging displaying intracytoplasmic translocated TDP43 (green signal) in motor neurons from dissociated organoids possibly rescued by morpholino (MOB) treatment.

Conclusion: SCOs represent a valuable system for modeling features of C9ALS pathology, investigating C9ALS pathomechanisms, and testing possible new treatments in vitro.

Disclosure: The authors report no disclosures.

OPR-004

Nusinersen in adults with 5q spinal muscular atrophy: a systematic review and meta-analysis

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Background and aims: Nusinersen has been thoroughly studied in clinical trials of infants and children with 5q spinal muscular atrophy (SMA) and has gained approval for the treatment of all SMA types and patients of all ages. Data on nusinersen administration in adults are scarce, based on real-world evidence.

Methods: The purpose of this meta-analysis is to provide the first review of the literature regarding the efficacy and safety of nusinersen in patients older than 12 years of age with genetically confirmed 5q-SMA. We systematically searched MEDLINE, EMBASE, the Cochrane Library and grey literature through December 2020. Cross-sectional studies, case reports, review articles and/or studies with follow-up less than 6-months were excluded. Two reviewers screened eligible studies, extracted data, and assessed risk of bias (RoB).

Results: We included 11 records (seven case reports, four cohorts) enrolling 428 SMA patients older than 12 years with a follow–up of at least 6–months (Table 1). PRISMA flow diagram is presented at Figure 1. Clinically meaningful improvement ($\geq$3-points) of Hammersmith Functional Motor Scale was observed in 35.3% (95%CI 22.1–49.7) and 43.7% (95%CI 35.7–51.6) of the patients during short–term ($\leq$6-months) and long-term (>6-months) follow–up, respectively. Severe adverse events were reported in 3.3% (95%CI 0.4–6.2); treatment withdrawal rate was 2.8% (95%CI 1.2–4.4) (Table 2).
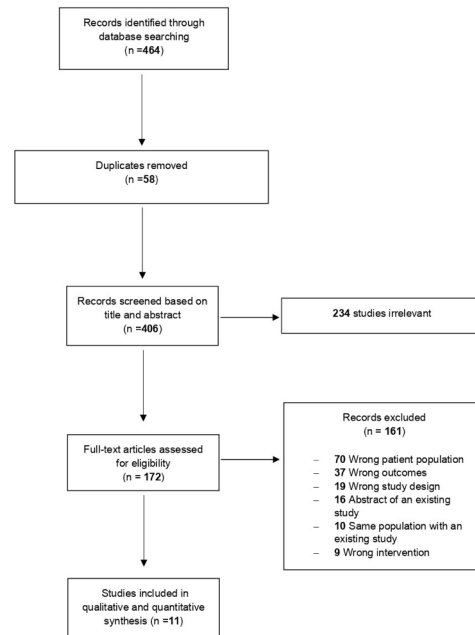

Figure 1. PRISMA Flow Diagram

Figure 1. PRISMA Flow Diagram

First Author	Study Type	Number of Patients (N)	N SMA type 1	N SMA type 2	N SMA type 3	N SMA type 4	Age at treatment, years (range)	Ambulant (%)	Previous surgery for scoliosis and/or severe scoliosis (%)	RoB *
DeWel 2020	Cohort	48	0	15	30	3	37.1 (20–66)	20.8	41.7	Low risk
Faravelli 2019	Case series	12	0	0	12	0	28.5 (15.0-34.8)	83.3	0	Fair
Hagenacker 2020	Cohort	139	2	47	89	1	37 (16- 65)	37	22	Low risk
Inan 2020	Case series	40	0	4	36	0	34.4 (19-60)	42.5	15	High risk
Jochmann 2020	Case series	7	0	4	3	0	45 (20-68)	14.2	42.8	Low risk
Maggi 2020	Cohort	116	0	13	103	0	34 (18–72)	34.5	13.8	Low risk
Moshe-Lilie 2020	Case series	22	0	9	13	0	36 (20-71)	9	77	Low risk
SHINE study 2020	Case series	7	0	1	6	0	14.4 (13-16)	71.4	na	Fair
Veerapandiyan 2020	Case series	12	1	4	7	0	22 (12–52)	25	66.7	Low risk
Walter 2019	Cohort	19	0	0	19	0	34 (18–59)	63	0	Low risk
Yeo 2020	Case series	6	0	0	6	0	29.9 (24.9-56.5)	67	0	Low risk
Total		428	3	97	324	4		36.4%	24%	

SMA: Spinal muscular atrophy, na: non-applicable
* Risk of Bias (RoB) was assessed using Newcastle-Ottawa scale for cohort studies and case series according to a tool proposed by Murad et al,BMJ Evidence-Based Medicine 2018.

Table 1. Baseline characteristics and risk of bias assessment of the 11 studies.

First Author	Number of Patients that received Nusinersen	Length of nusinersen treatment, range (months)	Number of patients with severe adverse events	Severe adverse events description	Number of patients who stopped treatment	Reasons of treatment withdrawal
DeWel 2020	16	6 to 14	0		na	0	na
Faravelli 2019	12	6	0		na	0	na
Hagenacker 2020	139	6 to 14	0		na	Adverse drug reactions or procedure-related events (n=2), patient's wish 4 (n=2)
Inan 2020	40	3 to 9	0		na	2 Difficulty of procedure (n=2)
Jochmann 2020	7	2 to 10	0		na	Sacral pressure ulcer close to the 1 injection site (n=1)
Maggi 2020	116	6 to 14	6	Hospitalization for postprocedure headache (n=5), renal colic requiring hospitalisation (n=1)	na	Lack of subjective benefit and poor tolerability of repeated lumbar 2 puncture (n=1)
Moshe-Lilie 2020	10	6 to 24	3	Bowel and bladder incontinence (n=1), bacterial meningitis (n=1), death by respiratory failure in the setting of pneumonia-shortly after treatment initiation (n=1)	na	Lack of improvement (n=1), recurrent pneumonia (n=1), or 3 proteinuria (n=1)
SHINE study 2020	7	64 to 82	3	Post-lumbar puncture headache that was considered severe and resolved with treatment (n=1), Pyuria and hematuria (n=1), Vesicoureteral reflux and pyelonephritis (n=1)	0	na
Veerapandiyan 2020	12	4 to 26	2	Hospitalization for an epidural blood patch (n=1), generalized tonic clonic seizure a day after the first maintenance dose (n=1)	0	na
Walter 2019	19	2 to 10			na	Subjective safety concerns regarding hydrocephalus development (n=1), 2 planned pregnancy (n=1)
Yeo 2020	6	14 to 21	2	Hospitalization for a fall with comminuted sacral compression fractures (n=1) and for leg cellulitis in the setting of chronic lower extremity lymphedema (n=1)	0	0

na: non-applicable

Table 2. Data regarding safety, adverse events and treatment withdrawal as defined and reported in each study.

Conclusion: Despite the low quality of evidence and the unmet need for randomized data to establish the safety and efficacy of nusinersen in adults, our meta-analysis confirms that nusinersen is a valuable treatment option for patients with longer-disease duration. Registration: PROSPERO database CRD42020223109

Disclosure: Nothing to disclose..

Multiple Sclerosis: Biomarkers and genetics

OPR-005

Effect of BDNF Val66Met polymorphism on hippocampal subfields in multiple sclerosis patients

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Background and aims: Brain-derived neurotrophic factor (BDNF) Val66Met polymorphism was shown to affect BDNF function. We aimed to explore BDNF Val66Met polymorphism effect on hippocampal subfields and its role in cognitive functioning in MS patients.

Methods: Using 3T scanner, we obtained dual-echo and 3DT1-weighted sequences from 50 MS patients and 15 healthy controls (HC). MS patients also underwent genotype analysis of BDNF, neurological and neuropsychological evaluation. Hippocampal subfields were segmented by using Freesurfer.

Results: The BDNF Val66Met polymorphism was found in 22 MS patients. Compared to HC, MS patients had lower volume in: bilateral hippocampus-amygdala transition area (HATA); cornus ammonis (CA)1, granule cell layer of dentate gyrus (GCL-DG), CA4 and CA3 of left hippocampal head; molecular layer (ML) of left hippocampal body; presubiculum of right hippocampal body and right fimbria. Compared to BDNF Val66Val, Val66Met MS patients had higher volume in: bilateral hippocampal tail; CA1, ML, CA3, CA4 and GCL-DG of left hippocampal head; CA1, ML and CA3 of left hippocampal body; left HATA and presubiculum of right hippocampal head. In MS patients, lower volume in left hippocampal tail was associated with worse visuo-spatial memory performance; lower volume in left hippocampal head with worse performance in semantic fluency; lower volume in bilateral hippocampal tail with worse performance in executive functions; and lower volume in presubiculum of right hippocampal head with higher fatigue scores.

Conclusion: BNDF Val66Met polymorphism resulted as a protective factor in MS. BDNF genotype might be a potential biomarker for predicting cognitive prognosis, and an interesting target to study for neuroprotective strategies.

Disclosure: Nothing to disclose..

OPR-006

Genetic factors implicated in the response to fingolimod in MS patients: results from a pharmacogenetic meta-analysis

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Background and aims: Multiple Sclerosis (MS) is a complex disease with high heterogeneity in terms of clinical presentation and treatment response. Pharmacogenetics can help to develop a more personalized approach and to improve disease management. Here we report the results of a genome-wide association study (GWAS) on fingolimod (FTY)-treated relapsing-remitting MS patients.

Methods: We included four cohorts of FTY-treated MS patients from San Raffaele Hospital in Milan, Italy (OSR1: 246 patients, OSR2: 98 patients), Brigham and Women's Hospital in Boston, USA (USA: 136 patients) and the Centre Hospitalier Universitaire de Toulouse, France (CHUT: 81 patients). We classified treatment response according to the NEDA (no evidence of disease activity) criterion at two years and time to first relapse (TFR). We performed a GWAS separately on each cohort and meta-analyzed them using a fixed-effect model.

Results: Three genome-wide significant variants were associated with TFR: rs9397818A on chr6 increases the risk of an earlier relapse and has an eQTL effect in whole blood on TFB1M, key to mitochondrial gene expression, and TIAM2, implicated in endothelial function and cell migration; rs2071572A is a risk allele intronic to synaptotagminV, involved in exocytosis of secretory vesicles, with an eQTL effect in brain cortex; finally the risk allele rs6124768A maps to CD40 locus and increases its expression according to a public eQTL database. No significant variants were identified in the NEDA analysis.

Conclusion: Genetic variants possibly implicated in cell migration, neuronal functions and immune response were associated with response to FTY. Functional studies are ongoing to validate our results.

Disclosure: Laura Ferrè has nothing to disclose.

OPR-007

Brain dysconnectivity damage contributes to neurofilament light level increase in multiple sclerosis: Multicenter study

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Background and aims: The predictive value of conventional lesion characteristics for clinical course and biomarkers in multiple sclerosis (MS) has been limited. This clinico-radiological paradox may be partly resolved by connectivity-based approaches incorporating the distribution and extent of brain network aberrations due to T2-hyperintense lesions. Using individual brain dysconnectivity mapping based on tractography, we tested the longitudinal associations between putative brain network involvement and levels of serum neurofilament light chain (sNfL), which is a proposed biomarker for axonal damage.

Methods: MS patients (n=328, mean age 42.9 years, 71% female) were prospectively enrolled at four European MS centres, reassessed at two-year follow-up (n=280). 3T magnetic resonance imaging (MRI) data were processed at one site using a harmonized pipeline. Disconnectome maps were calculated using BCBtoolkit, based on the individual lesion maps. Global disconnectivity (GD) was defined as the average probability of disconnectome across all voxels in each patient's white matter. sNfL concentrations were measured by an ultrasensitive Single molecule array (Simoa) assay. Robust linear mixed models (rLMM) with GD as dependent variable, patient as random factor, and sNfL, age, sex, diagnosis and treatment as fixed factors were run.
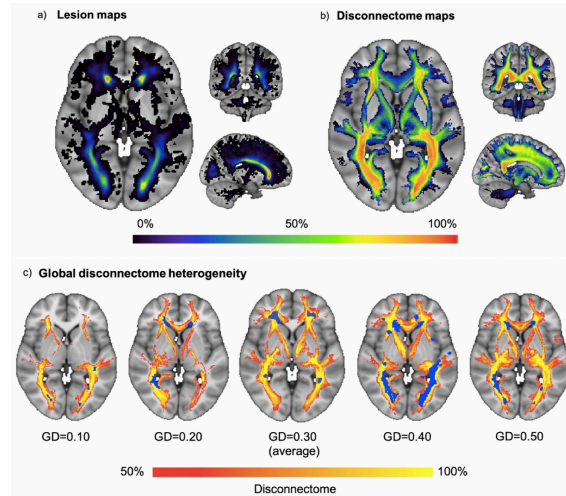

Figure 1. An overview with representative example slices of the probability distribution of A) lesion and B) disconnectome maps, along with examples of different levels of global dysconnectivity in C).

Results: rLMM revealed significant associations between GD and sNfL (t=2.30, p=0.022), age (t=5.01, p<0.001), and diagnosis (PMS; t=1.97, p<0.05), but no significant associations for sex, treatments or sNfL change.

Predictors	GD Estimates	GD CI	GD t	GD p	t2lv Estimates	t2lv CI	t2lv t	t2lv p
(Intercept)	-1.16	-1.77 – -0.55	-3.70	**<0.001**	-0.70	-0.83 – -0.56	-10.29	**<0.001**
sNfL	0.14	0.08 – 0.21	4.62	**<0.001**	0.05	0.02 – 0.09	2.89	**0.004**
Age	0.24	0.12 – 0.36	3.90	**<0.001**	0.08	-0.01 – 0.17	1.68	0.094
Sex [Female]	0.13	-0.08 – 0.34	1.19	0.234	0.03	-0.08 – 0.14	0.54	0.592
diagnosis [PMS]	1.39	0.70 – 2.09	3.94	**<0.001**	0.37	-0.00 – 0.74	1.95	0.052
diagnosis [RRMS]	0.52	-0.11 – 1.15	1.63	0.104	0.11	-0.03 – 0.26	1.56	0.121
treatment [Effective]	0.44	0.18 – 0.70	3.29	**0.001**	0.17	0.05 – 0.29	2.71	**0.007**
treatment [Highly-effective]	0.73	0.43 – 1.04	4.75	**<0.001**	0.35	0.15 – 0.55	3.49	**0.001**
Observations	294				294			
R² / R² adjusted	0.261 / 0.243				0.160 / 0.139			

Table 1. Linear regression for sNfL at baseline with global disconnectome maps and T2-lesion volume.

Predictors	GD Estimates	GD CI	GD t	GD p	t2lv Estimates	t2lv CI	t2lv t	t2lv p
(Intercept)	-1.11	-2.16 – -0.07	-2.09	**0.037**	-0.66	-1.31 – -0.01	-1.98	**0.047**
sNfL	0.03	0.00 – 0.05	2.30	**0.022**	-0.00	-0.02 – 0.01	-0.74	0.461
Timepoint	-0.00	-0.01 – 0.01	-0.79	0.432	0.02	0.01 – 0.02	7.41	**<0.001**
Age	0.32	0.19 – 0.44	5.01	**<0.001**	0.22	0.15 – 0.30	5.68	**<0.001**
Sex [Female]	0.11	-0.16 – 0.37	0.78	0.434	0.09	-0.08 – 0.25	1.01	0.312
diagnosis [PMS]	1.06	0.01 – 2.11	1.97	**0.049**	0.38	-0.27 – 1.04	1.15	0.249
diagnosis [RRMS]	1.01	-0.04 – 2.06	1.89	0.059	0.40	-0.25 – 1.05	1.20	0.229
treatment [Effective]	0.01	-0.02 – 0.04	0.85	0.394	-0.01	-0.03 – 0.01	-1.31	0.192
treatment [Highly-effective]	0.01	-0.02 – 0.04	0.86	0.389	0.00	-0.01 – 0.02	0.46	0.644
sNfL * Timepoint	-0.01	-0.03 – 0.00	-1.65	0.098	0.01	-0.00 – 0.01	1.87	0.061
Random Effects								
σ²	0.00				0.00			
τ₀₀	1.06 ID				0.41 ID			
ICC	1.00				1.00			
N	296 ID				296 ID			
Observations	506				506			
Marginal R² / Conditional R²	0.109 / 0.998				0.116 / 0.999			

Table 2. Robust linear mixed models predicting sNfL with global disconnectome maps and T2-lesion volume.

Conclusion: In our longitudinal prospective MS cohort, we showed significant associations between GD and sNfL. Our results demonstrate that the extent of global brain dysconnectivity is sensitive to a systemic biomarker of axonal damage in MS.

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OPR-008

Multilayer network analysis relates molecular and clinical features of multiple sclerosis

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Background and aims: Multiple Sclerosis is a complex disease covering a wide range of biological scales, from genes, to proteins and cells, to tissue damage (assessed by imaging) and finally to the phenotype. However, the exact interactions among each scale remain unclear. As a result, current methods for diagnosis and prognosis are often imprecise because they fail to capture this multi-scale level of complexity in MS.

Methods: Here, we conducted a systems biology study based on multi-level networks and regression models, which allows us to analyse multi-omics, imaging and clinical data obtained from MS patients to both aid in diagnosis, prognosis and increase our understanding of the underlying pathogenesis. Multi-scale networks were constructed using genomics, proteomics, cytomics, imaging (MRI and OCT), and clinical data from a prospective cohort of 350 MS patients and 90 matched controls from four MS centers and with two years follow-up. Structural networks were constructed using mutual information and boolean simulations, and then run on the proteomics and cytomics networks to identify pathways associated with MS and phenotype (mild vs severe cases).
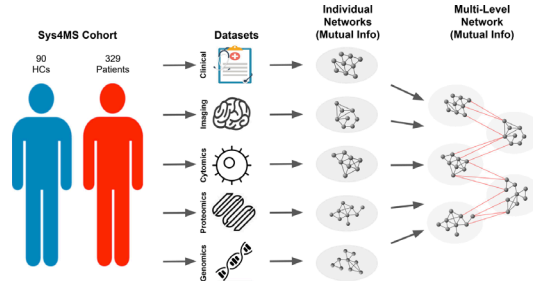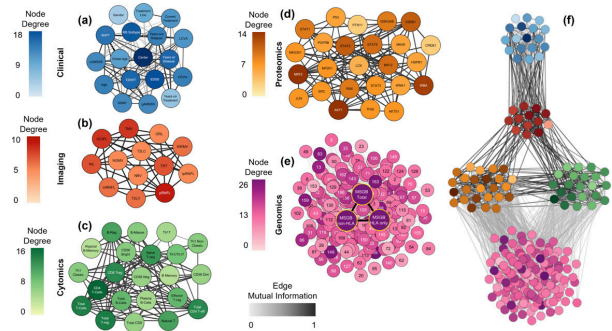

Illustration of network construction. The data from each layer is taken from the cohorts and used to create networks, where the nodes are the elements in the dataset (SNPs, proteins, cell types, OCT/MRI, and phenotypic data).

Topology of individual layer networks and the combined 5-layer network, constructed using all MS patients' data.

Results: We identified several regression models predicting phenotype based on protein-cell pathways, which outperformed genome–phenotype correlations. The most prominent pathway was GSK3AB – B memory cell pathway, that significantly predicted the phenotype (disability and brain atrophy), followed by IKBA – effector B cells and HSBP1-memory B cells.
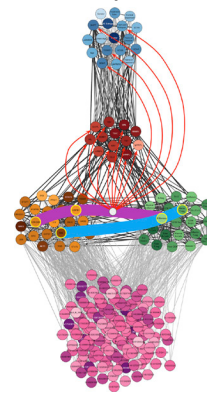
Example of one pathway (identified from the Boolean simulations) that significantly predicts various MS phenotypes.

Conclusion: The pathways identified in this analysis may be pursued as therapeutic targets or biomarkers for developing new therapeutics for MS.

Disclosure: This work was supported by the European Commission, Instituto de Salud Carlos III, Spain, the Italian Ministry of Health, the German Ministry of Science, the Norwegian Research Council and Biogen Norway.

OPR-009

Multiple sclerosis associated HLA variants affect the immunological T lymphocytes repertoire

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Background and aims: Genetic predisposition to multiple sclerosis (MS) includes >200 genetic loci, with the major histocompatibility complex (MHC) region accounting for 32 independent associations. We aim to investigate the impact of MHC MS-risk alleles on T lymphocytes repertoire in MS.

Methods: 183 untreated relapsing-remitting MS subjects have been studied. Class I and II HLA alleles were inferred from whole-genome genotyping data using SNP2HLA and Beagle_v3.3 tools. T-cell receptors (TCR) CD3 sequences were obtained from whole blood DNA according to the ImmunoSEQ hsTCRB kit (Adaptive Biotechnologies®). The weighted HLA-risk score (wHRS) was calculated for each individual. The inverse of the Simpson's Index (INV.S) was calculated as representative of immune repertoire diversity. Statistical analyses were performed within R environment and plink v.1.9.

Results: After quality controls and downsampling, the final set was composed by 144 individuals and 30 MS-risk MHC loci. Four loci showed association with INV.S (beta referring to the MS-risk allele): HLA DRB1 15*01 (p=0.014, beta=-1.02), rs11751659 (p=0.02, beta=0.79), rs9271366 (p=0.003, beta=-1.14), SNP_DRB1_32660116_A (p=0.036, beta=-0.5). A mild association was found between INV.S and wHRS (p=0.049), with individuals with a higher wHRS showing a lower diversity. Additionally, individuals carrying the risk allele showed a different percentage of clonotypes occupying the 10% of the repertoire, suggesting an expansion of certain clonotypes in the presence of the risk allele.

Conclusion: MS-risk MHC loci appear to influence TCR repertoire in MS patients, with the risk alleles reducing the diversity and inducing an expansion of specific clonotypes. Detailed analyses are ongoing to better define the amplified clonotypes and their role.

Disclosure: Authors declares no competing interests regarding this study.

OPR-010

Cerebrospinal fluid levels of CXCL12 and Osteopontin: potential early marker of primary progressive multiple sclerosis

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Background and aims: Both degenerative and inflammatory processes characterize primary progressive multiple sclerosis (PPMS). Like relapsing-remitting MS (RRMS) and secondary progressive MS, inflammatory infiltrates build up in the meningeal space, resulting in a severe disease course. PPMS patients represent an interesting cohort to investigate in vivo processes and possible biomarkers underlying disease progression.

Methods: Levels of 34 pro and anti-inflammatory cytokines and chemokines in the cerebrospinal fluid (CSF) were evaluated at the diagnosis in 16 PPMS and 80 RRMS patients. All patients underwent clinical evaluation, including Expanded Disability Status Scale (EDSS) assessment and a 3-T brain MRI with detection of white matter and cortical lesion number and volume and global and regional cortical thickness.

Results: Higher levels of CXCL12 (OR=3.97, CI95%[1.34–11.7]) and the monocyte–related osteopontin (OR=2.24, CI95%[1.01–4.99]) were associated with the diagnosis of PPMS, while levels of IL10 (OR=0.28, CI95%[0.09–0.96]) were significantly increased in RRMS group. No associations were found between examined molecules and EDSS; CXCL12 levels correlated with both increased GM lesion number and volume (p=0.001, r=0.832 and r=0.821, respectively). The pathway analysis confirmed the chronic inflammation is occurring in PPMS.

Conclusion: At the time of diagnosis, a specific CSF protein profile can recognize the presence of early intrathecal inflammatory processes, possibly stratifying PPMS with respect to RRMS. Elevated CSF levels of CXCL12 and Osteopontin suggested a key role of brain innate immunity and glia activity in MS. Therefore, these molecules could represent useful candidate biomarkers of MS progression and could have important implications for the pathogenesis and treatment of progressive MS.

Disclosure: No

Neurogenetics 1

OPR-011

Efficacy and safety results of the avalglucosidase alfa phase 3 COMET trial in late-onset Pompe disease patients

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Background and aims: The Phase 3 COMET trial (NCT02782741/Sanofi Genzyme) compares avalglucosidase alfa (n=51), a recombinant human GAA enzyme replacement therapy specifically designed for enhanced M6P-receptor targeting and enzyme uptake aimed at increased glycogen clearance, and alglucosidase alfa (n=49) in treatment-naïve patients with late-onset Pompe disease.

Methods: The primary objective was to determine the effect of avalglucosidase alfa on respiratory muscle function. Secondary/other objectives include effects on functional endurance, inspiratory/expiratory muscle strength, lower/upper extremity muscle strength, motor function, and health-related quality of life, and safety.

Results: At Week 49, change (LS mean±SE) from baseline in upright forced vital capacity (FVC) %predicted was 2.43% greater with avalglucosidase alfa (2.89% ±0.88%) than with alglucosidase alfa (0.46% ±0.93%). The primary study objective, achieving statistical non-inferiority (p=0.0074), was met. Testing for superiority was borderline significant (p=0.0626). Avalglucosidase alfa treatment resulted in a 30.01-meter and 4.71% greater improvement in the 6-Minute Walk Test (32.21±9.93 vs. 2.19±10.40 meters; 5.02±1.54 vs. 0.31±1.62%predicted). Positive results for avalglucosidase alfa were seen for all secondary and other efficacy endpoints. Treatment-emergent adverse events (AEs) occurred in 86.3% of avalglucosidase alfa-treated and 91.8% of alglucosidase alfa-treated participants. Five participants withdrew, four due to AEs, all with alglucosidase alfa. Serious AEs occurred in eight avalglucosidase alfa-treated and 12 alglucosidase alfa-treated participants. IgG antidrug antibody responses were similar for both. High titers (12,800) and neutralizing antibodies were more common for alglucosidase alfa.

Conclusion: Results demonstrate improvements in clinically meaningful outcomes and a more favorable safety profile with avalglucosidase alfa versus alglucosidase alfa.

Disclosure: The COMET trial is sponsored by Sanofi Genzyme.

OPR-012

Plasma neurofilaments as biomarkers in frontotemporal dementia associated with C9orf72 and GRN mutations

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Background and aims: C9orf72 and progranulin (GRN) mutations are the main genetic causes of frontotemporal dementia (FTD) and, for C9orf72, amyotrophic lateral sclerosis (ALS). Upcoming targeted therapies highlight the importance of easily-accessible, reliable biomarkers for the preclinical and clinical follow-up. We aimed to evaluate longitudinal changes of plasma neurofilament light chain (NfL) in mutation carriers and in healthy controls (HC).

Methods: Our study cohort consists of 352 individuals including 102 FTD and/or ALS patients (54 C9orf72 carriers and 48 GRN carriers), 85 presymptomatic carriers (PS: 48 C9orf72 and 37 GRN), and 165 HC. Participants were recruited through PREV-DEMALS and Predict-PGRN protocols, and the national research network on FTD/ALS. They underwent up to six blood samplings during a mean follow-up of four years. NfL dosage was performed with the SIMOA technique.

Results: In HC, NfL increased with age at sampling (r=0.766, p<0.0001) and slightly progressed over time, with a mean change rate of 4%/year. Patients had higher NfL compared to HC and PS (Fig.1). The causal gene had a major effect, GRN carriers having higher baseline values (p=0.014) and greater progression compared to C9orf72 carriers (p=0.016) (Fig.2). We proposed thresholds to differentiate symptomatic carriers from HC at each age class. NfL in PS were comparable to HC at baseline, with a subset displaying increased progression.
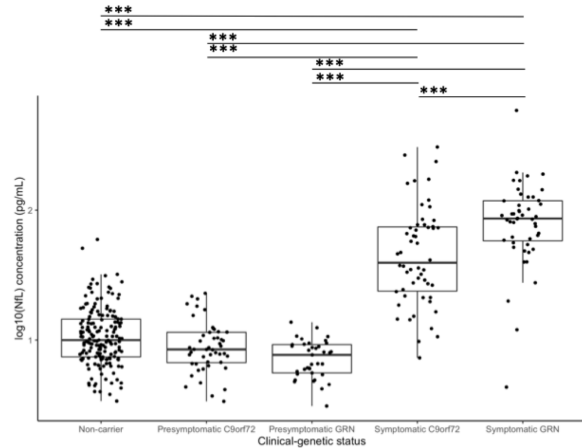

Figure 1. Baseline plasma NfL levels in patients, presymptomatic carriers and controls. Comparisons were performed with general linear model to account for all variables (gene/status, age, sex) and post hoc test (*: p<0.05; **: p<0.01; ***: p<0.001).
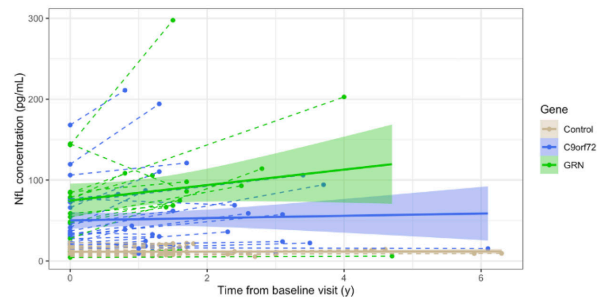

Figure 2. Longitudinal changes in mutation carriers and healthy controls. NfL variations from the first to the last observation, for 44 patients and 36 controls with longitudinal sampling, at the individual and group level (linear mixed-effects model).

Conclusion: NfL levels prove their usefulness in tracking the degenerative process in C9orf72 and GRN mutations. Combined with other biomarkers, they will hopefully allow to identify PS close to their clinical conversion, and define the optimal time window to deliver targeted therapies.

Disclosure: The authors declare no disclosures relevant to the abstract. ILB served as a member of advisory board for Prevail Therapeutics, and of steering committee for Alector, outside of the present work.

OPR-013

Gene association networks and miRNA-gene interactions reveal pathological pathways involving IL6 in Parkinson's disease

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Background and aims: Parkinson´s Disease (PD) is a complex disorder characterized by multiple contributing factors. The study investigated SNPs regulating interactions among genes, miRNA and their targets in order to highlight novel biomarkers or therapeutic targets for the treatment and management of PD.

Methods: The study included 342 patients affected by sporadic PD and 503 control samples. The OpenArray technology was utilized to screen patients for 120 SNPs selected by literature and bioinformatic approach, giving preference to non-coding variants that may affect regulatory gene networks relevant to PD. Statistical and bioinformatic analysis were performed to assess the association with PD and identify network of genes and miRNAs interactions.

Results: 26 SNPs were associated with PD risk, of which 12 SNPs were significant eQTL variants in different brain regions involved in motor and non-motor symptoms. Moreover, 11 novel susceptibility genes for PD were identified, which may alter multiple signaling pathways critically involved in cellular homeostasis and dopaminergic neurons wiring. A network of interconnected genes (APOE, CLU, IL6, IL7R, IL12B, INPP5D, MAPK1, MEF2C, MIF, TNFSF14) highlighted a major regulatory role of IL6 in the network. The study of miRNA-target gene networks highlighted a possible role of miR-499a and miR-196a2 in multiple neuro-inflammatory and neurodegenerative mechanisms in PD.

Conclusion: The study highlighted different networks of genes and miRNA-target gene interactions in PD. In particular, IL6 stands out as the most promising candidate either as prognostic biomarker of disease or as therapeutic target to fight neuro-inflammation and neurodegeneration in PD patients.

Disclosure: Nothing to disclose.

OPR-014

Phenotypic features and disease progression of the m.8344A>G MT-TK gene variant: MERRF syndrome and beyond

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Background and aims: Myoclonic epilepsy with ragged red fibres (MERRF) is a classic syndrome of mitochondrial DNA disease most commonly associated with the pathogenic m.8344A>G MT-TK gene variant. While phenotypic heterogeneity has been extensively described, disease progression is poorly characterised.

Methods: Single national centre, observational study (2009–2020). Data derived from the UK Mitochondrial Disease Patient Cohort.

Results: We identified 64 individuals (42 women) from 30 pedigrees and mean (SD; range) age of last follow up was 46.9 (17.4; 3–73) years. Common neurological features were proximal myopathy (73%), cerebellar ataxia (62%), seizures (59%), myoclonus (57%) and swallowing problems (49%). Other systemic manifestations comprised gastrointestinal dysmotility (51%), lipomatosis (36%), cardiac (29%) and respiratory involvement (29%). Sixteen individuals were asymptomatic. Myoclonus was associated with both epilepsy (2=19.5, p<0.001) and cerebellar ataxia (2=11.2, p=0.001). Mean (SD) m.8344A>G blood heteroplasmy was significantly higher in clinically affected individuals than asymptomatic carriers [71% (18%) vs 48% (17%), p<0.001]. We measured total disease burden using Newcastle Mitochondrial Disease Adult Scale and demonstrated the rate of disease progression was variable between patients (Figure 1); m.8344A>G blood heteroplasmy was a weak predictor of disease burden based on a multivariate regression model (p=0.015, R^2= 0.485).
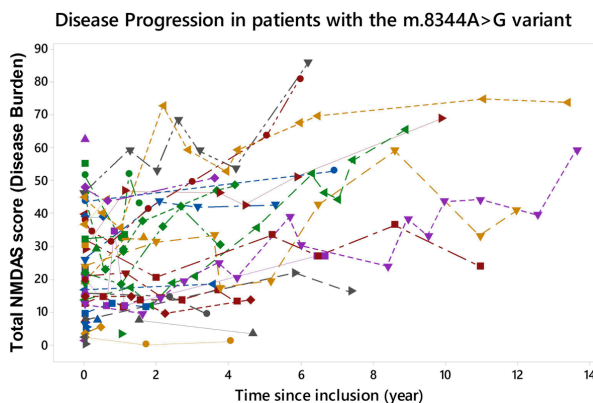
Disease Progression in adult patients with the m.8344A>G variant

Conclusion: Our findings provide insight into the natural history of m.8344A>G-related mitochondrial disease. The variability of phenotypic expression and disease progression has significant implications on the design of future clinical trials with robust modelling of disease progression necessitating wider datasets through international collaboration.

Disclosure: Nothing to disclose.

OPR-015

Efficacy and Safety With >3 Years of Inotersen Treatment for the Polyneuropathy of Hereditary Transthyretin Amyloidosis

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Background and aims: Hereditary transthyretin amyloidosis is a progressive, debilitating, and ultimately fatal disease that causes multisystem dysfunction. Here we report long-term efficacy and safety for inotersen, an antisense oligonucleotide inhibitor of transthyretin protein production.

Methods: Patients completing the NEURO-TTR trial (NCT01737398) enrolled in its open-label extension (OLE; NCT02175004). Assessments included modified Neuropathy Impairment Score +7 (mNIS+7), Norfolk Quality of Life–Diabetic Neuropathy questionnaire (Norfolk QOL-DN), and safety monitoring. As of July 28, 2020, efficacy is reported for patients from Europe and North America and safety is reported for all patients.

Results: Patients who switched from placebo to inotersen in the OLE (n=39) demonstrated slowing of neurologic disease progression compared with natural history (based on placebo projection); mean mNIS+7 and Norfolk QOL-DN scores at OLE baseline/1/2/3 years were 102.7/111.2/113.6/112.3 and 61.2/59.0/63.5/67.7, respectively. Patients receiving inotersen for 51 months (15 months in NEURO-TTR + 36 months in OLE; n=67) continued to show benefit, with mean mNIS+7 and Norfolk QOL-DN scores at OLE baseline/1/2/3 years of 84.3/90.7/98.1/95.1 and 50.3/52.4/53.1/57.2, respectively. Few patients (6/135; 4.4%) had serious treatment-related adverse events; there were no treatment-related deaths. Under enhanced monitoring, there have been no reports of grade four thrombocytopenia or acute glomerulonephritis despite increased duration of exposure. No new safety concerns were identified.

Conclusion: Extended treatment with inotersen for over three years slowed progression of the polyneuropathy associated with hereditary ATTR, with greater benefit observed in patients who initiated inotersen earlier. Long-term results further highlight the importance of early treatment. Enhanced monitoring has reduced risks of severe thrombocytopenia and acute glomerulonephritis.

Disclosure: Funding was provided by Akcea Therapeutics, an Ionis Company, and editorial assistance was provided by ApotheCom.

OPR-016

Three Newly Recognized Likely Pathogenic Variants of the TTR Gene Causing Hereditary Transthyretin Amyloidosis

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Background and aims: Hereditary transthyretin amyloidosis (hATTR/ATTRv) is a progressively debilitating, clinically heterogeneous, fatal disease that results from deposition of insoluble amyloid fibrils in various organs and tissues. Symptomatic patients exhibit cardiomyopathy, polyneuropathy, or both, depending on the TTR variant. Early diagnosis of hATTR can be facilitated with genetic testing; however, such testing identifies variants of uncertain significance (VUS) in a minority of cases. Although most VUS reflect benign genetic variation present in the human genome, a small percentage of VUS have the potential to be pathogenic. The Akcea/Ambry VUS Initiative is dedicated to gathering molecular, clinical, and inheritance data for each TTR VUS identified via genetic testing programs to reclassify TTR variants to a clinically actionable status (eg, variant likely pathogenic [VLP]) where appropriate.

Methods: The classification criteria used here are based on recommendations from the American College of Medical Genetics. They are stringent and comprehensive, requiring multiple distinct lines of evidence supporting pathogenesis. Variants were assessed for reclassification based on the totality of evidence available.

Results: Three TTR variants have been reclassified from VUS to VLP, including p.A65V (c.194C>T), p.D58H (c.172G>C), and p.T80I (c.239C>T). In each case, the totality of genetic and clinical evidence provided strong support for pathogenicity. The new classification of each variant will be submitted to the NIH ClinVar database.

Conclusion: Based on multiple lines of evidence, three TTR VUS were reclassified as VLP, thus resulting in a high likelihood of disease diagnosis for those and all subsequent patients. Confirmed hATTR diagnosis can facilitate access to approved therapies.

Disclosure: Funding was provided by Akcea Therapeutics, an Ionis Company; editorial assistance was provided by ApotheCom and scientific support was provided by Ambry Genetics.

Neuroimaging

OPR-017

Disease severity in Progressive Supranuclear Palsy determines the relationship between tau burden and synaptic density

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Background and aims: The in-vivo relationship between synaptic loss and tau accumulation in Progressive Supranuclear Palsy (PSP) is key to understanding the impact of tauopathy on functional decline.

Methods: We determine the correlation between synaptic density and tau accumulation in PSP – Richardson's Syndrome using [11C]UCB-J and [18F]AV-1451 PET imaging, respectively. PSP patients (n=22, m:f 10:12, mean age ±sd: 70.8 ±8.6) were compared to age-/sex-/education-matched controls (n=17, m:f 9:8, mean age ±sd:68.8 ±7.0). Disease severity was assessed with the PSP rating scale.

Results: Across all brain regions, averaging across patients, there was a positive correlation between [11C]UCB-J and [18F]AV1451 binding. The direction of this correlation varied as a function of disease severity (beta=-0.03, t=-3.0, r=-0.58, p<0.01) (Fig 1). Between brain regions, comparing [18F]AV-1451 in a cortical region versus [11C]UCB-J in an anatomically connected sub-cortical area, revealed significant negative correlations (r≤0.4, p<0.05).
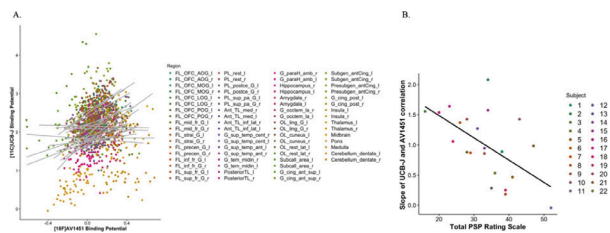

Figure 1. A) positive correlation between [11C]UCB-J and [18F] AV1451 non-displaceable binding potentials across all brain regions, B) Inter-individual variability in the correlations in A is determined by disease severity (PSP rating scale).

Conclusion: Brain regions with higher synaptic density are associated with a higher tau burden in PSP, while this association is a function of disease severity. Higher tau burden in cortical regions correlates with lower synaptic density in subcortical regions to which the cortical areas project. The effect of disease severity suggests a biphasic relationship between synaptic density and tauopathy: with densely connected regions initially more prone to tauopathy, followed by a loss of their connectivity in response to tauopathy. Given the importance of synaptic density for cognition, our study elucidates the pathophysiology of PSP and informs clinical trials' design at different disease stages.

**Disclosure:** Authors do not have any disclosures to make.

OPR-018

Increased Normal Appearing White Matter perfusion: an inflammatory marker in relapsing-remitting multiple sclerosis?

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Background and aims: Brain hemodynamic changes by Dynamic Susceptibility Contrast enhanced perfusion (DSC) in Multiple Sclerosis (MS) have been evaluated in few studies. The aim is to compare relapsing and remitting (RR) MS patients by assessing Cerebral Blood Flow (CBF), Cerebral Blood Volume (CBV), Mean Transit Time (MTT) with DSC.

Methods: We included RRMS patients with (REL) and those without (REM) relapse in the previous two months. Clinical features were correlated with radiological findings (Pearson's test). ANOVA for repeated measures was used to compare perfusion between FLAIR, T1 GD lesions and Normal Appearing White Matter (NAWM).
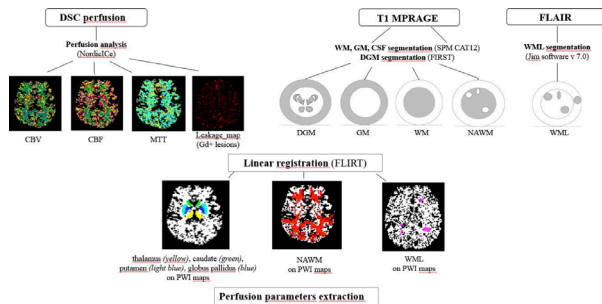
MRI DSC analysis pipeline and co-registrations with structural images

Results: 45 RRMS patients [(22 REL/23 REM); mean (SD) age 41.3(8.4); female 77.8%; mean disease duration (DD) 12.8(7.1); mean ARR-1year and 2years 0.7(1.2) and 0.4(0.7); mean cumulative number of relapses (CNR) 3.9(3.6). CNR, ARR-1y and 2y were different between REL and REM ($p<0.001$). FLAIR and T1 lesion load correlated with DD ($p<0.001$, $r=0.8$), CNR ($p<0.05$, $r=0.6$) and z-MSFC ($p<0.05$, $r=-0.7$). In REM, correlations between NAWM CBV and DD ($p<0.05$, $r=-0.6$) or between NAWM CBF and both DD ($p=0.001$, $r=-0.7$) and ARR-1y ($p<0.05$, $r=0.4$) were found. MTT was lower whereas CBF was higher in NAWM than in FLAIR lesions ($p<0.05$). A trend indicating a higher perfusion of GD compared to FLAIR lesions was observed in CBF ($p=0.054$).
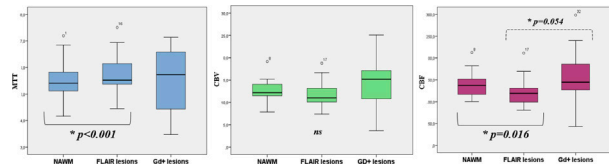
Comparisons of perfusion parameters among NAWM, FLAIR and GD lesions

Conclusion: In RRMS, a hyperperfusion of NAWM compared to FLAIR lesions was noted. Correlations between NAWM perfusion, DD and ARR-1y in REM patients seemed to suggest that an increased NAWM perfusion may be a radiological marker of inflammatory activity.

Disclosure: Authors have nothing to disclose

OPR-019

Progression of tau pathology across in-vivo stages of regional amyloid deposition

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Background and aims: Previous research has consistently found widespread tau aggregation in the presence of global amyloid- (A) pathology, but the association of A pathology severity with tau accumulation remains unclear. Here, we studied tau aggregation in relation to progressive stages of regional A deposition as determined by a recently established A PET staging approach.

Methods: We examined 244 cognitively unimpaired (CU) and 180 impaired (CI) subjects with concurrent T1 MRI, 18F-Florbetapir-PET, and 18F-Flortaucipir-PET (FTP) scans. An A PET staging method was used to stratify participants into four progressive stages of A deposition. Linear regressions adjusted for age, sex, and, if appropriate, clinical diagnosis were used to assess regional FTP uptake across A stages in CU and CI individuals. Longitudinal tau accumulation in the whole sample was assessed with linear mixed effects models adjusted for the same covariates.

Results: A deposition followed a consistent regional hierarchy that allowed staging 99% of individuals. Cross-sectionally, gradual FTP uptake increases in Braak I-II were observed from stages 1 to 4 in CU, though only A stage four in CU and stages 3 and 4 in CI revealed widespread tau deposition compared to stage 0 (Fig. 1). Similarly, stage 2 was associated with longitudinal Braak I-II FTP increases, but only A stages 3 and 4 showed faster tau accumulation rates in regions exceeding Braak I-II (Fig. 2).
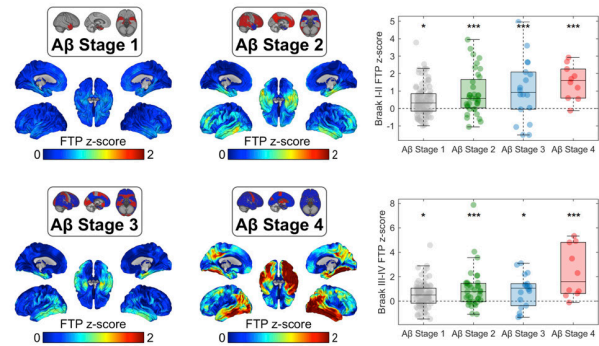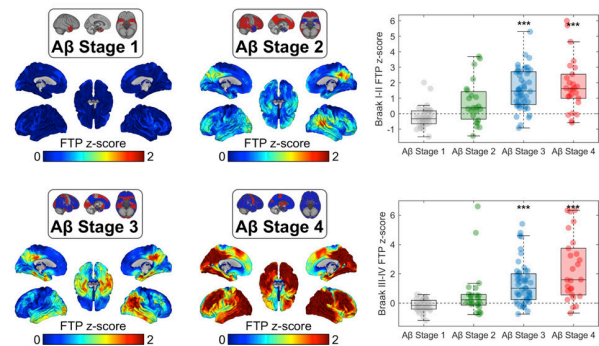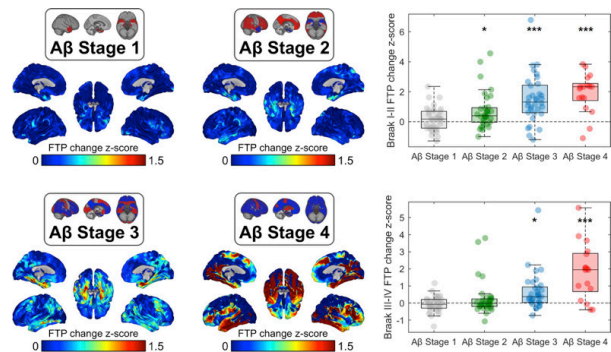

Cross-sectional flortaucipir PET patterns and flortaucipir uptake in Braak areas I-II and III-IV, referenced to Stage 0 subjects, across in vivo stages of regional amyloid deposition for cognitively unimpaired (A) and impaired (B) participants.

Longitudinal flortaucipir uptake change patterns and uptake change in Braak areas I-II and III-IV, referenced to Stage 0 subjects, across in vivo stages of regional amyloid deposition

Conclusion: The induction of severe and widespread tau pathology seems to occur at advanced stages of A deposition, which only cover a subpopulation of A-positive individuals as conventionally defined.

Disclosure: No disclosures

OPR-020

Differential diagnosis between common neurodegenerative dementias using metabolic brain images and machine learning

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Background and aims: FDG-PET scanning can reveal characteristic patterns of glucose hypometabolism in neurodegenerative dementias. Scans are usually assessed visually, however use of statistical analysis and machine learning provides additional information and increases FDG-PET clinical utility.

Methods: We analysed 67 FDG-PET scans from three dementia cohorts (27 Alzheimer's dementia (AD), eight dementia with Lewy bodies (DLB), 20 frontotemporal dementia (FTD)) and 12 normal controls (NC). Patients were diagnosed clinically and by visual assessment of FDG-PET scans. Scans were then pre-processed and "SingleCase" SPM t-maps created with SPM12. T-maps were classified into one of four (dementia syndrome or NC) categories by an expert reader. T-maps were imported to Orange and embedded with Inception v3 embedder (Google's deep neural network for image recognition). Embedded images were projected into two dimensional space using t-SNE. Five different machine learning methods (k-nearest neighbour (k-NN), logistic regression, neural network, SVM and random forest) were implemented and evaluated after 10-fold cross-validation. Their performance against clinical assessment and visual read was assessed.

Results: T-SNE visualization revealed a clear separation of patients from NC. There was some overlap between FTD and AD cohorts. DLB scans were clustered together, but placed within the AD cluster, Figure 1. Models achieved 75–82% classification accuracy. DLB was the most difficult class to predict. Confusion matrix of the best model (k-NN) is shown on Figure 2.
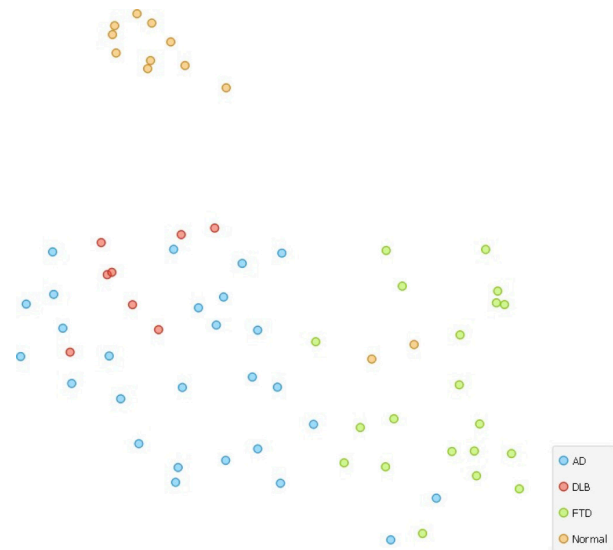

Image map after projection of images to two-dimensional space with t-SNE.

	Predicted				
	AD	**DLB**	**FTD**	**Normal**	**Σ**
AD	22	4	1	0	27
DLB	1	7	0	0	8
FTD	3	0	16	1	20
Normal	0	0	2	10	12
Σ	26	11	19	11	67

Confusion matrix of k-NN model (82% overall accuracy).

Conclusion: Computer vision is gaining popularity. We presented its possible application to FDG-PET scans and "SingleCase" SPM t-maps in differential diagnosis of common dementias. Popular machine learning methods achieved high overall classification/diagnostic accuracy.

Disclosure: No disclosures.

OPR-021

Semiquantitative evaluation of brain glucose metabolism in anti-leucine-rich glioma- inactivated-1protein encephalitis

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Background and aims: Putaminal hypermetabolism on [18F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) in anti-leucine-rich, glioma-inactivated-1 protein (LGI1) antibody-associated autoimmune encephalitis (AE) has been previously reported. However, the accuracy of FDG-PET in distinguishing LGI1-AE from other AE's and neurodegenerative conditions is not known. Further, the presence of other subcortical and cortical metabolic abnormalities and prognostic value of FDG-PET in LGI1-AE is not clear.

Methods: Brain FDG-PET scans from 49 age- and sex-matched subjects (13 LGI1-AE, 15 non-LGI1-AE, 11 Alzheimer's disease (AD), 10 negative controls (NC)) were analyzed. Regions of interest were delineated using Automated Anatomic Labelling atlas. Putaminal standardized uptake value ratios (SUVR) with normalization to global brain (P-SUVRg), thalamus (P/Th) and midbrain (P/Mi) were evaluated for diagnostic accuracy. SUVRg was applied for all other analyses.

Results: P-SUVRg, P/Th and P/Mi were higher in LGI1-AE vs. non-LGI1-AE, AD and NC (all p<0.05, Bonferroni-corrected). P/Mi and P-SUVRg robustly differentiated LGI1-AE from NC, non-LGI1-AE and AD (areas under curve range 0.84-0.99; Fig. 1). Mediotemporal SUVRg was increased in both LGI1-AE and non-LGI1-AE vs. NC (p<0.05 for both). Additionally, LGI1-AE-patients showed hypometabolism in inferior frontal and parietal lobes, and hypermetabolism in globus pallidus, caudate, pons, olfactory and inferior occipital lobes when compared to NC (Fig. 2). Bilateral orbitofrontal and cingulate gyrus hypometabolism were associated with poorer outcome at average 19.7 months follow-up (Fig. 3).
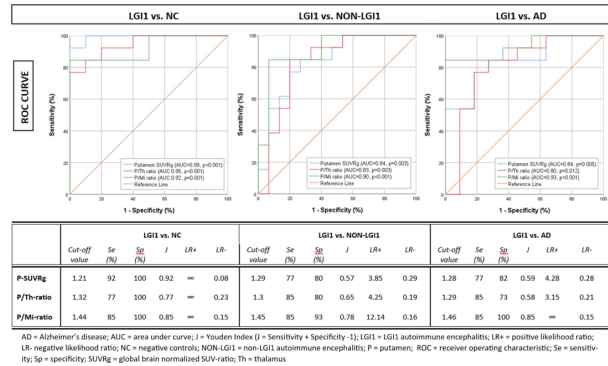

	LGI1 vs. NC						LGI1 vs. NON-LGI1						LGI1 vs. AD					
	Cut-off value	Se (%)	Sp (%)	J	LR+	LR-	Cut-off value	Se (%)	Sp (%)	J	LR+	LR-	Cut-off value	Se (%)	Sp (%)	J	LR+	LR-
P-SUVRg	1.21	92	100	0.92	∞	0.08	1.29	77	80	0.57	3.85	0.29	1.28	77	82	0.59	4.28	0.28
P/Th-ratio	1.32	77	100	0.77	∞	0.23	1.3	85	80	0.65	4.25	0.19	1.29	85	73	0.58	3.15	0.21
P/Mi-ratio	1.44	85	100	0.85	∞	0.15	1.45	85	93	0.78	12.14	0.16	1.46	85	100	∞		0.15

AD = Alzheimer's disease; AUC = area under curve; J = Youden Index (J = Sensitivity + Specificity -1); LGI1 = LGI1 autoimmune encephalitis; LR+ = positive likelihood ratio; LR- negative likelihood ratio; NC = negative controls; NON-LGI1 = non-LGI1 autoimmune encephalitis; P = putamen; ROC = receiver operating characteristic; Se = sensitivity; Sp = specificity; SUVRg = global brain normalized SUV-ratio; Th = thalamus

Figure 1

Caudate Nucl = Caudate Nucleus
LGI1 = LGI1 autoimmune encephalitis
Frontal Inf Oper = opercular part of inferior frontal gyrus
Frontal Inf Orb = orbital part of inferior frontal gyrus
Frontal Inf Tri = triangular part of inferior frontal gyrus
Frontal Mid Orb = orbital part of middle frontal gyrus
NC = negative control
Occipital Inf = inferior occipital lobe
Parietal Inf = inferior parietal lobe
SUVRg = global normalized standardized uptake value ratio

*p<0.05, **p<0.01, ***p<0.001 (Mann-Whitney U-test, significant at the level of p<0.05)
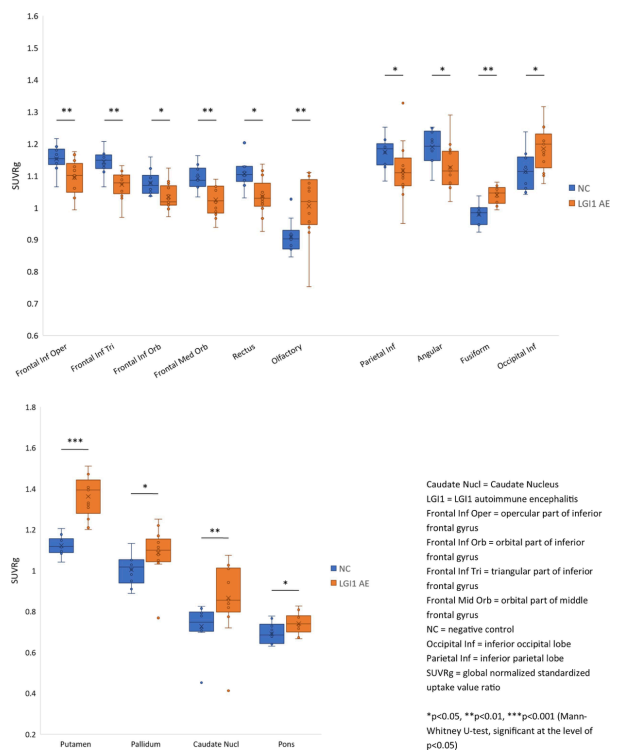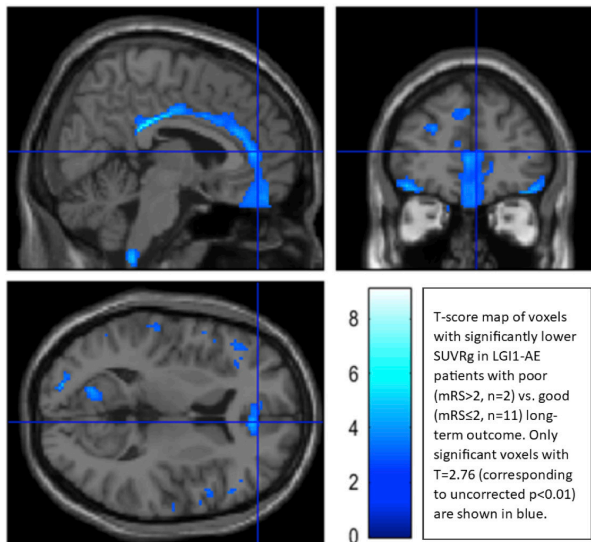
Figure 2

mRS = modified Rankin Scale

Figure 3

Conclusion: P/Mi and P-SUVRg can be used to aid in diagnosing LGI1-AE. Metabolic abnormalities in LGI1-AE extend beyond putamen and mediotemporal lobe into other subcortical and cortical regions. FDG-PET can aid in prognostication of LGI1-AE.
Disclosure: Nothing to disclose

OPR-022

Structural and functional cerebellar alterations in Parkinson's disease with postural instability and gait disorders

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Background and aims: This study aimed at assessing structural and functional cerebellar alterations in Parkinson's disease patients with postural instability and gait disorders (PD-PIGD).
Methods: 21 PD-PIGD patients and 23 age and sex-matched healthy controls underwent clinical, structural and functional MRI, including a motor-task (foot anti-phase movements) and a dual-task (foot anti-phase movements while counting backwards by threes). Local grey matter cerebellar volumes were evaluated automatically using an atlas propagation and label fusion strategy based on the freely available human cerebellum template and probabilistic atlas (SUIT). FMRI images were co-registered with structural images and fMRI analysis was focused on cerebellum.
Results: PD-PIGD patients showed reduced volume of left cerebellum lobules VI and X, right crus 1 and 2, bilateral lobules VIIb, VIIIa and vermis VIIb relative to healthy controls. During fMRI motor-task, PD-PIGD patients showed increased recruitment of right cerebellum crus 1 and bilateral crus 2 and a reduced activity of right cerebellum lobule VIIIa relative to healthy subjects. During fMRI dual-task, PD-PIGD patients showed increased activity of cerebellum crus 2 relative to healthy controls.
Conclusion: PD-PIGD patients showed reduced volumes in several cerebellar motor and non-motor areas relative to healthy controls. During both fMRI motor-task and dual-task, patients showed greater activation of cognitive cerebellar areas (crus 1-2) relative to healthy subjects and a reduced activity of a motor area (lobule VIIIb) during fMRI motor-task. The increased activity of non-motor cerebellar areas might be a consequence of grey matter atrophy or an attempt to compensate the functional failure of cerebellar motor areas.
Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Neuroimmunology 1

OPR-023

New-onset status epilepticus caused by auto-immune encephalitis

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Background and aims: Auto-immune encephalitis is a severe, but curable, neurological disease. Many patients have fulminant seizures or status epilepticus (SE). The aim of this study was to describe the prevalence of an auto-immune aetiology of SE (AESE) and to identify factors pointing towards AESE.

Methods: In this prospective multicenter observational cohort study, adults were included with new-onset SE of unknown aetiology. At inclusion, patient- and SE characteristics were collected, and CSF was obtained. All samples were tested by immunohistochemistry and commercial cell-based assays. One year after inclusion, follow-up diagnoses were obtained and reviewed. Characteristics of patients with AESE were compared to the non-AESE patients.

Results: 50 patients were included with a median age of 57 years (IQR 47–72, range 23–86). 38% of the patients (n=19) had definite or probable AESE, of whom nine patients (18%) had neuronal antibodies (three anti-aminobutyric acid B receptor [GABABR], two N-methyl-D-aspartate receptor [NMDAR], two leucine-rich glioma-inactivated 1 [LGI1], 1 -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor [AMPAR], and one Glutamic-Acid-Decarboxylase 65 [GAD65]). The patients with definite or probable AESE were younger (p=0.040), more often had super-refractory SE (p=0.007), a systemic tumour (p=0.036), behavioral changes before SE (p=0.016), MRI hyperintensities temporal (p<0.0001), and pleocytosis in CSF (p<0.0001).

Conclusion: New-onset SE frequently has an auto-immune aetiology. Neuronal antibody testing should be performed routinely in all patients with SE with unknown aetiology. Additional to antibody testing, thorough evaluation of MRI and complete CSF evaluation seem useful to identify those with AESE.

Disclosure: Nothing to disclose.

OPR-024

Are there antibodies to neuronal surface antigens in patients with a clinical diagnosis of neurodegenerative disorder?

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Background and aims: Auto-immune encephalitis due to antibodies against neuronal surface antigens (NSA-Ab) frequently present with cognitive impairment, often as the first and prevalent manifestation, but few studies have systematically assessed the frequency of NSA-Ab in consecutive patients with established neurodegenerative disorders.

Methods: We studied sera of 93 patients (41F, 52M), aged 69.2±9.4 years, with neurodegenerative conditions, and of 50 population controls aged over 60 years. NSA-Ab were investigated by antigen-specific cell-based assays (CBAs). After testing, we evaluated the association between the NSA-Ab and clinical, CSF and radiological features.

Results: The patients included 13/93 (13.8%) who had specific NSA-Ab: Six GlyR, three GABAAR (1 also positive for AMPAR) two LGI1, one CASPR2 and one GABABR. One of the 50 controls (2%) was positive for NMDAR-Ab (p=0.20). No difference was observed in antibody frequency between patients presenting with parkinsonism and those presenting with dementia (p=0.55); however, NSA-Ab were more frequent in those with unclassified forms of dementia (5/13, 38.5%) than in those with unclassified parkinsonism (2/9, 22.2%) or classified forms of dementia (4/43, 9.3%) or parkinsonism (2/28, 7.1%) (p=0.03). A logistic regression analysis demonstrated that an unclassified diagnosis (p=0.02) and an irregular progression (p=0.024) were predictors of seropositive status.

Conclusion: NSA-Abs are relatively frequent in patients with neurodegenerative disorders, particularly in those with an irregular disease progression of atypical clinical features, inconsistent with a recognized diagnosis. The significance of these antibodies and their possible primary or secondary roles need to be investigated in prospective studies.

Disclosure: Nothing to disclose.

OPR-025

Seizure-related six homolog like two (SEZ6L2) auto-immunity: Neurologic syndrome and antibody effects

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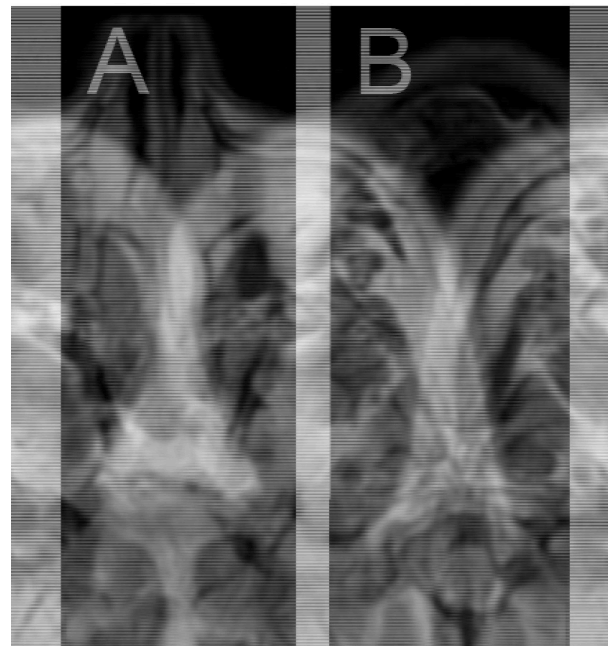
Background and aims: SEZ6L2 is a type 1 transmembrane protein highly expressed in the brain. We aim to describe the clinical syndrome of four new patients with SEZ6L2-ab, study the antibody characteristics, and evaluate their effects on neuronal cultures.

Methods: SEZ6L2-ab were initially identified in serum and CSF of a patient with cerebellar ataxia by immunohistochemistry on rat brain sections and immunoprecipitation from rat cerebellar neurons. We used a cell-based assay (CBA) of HEK293 cells transfected with SEZ6L2 to test the serum of 95 patients with unclassified neuropil antibodies, 331 with different neurological disorders, and 10 normal subjects. Additional studies included characterization of IgG subclasses and the effects of SEZ6L2-ab on cultures of rat hippocampal neurons.
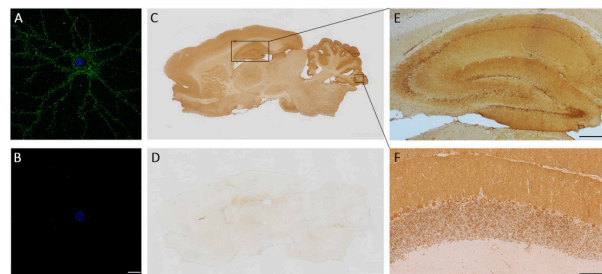
Results: In addition to the index patient, SEZ6L2-ab were identified by CBA in 3/95 patients with unclassified neuropil antibodies but in none of the 341 controls. The median age of the four patients was 62 years (range: 54–69) and two were female. Patients presented with subacute gait ataxia, dysarthria and mild extrapyramidal symptoms. Initial brain MRI was normal and CSF pleocytosis was found in only one patient. None improved with immunotherapy. SEZ6L2-ab recognized conformational epitopes. IgG4 SEZ6L2-abs was found in all four patients, and it was the predominant subclass in 2. SEZ6L2-abs did not alter the number of total or synaptic SEZ6L2 or GluA1 clusters on the surface of hippocampal neurons.

Immunoreactivity of SEZ6L2-ab in hippocampal neurons and rat brain sections.

Initial and follow-up brain MRI of patient 2

Conclusion: SEZ6L2-ab associate with a subacute cerebellar syndrome with frequent extrapyramidal symptoms. The potential pathogenic effect of the antibodies is not mediated by internalization of the antigen.
Disclosure: No disclosures.

OPR-026

Safety and tolerability of efgartigimod in patients with generalized myasthenia gravis: phase 3 adapt study results

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Background and aims: Efgartigimod, a human IgG1 antibody Fc-fragment, blocks the neonatal Fc receptor, which decreases recycling of IgG and reduces pathogenic autoantibody levels. In a phase 2 study, it demonstrated efficacy and was well tolerated in patients with generalized myasthenia gravis (gMG), an IgG antibody-mediated disease.

Methods: ADAPT was a phase 3, randomized, double-blind, placebo controlled, global, multicenter 26-week study that evaluated the safety and efficacy of efgartigimod in patients with gMG. Participants were randomized 1:1 to receive four weekly 10mg/kg infusions of efgartigimod or placebo with subsequent treatment cycles administered according to clinical response.

Results: 167 (129 AChR-Ab+ and 38 AChR-Ab-) patients were randomized. Significantly more patients treated with efgartigimod, compared to placebo, achieved sustained statistically and clinically significant improvement in both MG-ADL and QMG scores. The majority of adverse events (AEs) were mild or moderate. Infections were of special interest and occurred with similar frequency in efgartigimod and placebo treated patients (46.4% and 37.3%, respectively). The type and severity of infections were similar between groups, with no serious or opportunistic infections in the efgartigimod group. Headache was the most common AE (efgartigimod: 28.6%, placebo: 27.7%), but none were serious or required treatment interruption. Most patients experienced headache only once. Infusion related reactions were infrequent, despite the absence of premedication, occurring in 3.6% of efgartigimod and 9.6% of placebo patients, none were serious or required a change in efgartigimod dose and no hypersensitivity or anaphylactic reactions were reported.

Conclusion: Efgartigimod was well tolerated and clinically efficacious in patients with gMG.

Disclosure: The ADAPT study was funded by argenx.

Neuroepidemiology

OPR-027

A nationwide study of the incidence, prevalence and mortality of Parkinson's disease in the Norwegian population

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Background and aims: Epidemiological studies of Parkinson's disease (PD) show variable and partially conflicting findings with regard to incidence, prevalence and mortality. These differences are commonly attributed to technical and methodological factors, including small sample sizes, differences in diagnostic practices, and population heterogeneity. We aimed to determine the nationwide incidence, prevalence and mortality of PD in the Norwegian population.

Methods: We used the Norwegian Prescription Database, a population-based registry of drug prescriptions dispensed from Norwegian pharmacies, to assess the incidence, prevalence and mortality of PD over the period 2004-2017. PD diagnosis was defined by proxy, based on the prescription dopaminergic drugs over a continuous time. In total, 13,053 male- and 10,143 female-PD patients were identified.

Results: PD incidence and prevalence increased with age, peaking at 85 years (Fig. 1). The male/female prevalence ratio was 1.5 across all ages, but the incidence ratio increased with age, from 1.4 in those <60 years, to 2.03 among those >90 years. PD prevalence increased during the observation time, with larger changes observed in the older age groups. While in all ages, mortality was higher in PD compared to the general population, PD mortality odds ratios decreased with age, approaching 1.0 among individuals >90 years old, and were generally higher in females than in males (See Fig. 2 & Fig. 3).
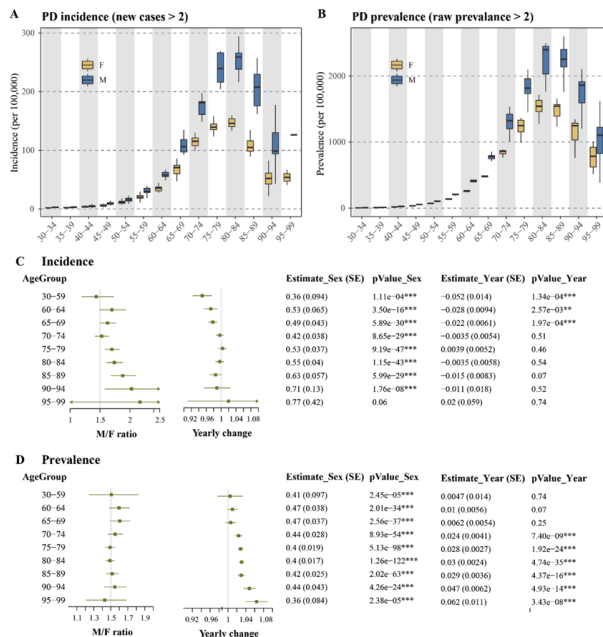

Fig. 1 Incidence and prevalence of PD in the Norwegian population during 2005–2016; (A,B) Incidence and prevalence, (C,D) The impact of the time period and sex were assed individually for each age group
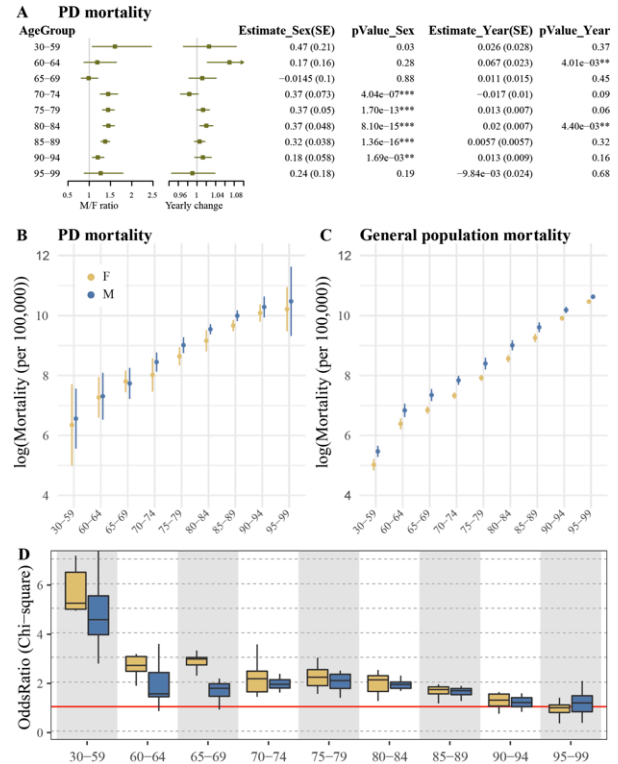

Fig. 2 Mortality of PD in the Norwegian population during 2005-2016; (A) The impact of the time period and sex on PD mortality, . (B,C) Mortality per 100,000 person-years in PD , (D). Death odds ratio
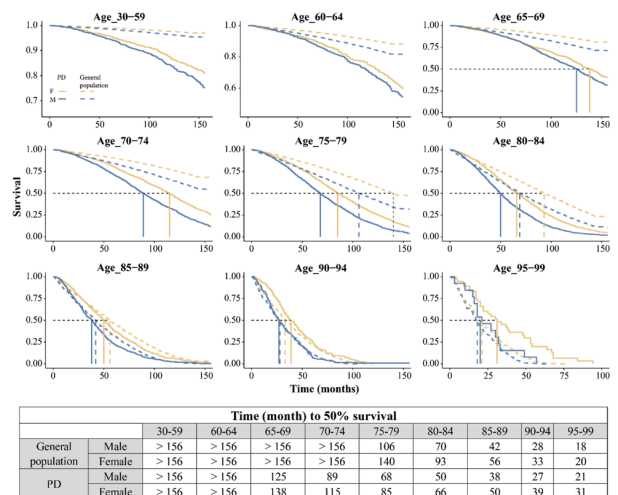

Time (month) to 50% survival		30-59	60-64	65-69	70-74	75-79	80-84	85-89	90-94	95-99
General population	Male	> 156	> 156	> 156	> 156	106	70	42	28	18
	Female	> 156	> 156	> 156	> 156	140	93	56	33	20
PD	Male	> 156	> 156	> 156	125	89	50	38	27	21
	Female	> 156	> 156	138	115	85	66	50	39	31

Fig. 3 Kaplan Meier survival analysis showing sex differences

Conclusion: PD epidemiology, including sex-differences, is extremely dynamic and is highly age and time-period dependent. Sex differences in PD mortality are unlikely to stem from disease-specific negative impact of survival in males.

Disclosure: No disclosures

OPR-028

Phantom menace: the risk of low polio vaccine coverage in Brazil – a cross-sectional study

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Background and aims: Poliomyelitis (PM) is a viral infectious disease that affects CNS by causing acute flaccid paralysis and has been eradicated from Brazil. However, given the reduction in vaccination coverage (VC), we aim to analyze this new scenario, especially the pandemic effects on 2020 data.

Methods: This is a cross-sectional study with information from Brazil's Information System from the Immunization Nacional Program about poliomyelitis (ICD10-A80), described as "poliomelite" or "poliomelite 4 anos", involving data from January 2010 to December 2020.

Results: We identified that the best campaign years were in 2011 (101.33%) and 2013 (100.71%). However, the coverage of 80%, WHO's recommendation for herd immunity, is not achieved since 2016. In 2020, four out of the five Brazilian regions had their worst vaccination rate in the decade and only the southern region figured over 80%. As such, the regional disparity is visible: the North had 54.64% of vaccination coverage in 2020, while the South obtained 84.84%. Further, we found that immunization against PM, in a national perspective, is presenting a downward trend (APC=-3,88%;CI 95%=-5,2%;-2,6%).
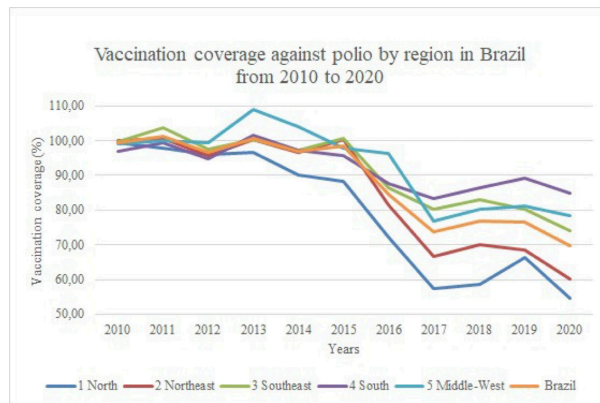

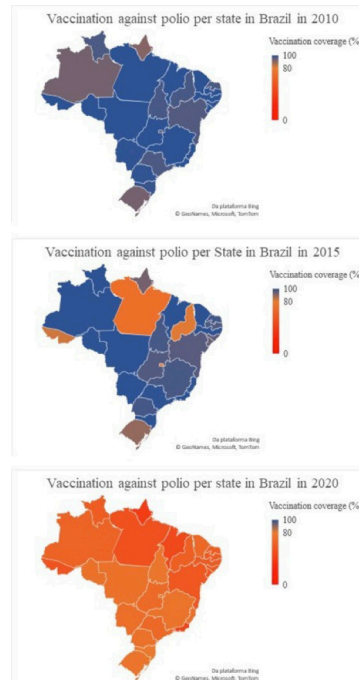Fig. 1: Temporal analysis of polio vaccination coverage by Brazilian regions.

Fig. 2: Evolution of the polio vaccination rate in Brazilian states over time. States colored orange or red have not reached the WHO recommended vaccination rate.
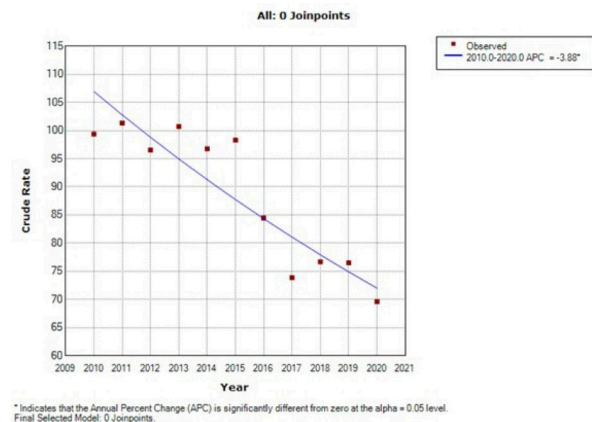

Fig. 3: Trend curve of polio vaccination rate behavior over the past decade.

Conclusion: We provide worrying information about immunization against PM in Brazil as our national health system (and neurology services) are not prepared to fight this disease, eradicated in 1989.

Disclosure: Nothing to disclose.

OPR-029

Meningitis in the 21th century – A cross-sectional study from brazilian healthcare database

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Background and aims: Multifactorial Meningitis (MM) is a group of diseases of compulsory notification in Brazil, defined by inflammation of the meninges due to viral, fungal, or bacterial agents. We aim to investigate the epidemiological rates of these diseases in the country.

Methods: We gathered information about MM (ICD10 – G00/A39/A87) from Brazil's Information System for Notifiable Diseases (SINAN), including data from January 2001 to June 2020. Population data were collected from the Brazilian Institute of Geography and Statistics (IBGE).

Results: We identified 432,426 cases of meningitis, among which 43,888 (10.2%) died. The general incidence was 11.2 cases/100,000 hab. (95%CI: 10.69–11.70; SD=3.85). The mean lethality of the disease was 10.15% (95%CI: 10.06–10.2). The average mortality was 11.44 per million (95%CI: 10.77–12.10; SD: 5.11). Individuals aged 80 or over had the highest lethality: 33.44% (95%CI: 31.61–35.32); while children aged 5–9 years had the lowest rate: 3.58% (95%CI: 3.45–3.71). We also observed a downward trend (APC= -1,91%; CI95%=-3,3%; -0,5%) in the lethality curve of MM in Brazil.
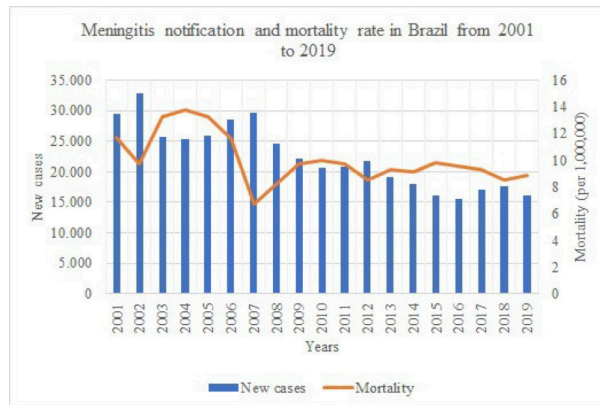

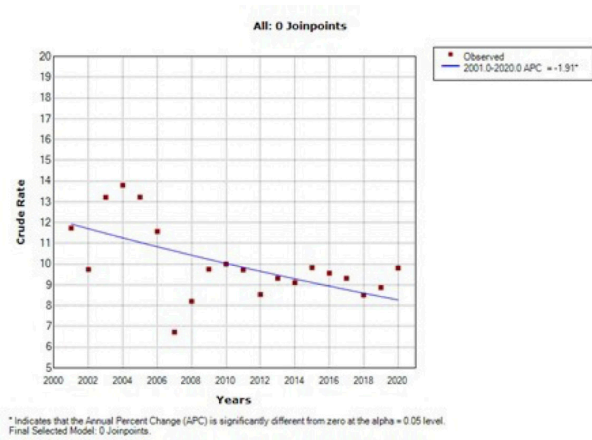Fig. 1: Incidence and mortality of MM over time in Brazil.

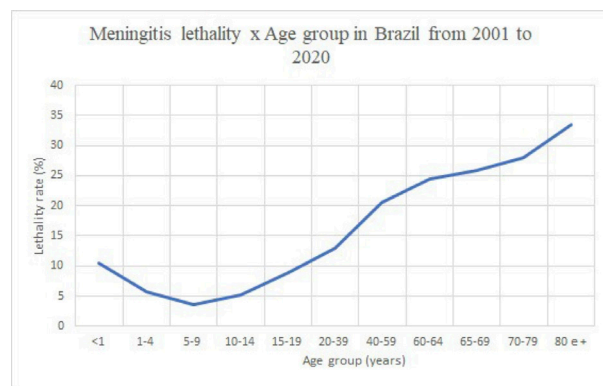Fig. 2: Trend curve of MM lethality over time.

Fig. 3: The behavior of the MM lethality with aging.

Conclusion: The study reveals a notorious incidence of MM in Brazil. However, the lethality trend has been downward in this century, which may be an effect of improving health care and the epidemiological surveillance system for infectious diseases. Furthermore, special attention to the elderly is crucial in these cases as a higher lethality rate is found among this group.

Disclosure: Nothing to disclose.

OPR-030

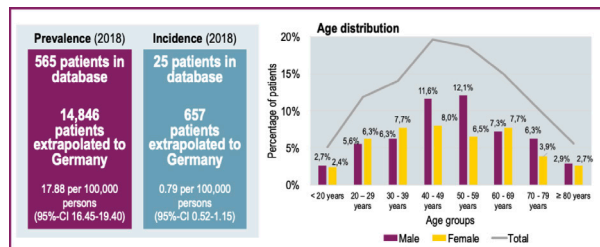### Prevalence, incidence, and characteristics of narcolepsy patients in Germany – A population-representative study

U. Kallweit [1], G. Nilius [2], D. Trümper [3], T. Schubert [4], T. Vogelmann [4]

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Background and aims: Previous studies estimated a prevalence of 47 narcolepsy patients per 100,000 persons in Europe and yearly incidence of 0.64–1.37 per 100,000. Epidemiological information for narcolepsy is limited, therefore this study aimed to estimate diagnostic prevalence and incidence and to describe narcolepsy patient characteristics in Germany.

Methods: This study used the InGef research database, an anonymized representative dataset of four million persons covered by statutory health insurance in Germany, adjusted to the age/gender distribution of the German population. Patients with confirmed narcolepsy diagnoses in 2018 (using ICD-10 codes) were included. Mid-p exact tests were used to calculate 95% confidence intervals (CIs). Patients with narcolepsy diagnoses and narcolepsy-targeting therapy in 2014–2018 were included to describe resource use in the year prior to diagnosis.

Results: In 2018, per 100,000 persons, diagnostic prevalence was estimated as 17.88 (95%-CI 16.45–19.40), and 12-month incidence as 0.79 (0.52–1.15). Patient characteristics are shown in Figure 2. 46% patients were in psycho-behavioural therapeutic treatment and 61% of employees had sick-leave days (Figure 3). 28% received antibiotics compared to 20% in the general population.

Incidence, prevalence and age distribution of narcolepsy in Germany
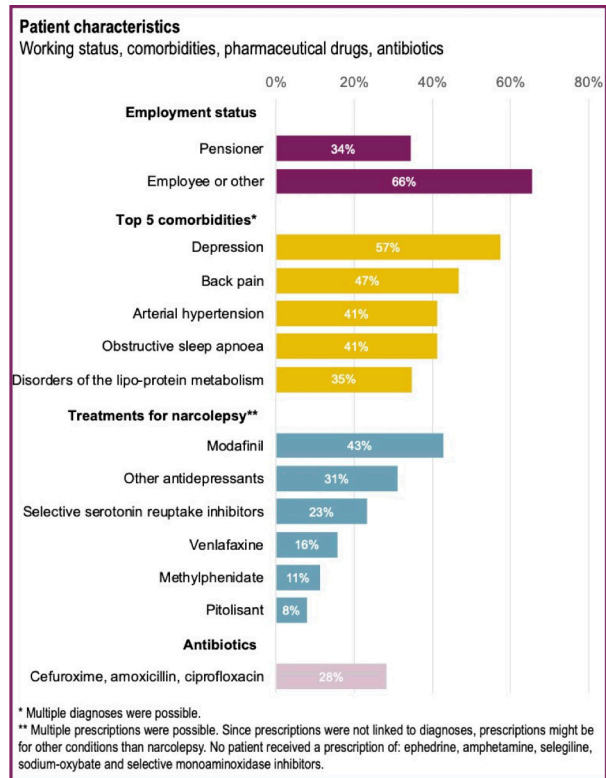
Patients characteristics 2013–2018
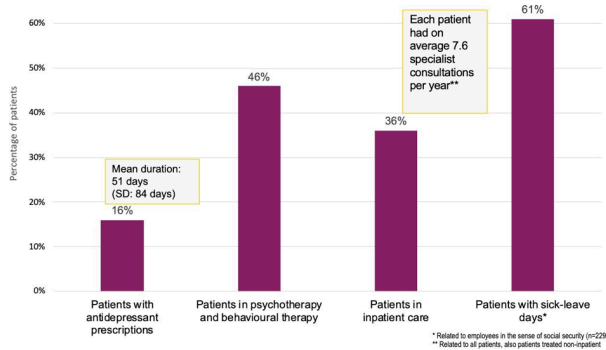
Health-care resource use in the year prior to narcolepsy diagnosis 2013–2018

Conclusion: Diagnostic prevalence was lower and incidence consistent with previous reports, though previous estimates may diverge in terms of age/gender-distributions. Patients showed a significant utilization of the health resources, incl. sick-leave days. Almost half of the patients underwent psycho-behavioural treatment in the year prior to diagnosis, which might indicate high burden of mental disease or an incorrect referral due to lack of symptom recognition. The increased use of antibiotics could indicate more frequent infections than in the general population.

Disclosure: This study was financially supported by Jazz Pharmaceuticals

Neurorehabilitation

OPR-031

Assessing communicative abilities in patients with severe acquired brain injury by Functional Communication Measures.

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Background and aims: The assessment of communicative abilities in patients with acquired brain injury (ABI) is challenging, especially in patients emerging from Minimally Conscious State (eMCS). The Functional Communication Measures (FCMs) assess communicative and swallowing abilities on a one (least functional) to seven (most functional) scale in collaborative patients with brain injury (Mullen, 2004). The present pilot study aimed at evaluating 1. the inter-rater agreement of an Italian short version of FCMs in a cohort of patients with severe ABI; 2. the usefulness of FCMs in profiling patients emerging from Disorder of Consciousness.

Methods: Aim 1: The Italian version of short FCMs including seven items (attention, memory, augmentative-alternative communication, motor speech, spoken language comprehension and expression, swallowing) was blindly administered by two speech-therapists to eight conscious patients with sABI (two females; mean age=63.4±17.2 years, mean Level of Cognitive Functioning=6.5±1.4). The inter-rater reliability was calculated for each FCMs scale. Aim 2: Two patients in eMCS (both females, 74- and 64-year-old) were evaluated by short FCMs, Coma Recovery Scale Revised (CRS-R) and Disability Rating Scale (DRS).

Results: Inter-rater agreement was very high for swallowing and attention scales, and moderate or substantial for the remaining items. The two eMCS patients showed the same DRS-R and CRS-R total scores, and yet the FMCs scales attention, swallowing, motor-speech and spoken language expression revealed different functional communication abilities.

Conclusion: This pilot study showed a good inter-rater reliability of the Italian version of FCMs. This clinical tool seems to allow fine-grained characterization of patients' cognitive abilities.

Disclosure: The authors reports no disclosures.

OPR-032

Multicentre longitudinal study on predictors of long-term mortality in Disorders of Consciousness

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Background and aims: The 12-month mortality rate of patients with prolonged Disorders of Consciousness (DoC) is high (approximately 48%) due to high risk for severe medical complications. The present international multicentre longitudinal study, performed by the Special Interest Group on DoC of the International Brain Injury Association, aimed at identifying predictors, easy to collect at the bedside, for long-term outcome including mortality.

Methods: 12 specialized centres enrolled patients in Vegetative (VS) or in Minimally Conscious State (MCS) within three months from acquired brain injury. Demographic, anamnestic, clinical, and neurophysiologic data were collected at enrolment; patients were followed up to 24 months post-injury.

Results: From a consecutive sample of 147 patients with DoC, data on mortality were available for 143 traumatic (n=55) and non-traumatic (n=88) patients (VS=68, 19 females; mean age=51.1±19.5; MCS=75, 22 females; mean age=46.8±20.0). Within 24 months after brain injury, 41/143 patients (28.7%) died. Mortality rate was higher in VS (42.6%) than in MCS (16%; p<0.001). Multivariate regression showed that significant predictors of mortality were older age and lower Coma Recovery Scale-Revised total score in the VS group, and female sex and absence of alpha rhythm on EEG in the MCS group.

Conclusion: The present longitudinal study demonstrated that lower level of consciousness (as measured by CRS-R total score), older age, female sex, and alteration of thalamocortical connections (as evaluated by conventional EEG) at enrolment were independent predictors of long-term mortality. These multimodal bedside findings can help clinicians and families navigate the complex clinical decision-making process.

Disclosure: The authors report no disclosures.

OPR-033

Bilateral sequential TBS in rehabilitation of post-stroke hemiparesis – feasibility and safety study

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Background and aims: We previously showed that bilateral sequential stimulation consisting of stimulation of the non-dominant M1 with an excitatory protocol preceded by the inhibitory one over dominant M1 with theta-burst stimulation (TBS) can improve motor skill learning in healthy participants. This study's aim was to check whether a similar approach would be suitable for use in the rehabilitation of post-stroke hemiparesis.

Methods: 10 patients (mean age 58 years [range 38–69]) with hemiparesis due to MCI stroke, in the subacute post-stroke recovery phase, were enrolled in the study. They all had daily physio and occupational therapy for four weeks. During the 1st and 2nd week, bilateral sequential TBS was delivered (using standard cTBS and iTBS protocols) each day before therapy procedures. Hand tapping (HT), simple reaction time (RT), and the Purdue peg-board task (PPT) were measured, for each hand, before therapy, after the first and the second week, after the end of therapy (4th week), and a month following completion of the therapy.

Results: Healthy hand showed clear improvement with time, consistent with the learning/training effect of repeated practice. Paretic hand showed significant improvement in HT, while RT showed variable results. No adverse effects were reported apart from an occasional mild headache at the area of the coil contact with the scalp.

Conclusion: Bilateral sequential TBS is feasible for use to boost the effectiveness of physio and occupational therapy in subacute post-stroke hemiparesis. There seem to have no major safety issues and no untoward effects on the healthy hand. Further control studies are needed.

Disclosure: This study was supported by the Ministry for Education, Science and Technological Development of Republic of Serbia [grant number 175012].

OPR-034

EFFECTIVENESS OF A COGNITIVE REHABILITATION PROGRAM IN PATIENTS WITH ULTIPLE SCLEROSIS (MS)

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Background and aims: Cognitive rehabilitation is an approach to improve the functional status of multiple sclerosis (MS) patients. Specifically, cognitive rehabilitation using virtual tools has been supported by neuroimaging findings, where an increase in grey matter volume (GMV) and cognitive improvement after therapy have been reported.

Methods: Prospective observational study designed to identify the effectiveness of a cognitive rehabilitation (with NeuronUP online tool) and their associated functional and structural changes in Magnetic Resonance Image (MRI) studies in MS patients. Fifteen patients with MS were included (age=43.76; 11 women). Time of disease evolution = 10.6 years; Expanded Disability Status Scale=2.75. Three sessions (for 45 minutes) a week were planned during eight consecutive weeks. The rehabilitation program was focused on: attention, processing speed, memory, language, executive functions, visuospatial ability and social cognition. A neuropsychological evaluation and a functional MRI were performed before and after intervention.

Results: Significant improvements in inmediate verbal memory (p=0.017), delayed visual memory (p=0,009), working memory (p=0,001) and verbal semantic fluency (p=0.012) were observed. Subjective perception of cognitive status improved too (p=0.004). Patients showed a significant increase of GMV after the cognitive rehabilitation program in frontal, parietal, temporal lobes, and cerebellum. The most significant increase was inthe primary motor cortex of both hemispheres. GMV differences were also shown at premotor regions of both hemispheres.
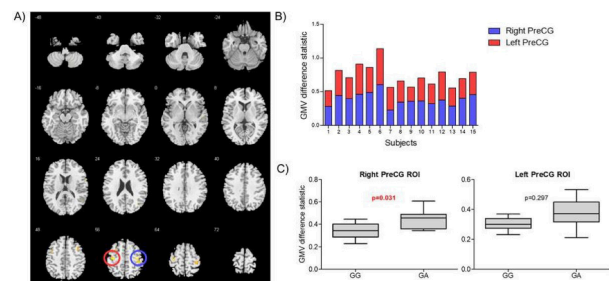
Changes of grey matter volume (GMV) after the cognitive rehabilitation program.

Conclusion: Cognitive treatment is an effective approach to improve cognitive status in MS and can induce changes in cortical reorganization, which will help to improve either cognitive or brain reserve.

Disclosure: No disclosure to declare.

OPR-035

Apomorphine therapy for patients with chronic disorders of consciousness: a multimodal open-label study

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[1] Liege, Belgium, [2] Recco, Italy, [3] CHN William Lennox, Ottignies-Louvain-la-Neuve, Belgium, [4] NeuroHealing Pharmaceuticals Inc., Waban, MA, United States

Background and aims: Apomorphine, a repurposed dopaminergic drug, is a promising therapy to improve the recovery of patients with disorders of consciousness (DOC), with a postulated action on the mesocircuit. This prospective open-label study aimed to confirm preliminary results on clinical efficacy and investigate its action on brain function.
Methods: Six patients with chronic DOC (four male, four traumatic, 38.8 year-old average, 99 days post-onset average) received daily subcutaneous apomorphine therapy for 30 days. Multimodal monitoring was performed from 30 days before to 30 days after treatment. Outcome measures included repeated behavioural scales, high-density electroencephalography (hdEEG) and positron emission tomography (PET).
Results: Compared to baseline, three patients improved their behavioural diagnosis during treatment, two additional patients improved during the 12-month follow-up and the last patient emerged before treatment start but improved on all rehabilitation scales during treatment. Mean Coma Recovery Scale-Revised scores improved during treatment (2.1 points) and 30-day washout (5.2 points) periods, compared to baseline (Table 1). Healthcare staff and family rated the patient's clinical condition 20.5% and 30.9% better after treatment, respectively (Table 2). Alpha-band hdEEG functional connectivity measured by network centrality increased by 13.6% on average after treatment (Fig. 1). Wholebrain fluorodeoxyglucose metabolism increased by 12.4% on average between PET before and after treatment.

Patient	Aetiology	Time since injury	Outcome measure	Inpatient phase Baseline 30 days	Inpatient phase Treatment 30 days	Inpatient phase Washout 30 days	Follow-up 6 months	Follow-up 12 months	Follow-up 24 months
P1	Haemorrhage	3.4 months	Mean CRS-R score (0-23)	5,6	8,0	8,8			
			Most frequent diagnosis	UWS	MCS-	MCS-	MCS+	dead	dead
			Final clinical diagnosis	MCS-	MCS+	MCS+			
P2	Traumatic brain injury	4.7 months	Mean CRS-R score (0-23)	9,1	9,3	10,6			
			Most frequent diagnosis	MCS-	MCS-	MCS-		EMCS	EMCS
			Final clinical diagnosis	MCS-	MCS-	MCS-	MCS-		
P3	Traumatic brain injury	3.0 months	Mean CRS-R score (0-23)	17,3	19,7	22,0			
			Most frequent diagnosis	MCS+	EMCS	EMCS			
			Final clinical diagnosis	MCS+	EMCS	EMCS	EMCS	EMCS	
P4	Traumatic brain injury	2.0 months	Mean CRS-R score (0-23)	13,9	12,7	20,2			
			Most frequent diagnosis	MCS+	MCS+	EMCS			
			Final clinical diagnosis	EMCS	EMCS	EMCS	EMCS	EMCS	
P5	Haemorrhage	3.2 months	Mean CRS-R score (0-23)	7,9	8,8	9,6			
			Most frequent diagnosis	MCS-	MCS-	MCS-			
			Final clinical diagnosis	MCS-	MCS-	MCS-	MCS+		
P6	Traumatic brain injury	3.3 months	Mean CRS-R score (0-23)	3,2	11,2	17,0			
			Most frequent diagnosis	UWS	MCS+	MCS+			
			Final clinical diagnosis	UWS	MCS+	MCS+			

Table 1. Coma Recovery Scale – Revised (CRS-R) results. Demographics, mean CRS-R total scores, most frequently observed diagnoses and final clinical diagnoses for 30-day inpatient periods, as well as clinical diagnoses during follow-up when available.

Question (% of maximum)	BEFORE (mean) Staff	BEFORE (mean) Family	AFTER (mean) Staff	AFTER (mean) Family	DIFFERENCE BEFORE-AFTER Staff	DIFFERENCE BEFORE-AFTER Family
Presence	38,9	37,4	63,6	69,7	+24,7	+32,3
Verbal comprehension	31,8	32,9	57,1	68,2	+25,3	+35,3
Communication	21,8	24,6	48,6	68,3	+26,8	+43,7
Spontaneous motricity	29,0	28,5	57,7	60,0	+28,7	+31,5
Voluntary motricity	27,9	22,6	44,9	53,3	+17,0	+30,7
Comfort	49,4	49,1	65,0	71,3	+15,6	+22,2
Arousal	56,5	55,4	71,5	72,9	+15,0	+17,4
Emotions	46,5	40,8	57,3	75,2	+10,8	+34,4
Treatment effect			70,1	53,8		
Treatment tolerance			72,0	79,7		
Mean for all questions	37,7	36,4	60,8	67,2	+20,5	+30,9

Table 2. Caregivers' questionnaire. Rating of the patient's clinical condition by three members of the clinical staff and by the patient's family, assessed immediately before and one week after the end of apomorphine treatment.
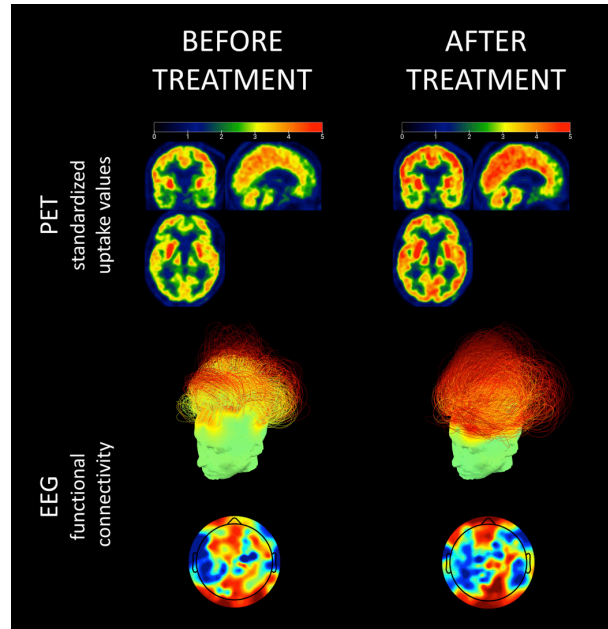

Fig. 1. Positron emission tomography (PET) and electroencephalography (EEG). Wholebrain metabolism in a representative patient (P6; top row), topographs of mean alpha-band networks (middle row) and alpha participation coefficient maps (lower row).

Conclusion: Multimodal improvements were observed in chronic DOC patients after a 30-day treatment regimen with apomorphine. These results suggest a beneficial action on consciousness that is associated with increased brain connectivity and metabolism. These results will need to be confirmed in a subsequent multicentre randomized placebo-controlled trial (EudraCT:2018-003144-23; Clinicaltrials.gov:NCT03623828).

Miscellaneous: Neuro-ophthalmology/ neuro-otology and the arts

OPR-036

Sonic Support Group: releasing the therapeutic potential of art for NHS staff and frontline workers.

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[1] Department of Neurology, Imperial College Healthcare NHS Trust, London, United Kingdom, [2] Independent artist, London, United Kingdom, [3] Department of Neurology, St Georges University Hospitals NHS Foundation Trust, London, United Kingdom, [4] Department of Neurology, Barts Health NHS Trust, London, United Kingdom

Background and aims: The COVID-19 pandemic is putting exceptional emotional strain on frontline workers while severely restricting their opportunities to maintain their wellbeing, including access to art. This is a joint initiative between Neurofringe – a group of UK neurologists interested in the intersections of neuroscience, art and society – and London-based artist Abbas Zahedi.

Methods: The Sonic Support Group pilot is aimed at frontline workers and NHS staff. Keyworkers are granted access to Zahedi's currently dormant exhibition, Ouranophobia SW3, providing them with a moment of respite from their work. This re-presentation of Ouranophobia SW3 for frontline staff is made possible under government guidance for hosting physical support groups. To minimise risk, access to the space is limited to single visitors at any one time. Amendments to safety measures are considered in line with Government guidance.

Results: Ouranophobia SW3 contains site-specific sound and physical art works, situated within a disused sorting office in Chelsea (South-West London). Elements of the exhibition relate to Zahedi's own experiences exploring themes of grief, loss and sensory deprivation – aspects of reality we now face on an unprecedented scale. The 'thera-poetic' potential of the exhibition within the physicality of the site provides a framework through which the escalating levels of workplace trauma we are seeing today can begin to be alleviated.

Conclusion: The Sonic Support Group intends to highlight the essential capacity for care that is present in art and to become a catalyst towards reimagining what it means to support one another in times of need.

Disclosure: Nothing to disclose.

OPR-037

Convergence spasm: a clinical and video-oculographic series of 12 patients

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Background and aims: Convergence spasm (CS) is mostly a non-organic disorder featuring intermittent episodes of convergence, accommodation and miosis. There are few studies assessing CS patients, and formal recording is lacking. This study aims to summarize CS clinical features, mimickers, and outcome, and to provide infrared pupilography (IP) data in a group of patients.

Methods: A retrospective analysis of CS cases referred to our neuro-ophthalmology clinic from 2014 to 2020 was performed.

Results: A total of 12 (83% female; mean age onset of symptoms, 37.3±16.0 years-old) cases were collected. There was history of depression and functional disorder in 50% and 41.7% patients, respectively. Main presentation was intermittent diplopia (91.7%). Diagnostic possibilities on referral included sixth nerve palsy (6NP) (41.7%), internuclear ophthalmoplegia (INO) (33.3%), myasthenia gravis (16.7%) and neuromyotonia (16.7%). Organicity had been ruled out. CS diagnosis was made in average 27.6±53.5 months after initial medical encounter. IP was performed in eight patients. In all except one patient, convergence preceded miosis by around 260 (range 100–600) milliseconds. In 33.3% patients CS episodes were spontaneous while in 66.7% were triggered by lateral versions. Abduction pseudo-limitation and abducting nystagmus were present in 25.0% and 37.5% patients, respectively. Apart from reassurement, treatment was needed in 50%. Improvement was noted in 50% of those treated.

Conclusion: CS commonly mimics neurologic disorders, including 6NP and INO, explaining diagnosis delay in our series. Eye recording showing evidence of convergence preceding miosis might be useful in difficult cases. Spontaneous resolution is possible, but targeted therapies are needed in 50% of patients.

Disclosure: No disclosures.

OPR-038

Longitudinal whole-brain metabolic network changes following acute unilateral vestibulopathy

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Background and aims: Symptoms of acute unilateral vestibulopathy (AUV) partially recover due to adaptive brain plasticity. In this study, we analysed whole-brain metabolic connectivity changes after AUV by longitudinal 18F-FDG-PET imaging.

Methods: 22 patients with AUV underwent resting state 18F-FDG-PET scans in the acute phase (mean: 6d) and after partial behavioural compensation (mean: 6m). PET data were compared to 22 matched controls. Images were flipped, reconstructed, registered, filtered, normalized, and segmented (AAL2/3 atlas). Pearson's correlations between all segmented brain regions were performed ($r>0.5$/ $p<0.001$). Functional metabolic connections between and within hemispheres, and in vestibular/multisensory/motor/ cognitive networks were calculated.

Results: Patients had severe vestibular asymmetry in the acute stage (mean horizontal slow-phase velocity (SPV): 9.9°/sec, subjective visual vertical (SVV): 7.6°), which recovered until 6m after AUV (SPV: 0.7°/sec, SVV: 1.7°). As compared to controls, whole-brain metabolic network analysis indicated a significant drop in the total number of connections (830 vs. 440), and specifically in interhemispheric projections between homotopic multisensory regions in the acute stage. In the chronic stage, the asymmetry in interhemispheric connections of homotopic regions persisted. Multisensory network connectivity relatively increased in the ipsilesional hemisphere compared to the early stage. Patients with a persistent caloric vestibular deficit had a higher asymmetry index compared to those with reconstituted peripheral function.

Conclusion: AUV disrupts the symmetry of multisensory metabolic networks between hemispheres persistently and mostly in patients with a chronic peripheral vestibular deficit. These data may be important for the understanding of higher sensory network dysfunction and conversion risk to functional dizziness after AUV.

Disclosure: Nothing to disclose.

OPR-039

Novel diagnostic index test CATCH2 improves detection of acute vestibular stroke (EMVERT study)

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Background and aims: Patients with acute vertigo and dizziness account for about 4% of all visits in the emergency department (ED). Stroke is the underlying cause in 4-15%. About 10% of all vestibular strokes are missed at first contact. Therefore, improvement of the diagnostic algorithms is urgently needed.

Methods: 410 consecutive patients with acute vertigo, dizziness or imbalance were included in the prospective EMVERT study in the ED of a university hospital (LMU Munich). All patients underwent a structured history taking, clinical neurological exam and neurophysiological assessment (including videooculography, mobile posturography) in the ED. A cranial MRI was performed within seven days to detect stroke. Post-hoc analysis identified factors, which had the highest accuracy to indicate vestibular stroke in the acute setting.

Results: A novel diagnostic index test, called CATCH2, was composed, which included the following features: C – central clinical signs and symptoms (e.g. dysarthria, hemiataxia), A – age >60 years, T – triggers absent, C – cover test with skew deviation, H – head impulse test normal, H – history of vertigo or dizziness absent. Each feature was weighted with one point, if present. For sum values of four of six points, the AUC to detect vestibular stroke was 0.90, the sensitivity 91% and specificity 87%. CATCH2 outperformed ABCD2 (sensitivity: 64%, specificity: 53%) and HINTS (sensitivity: 86%, specificity: 36%).

Conclusion: CATCH2 is a reliable and clinically feasible diagnostic index test to detect acute vestibular stroke in patients with different presentations of vertigo and dizziness (including those without spontaneous nystagmus.

Disclosure: No disclosures.

OPR-198

Biallelic variants in the molecular chaperone DNAJB4 are a genetic cause of myopathy with respiratory muscle involvement

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Background and aims: DNAJB4 is a molecular chaperone and member of the heat shock protein family. It was identified as a tumour suppressor gene and is associated with prolonged survival in lung cancer.

Methods: We have screened our database of >2,000 exomes of patients with neuromuscular disorders and identified two patients with likely pathogenic variants in DNAJB4. Family C was found through international collaboration.

Results: We identified four individuals from three unrelated families with severe diaphragmatic weakness diagnosed after the development of acute respiratory failure, which led to permanent mechanical ventilation. All had no apparent muscle involvement at the time of diagnosis, but they did have some degree of spinal rigidity. One of the patients died at 11 due to respiratory insufficiency. CK levels were normal. Muscle MRI of two probands showed a similar selective involvement of semitendinosus and semimembranosus muscles. Muscle biopsy of one of the patients showed frequent eosinophilic sarcoplasmic inclusions and presence of few rimmed vacuoles. Ultrastructural study revealed sarcoplasmic accumulation of dense granulofilamentous material suggestive of myofibrillar myopathy. All the patients carried homozygous, very rare, damaging variants in the DNAJB4 gene: two stop gains (c.856A>T: p.Lys286* and c.74G>A: p.Arg25*) and a missense change (c.785T>C: p. Leu262Ser) predicted highly damaging by the in-silico tools. The variant segregated with the disease. Protein studies revealed absence of DNAJB4 protein in a patient muscle and fibroblasts compared to control.
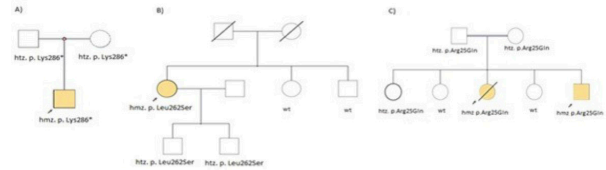
Pedigrees of three families carrying homozygous, very rare, damaging variants in the DNAJB4 gene.
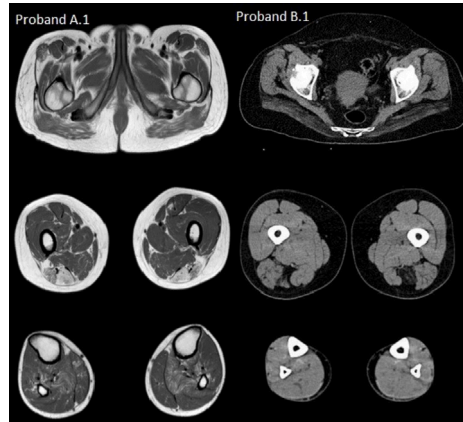
Muscle MRI of two probands showing a similar selective involvement of semitendinosus and semimembranosus muscles
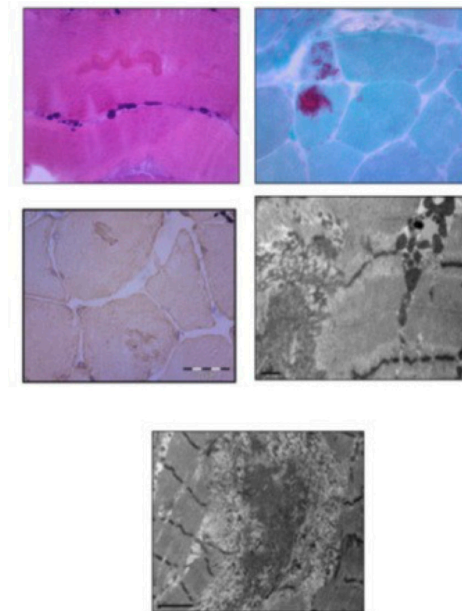
MB of the proband AII:1 showed frequent eosinophilic sarcoplasmic inclusions and Ultrastructural study revealed sarcoplasmic accumulation of dense granulofilamentous material suggestive of myofibrillar myopathy.

Conclusion: We established recessive mutations in DNAJB4 as a possible cause of a novel form of neuromuscular disorder.

Ageing and Dementia 1

OPR-040

Cortical remodeling across the lifespan in healthy brain reveals structural network vulnerability to neurodegeneration

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Background and aims: Aging is the main risk factor for most of the neurodegenerative diseases. The aim of this study was to investigate typical cortical thinning changes across lifespan in the healthy brain revealing structural network vulnerability to neurodegeneration.

Methods: The cohort included 128 healthy individuals aged 20–85 years that underwent an MRI scan. Structural T1-weighted images were used to estimate vertex-wise cortical thickness maps, then grouped into 83 regions.

For each region, cortical thickness trajectory with advancing age was estimated, including sex as covariate. Additionally, all regions were ranked based on their relative thickness at the end of the observed lifetime, assessing regional changes over time. Finally, regional mean thickness was correlated with relative change over time.

Results: The highest cortical thinning was observed in the temporal lobe (parahippocampal, entorhinal, superior and middle temporal and fusiform), in the frontal lobe (lateral orbitofrontal, superior and inferior frontal and rostral anterior cingulate), in the parietal lobe (the isthmus of cingulate, precuneus, supramarginal and inferior parietal) and in the insular cortex. Interestingly, occipital regions (cuneus, lateral occipital, lingual, pericalcarine), and motor and premotor areas (precentral, postcentral and paracentral regions) showed the least cortical thickness change relative to the whole brain. Finally, positive correlation was found between mean regional thickness and its relative change over time.

Conclusion: This study highlights structural vulnerability of brain regions to aging. Furthermore, results provide information concerning trajectories of normal brain aging, identifying those areas that might be more vulnerable to the attack of neurodegeneration.

Disclosure: Supported by: European Research Council (StG-2016_714388_NeuroTRACK).

OPR-041

Ocrelizumab treatment in patients with relapsing-remitting and progressive MS: a real-world experience

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Background and aims: We aim to provide first experience real-world effectiveness and safety data in relapsing-remitting (RR-), primary-progressive (PP-) and secondary-progressive multiple sclerosis (SP-MS) patients and to evaluate possible predictors of treatment response.

Methods: Demographic characteristics, effectiveness outcomes (Expanded Disability Status Scale (EDSS) progression, radiological activity data, NEDA-3 status), immunological parameters and adverse events (AEs) were recorded at baseline and throughout the follow-up (FU).

Results: 153 subjects were included in the analysis (93 RR-MS, 43 PP-MS, 17 SP-MS; 60% females); baseline mean(SD) age was 41.9(11.4) years, mean(SD) disease duration (DD) 10.3(9.9) years, mean(SD) annualized relapse rate (ARR) 0.5 (0.7), median(IQR) EDSS 3.5 (2–5.5). At two years-FU, percentage disability worsening-free patients were 90.5%, 64.7% and 68.8%, of MRI-activity-free patients 67.1%, 72.7% and 81.3% and of NEDA-3 patients 62.1%, 54.6% and 55.1% for RR-MS, PP-MS and SP-MS, respectively. Lower baseline EDSS, shorter DD, younger age, higher ARR and baseline MRI-activity were associated with reduced risk of disability worsening, while previous DMT exposure and baseline MRI-activity with increased risk of radiological activity. Treatment-naïve patients had higher probability of achieving NEDA-3. At six months-FU CD8+ cell count were higher in "early inflammatory" vs stable patients (464 vs 339; p=0.001). Upper respiratory tract infections were the most frequently observed AEs.

Conclusion: We showed that ocrelizumab is a good and globally safe treatment option in patients with RR-MS, PP-MS and SP-MS, especially if initiating treatment in the early phases of the disease and for treatment-naïve patients. Our data suggest that higher levels of CD8+ cells could be associated to early inflammatory activity.

Disclosure: The present study received no fundings

OPR-042

THE BRAIN CORRELATES OF BEHAVIORAL DISTURBANCES IN FRONTOTEMPORAL DEMENTIA

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Background and aims: Various studies have researched singular or clusters of behaviors in frontotemporal dementia (FTD) correlating them with regional brain atrophy in structural MRI data, or hypometabolism in FDG-PET images, but a multimodal approach is lacking. We identify the brain correlates of modes of variation (i.e., factors) explaining the variability of behavioral and psychological symptoms (BPSD) in frontotemporal dementia (FTD) using multimodal imaging.

Methods: Imaging and behavioral data from 93 FTD patients acquired at NIH were analyzed. They underwent extended neuropsychological assessment including several scales measuring BPSD (UCLA NPI, FrSBe, and Neurobehavioral rating scale), T1-weighted MRI, and FDG-PET imaging. Factor analysis was used on the behavioral data to identify modes of variation of BPSD potentially pointing to few common neurobiological substrates across the FTD sample. The identified modes were then related to intersubject brain variability using a newly developed fusion method run on maps of gray matter volume and FDG metabolism obtained.

Results: A factor related to decreased emotional/cognitive interaction (loading scores of apathy, executive dysfunction, withdrawal) correlated with volume and function of the right anterior cingulate and orbito-frontal cortex. A factor expressing variability on mutacism versus disinhibition/euphoria continuum was associated with dysfunction of the right superior primary motor cortex. A factor related to the presence of hallucinations/delusions/suspiciousness was associated with dysfunction of the right anterior insula.

Conclusion: BPSD variability in patients with FTD can be explained by three major modes of variations, each associated with intersubject brain structure/function variability of the right frontal lobe.

Disclosure: I have no actual or potential conflict of interest in relation to this program/presentation.

OPR-043

Sex influences the effect of cognitive reserve on Subjective Cognitive Decline

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Background and aims: Subjective Cognitive Decline (SCD) is as a self-experienced decline in cognitive capacity with normal performance on standardized cognitive tests and has been shown to increase risk of Alzheimer's disease. The aim of our study was to evaluate factors influencing age at onset and severity of SCD.

Methods: We included 382 SCD patients, who underwent clinical evaluation, neuropsychological assessment, evaluation of premorbid intelligence by the Test di Intelligenza Breve (TIB), cognitive complaints by the Memory Assessment Clinics-Questionnaire (MAC-Q), and depressive symptoms by Hamilton Depression Rating Scale (HDRS), and Apolipoprotein E (ApoE) genotyping.

Results: Proportion between women and men was significantly different (68.6%, 95% C.I. 65.0–73.3 vs 31.4%, 95% C.I. 29.0–34.4). Women were younger than men at onset of SCD and at the baseline visit (p=0.02), had lower years of education (p=0.007), lower TIB scores (p<0.001), and higher HDRS (6.3±4.1 vs 5.12±3.8, p=0.007) and MAC-Q scores (26.3±3.1 vs 25.0±2.7, p=0.012) (Fig1). TIB was directly associated with age at onset of SCD both in women and in men, while years of education was inversely associated with age at onset only in women (Fig.2). On the whole sample, sex was the only factor influencing MAC-Q. When we ranked patients according to sex, TIB was directly associated with MAC-Q only in men.

	Women n = 262	Men n = 120	P
Age at baseline in years	61.7 (±9.0)	64.1 (± 8.4)	0.020
Age at onset in years	57.8 (± 9.5)	60.9 (± 8.4)	0.026
Disease duration in years	3.9 (± 3.6)	3.4 (± 3.4)	0.726
Family history of AD	50.8 %	48.4 %	0.738
Years of education	11.5 (± 4.6)	12.90 (± 4.2)	0.007
TIB	109.0 (± 7.4)	114.8 (± 5.4)	<0.001
MMSE	27.9 (± 2.0)	28.4 (± 1.9)	0.039
HDRS	6.3 (± 4.1)	5.12 (± 3.8)	0.007
MAC-Q	26.3 (± 3.1)	25.0 (± 2.7)	0.012
APOE ε4+	22.2 %	41.7 %	0.013

Comparison of baseline features between women and men in SCD.
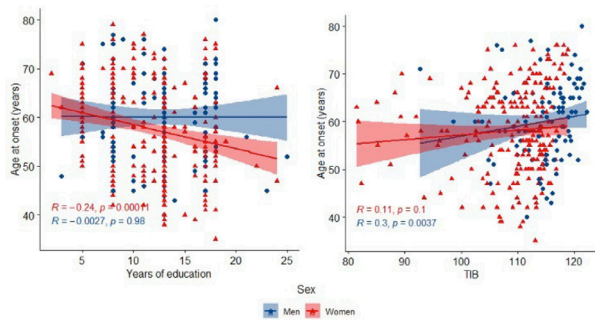
Correlation between premorbid intelligence and years of education with age at onset of SCD in women and men.

Conclusion: While premorbid intelligence was associated with both age at onset and severity of cognitive complaints in men, premorbid intelligence and years of education had opposite effect on age at onset of SCD in women. Sex might modulate the effect of cognitive reserve on SCD.

Disclosure: Nothing to disclose.

OPR-044

In-depth phenotypic description of TBK1 mutations; a frequent cause of FTD and ALS in the Flanders-Belgian population

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Background and aims: Pathogenic LOF and missense mutations in the TBK1 gene are associated with frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS). We report the prevalence and phenotype of TBK1 mutation carriers in the Flanders-Belgian population.

Methods: Screening Flanders-Belgian FTD (n=678), ALS (n=220) and FTD-ALS (n=46) patient cohorts for mutations in TBK1 revealed 19 carriers of pathogenic mutations. We sampled and screened family members, totalling a carrier cohort of 47 individuals. We collected clinical and neuropathological data.

Results: Overall, frequency of TBK1 mutations was 2.0%, with 1.3% in FTD, 3.6% in ALS and 4.3% in FTD-ALS. Among 47 carriers, 30 were affected: FTD (n=11, 36.7%), ALS (n=10, 33.3%), unspecified dementia (n=5, 16.7%), FTD-ALS (n=2, 6.7%), mild cognitive impairment (n=1, 3.3%) and Alzheimer's disease (n=1, 3.3%). In the FTD group, behavioral variant FTD (bvFTD) was the most common phenotype (81.8%) but primary progressive aphasia also occurred (18.2%). Mean onset age and disease duration were 63.0 and 6.4 years (ranges 41–86 and 0–24 years). ALS patients had a significantly shorter disease duration averaging 2.6 years (range 0–6). Neuropathology confirmed FTLD-TDP type B.
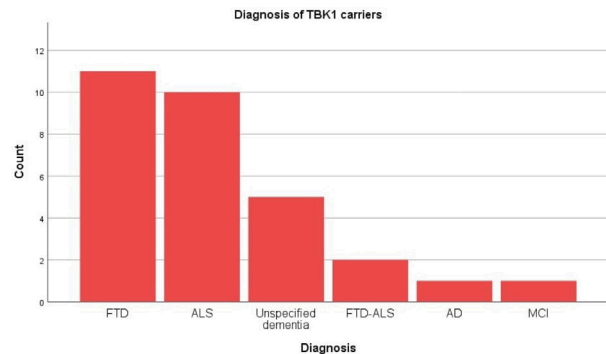
Clinical diagnoses of TBK1 mutation carriers
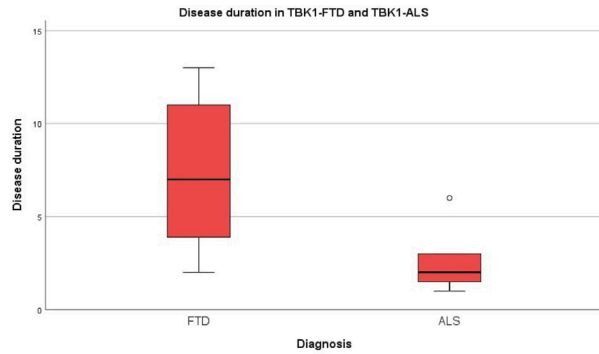
Disease duration in patients with TBK1-FTD compared with TBK1-ALS. A significantly shorter disease duration was seen in the latter.
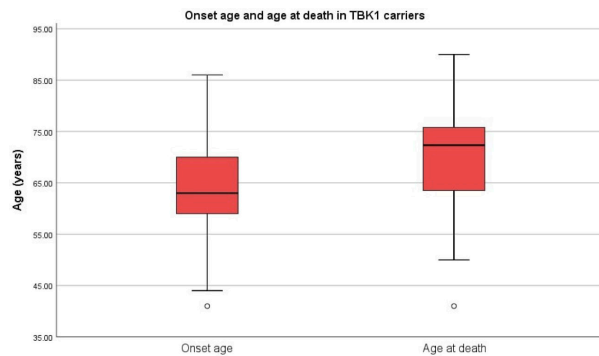
Representation of the range of onset ages and ages at death in symptomatic TBK1 mutation carriers

Conclusion: Pathogenic mutations in TBK1 are a frequent cause of FTD, ALS and particularly of FTD plus ALS in the Flanders-Belgian population. The most common phenotypes were FTD (81.8% bvFTD, 18.2% PPA), ALS and unspecified dementia. Disease duration significantly correlated with clinical phenotype. Neuropathology showed FTLD-TDP type B.
Disclosure: Nothing to disclose.

OPR-045

Extensive genetic and phenotypic description of MAPT p.R406W in the Flanders-Belgian population

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Background and aims: The missense mutation p.R406W in the MAPT gene is associated with frontotemporal lobar degeneration (FTLD) pathology and an atypical, Alzheimer's disease (AD)-like phenotype. In our Flanders-Belgian patient cohort, we identified 10 p.R406W carriers. Of three index carriers, we sampled family members, generating a total cohort of 55 p.R406W carriers. We analysed phenotypical and genetic characteristics.
Methods: Longitudinal follow-up over 19 years provided clinical and neuropathologic data. We investigated potential modifying effects of MAPT H1/H2 and APOE genotypes.
Results: Of 55 p.R406W carriers, 39 were symptomatic. Allele-based haplotype sharing analysis confirmed a genetic kinship among all carriers suggesting a common ancestor. Frequent diagnoses were dementia (unspecified) (43.6%), AD (28.2%) and behavioral variant FTD (bvFTD) (25.6%). Average onset age and disease duration were 59.8 and 12.7 years (ranges 40–75, 5–25). Age at death differed significantly between clinical subgroups (69.3 in bvFTD, 78.3 in AD). Common symptoms among carriers were disinhibition and behavioural problems in all groups (72.7%). CSF biomarker profiles showed decreased A1-42 and A1-42/A1-40 ratio, and elevated P-tau and T-tau. Neuropathology is FTLD-tau. We observed a shorter disease duration in carriers of an APOE 4 allele compared to non-carriers.
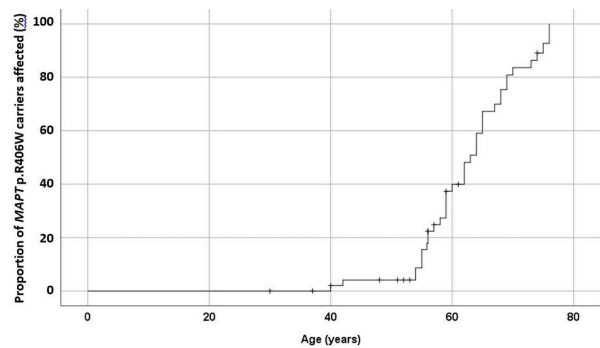

Figure 1. Risk liability curve for MAPT p.R406W mutation carriers.

Risk liability curve for MAPT p.R406W mutation carriers

Diagnosis	Neuroimaging		CSF biomarkers			
	Primarily HC/TP/T involvement	Primarily FT involvement	Decreased Aβ₁₋₄₂	Decreased Aβ₁₋₄₂/ Aβ₁₋₄₀	Elevated T-tau	Elevated P-tau
bvFTD (n = 7)	42.9% (n = 3)	28.6% (n = 2)	100% (n = 1)	NA	0% (n = 1)	0% (n = 1)
AD (n = 7)	57.1% (n = 4)	14.3% (n = 1)	100% (n = 4)	75% (n = 4)	50% (n = 4)	50% (n = 4)
D (n = 1)	0%	0%	NA	NA	NA	NA
MCI (n = 1)	0%	0%	NA	NA	NA	NA

Table 7. Trends in results of neuroimaging and CSF biomarkers in *MAPT* p.R406W mutation carriers with sufficient clinical data. Alzheimer's disease (AD), behavioral variant frontotemporal dementia (bvFTD), mild cognitive impairment (MCI), temporal (T), frontotemporal (FT), temporoparietal (TP), hippocampal (HC), amyloid β₁₋₄₂ (Aβ₁₋₄₂), amyloid β₁₋₄₀ (Aβ₁₋₄₀), total tau (T-tau), hyperphosporylated tau (P-tau).

Results of neuroimaging and CSF biomarkers in mutation carriers. Alzheimer's disease (AD), behavioral variant frontotemporal dementia (bvFTD), mild cognitive impairment (MCI), temporal (T), frontotemporal (FT), temporoparietal (TP), hippocampal (HC), amyl
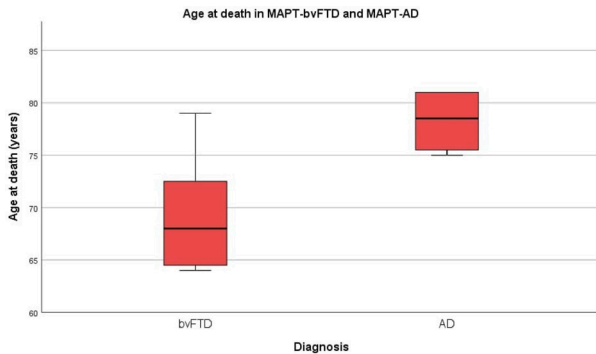

Figure 2. Age at death in p.R406W MAPT mutation carriers with a clinical phenotype of bvFTD compared to clinical AD. A significantly earlier death was found in bvFTD.

Conclusion: We observed a nonconforming clinical phenotype of p.R406W carriers in the Flemish-Belgian cohort with 25.6% bvFTD. Contrary to previous reports, prominent behavioural symptoms were highly frequent in the entire cohort (72.7%). Ages at onset and death varied widely but, intriguingly, correlated with clinical diagnosis, lower in bvFTD than AD phenotypes. CSF biomarkers showed some AD-like abnormalities.

Disclosure: Nothing to disclose.

OPR-046

Accuracy of 18F-FDG PET at the individual level in MCI-LB versus MCI-AD

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Background and aims: 18F-FDG PET is an established supportive biomarker in dementia with Lewy bodies (DLB) but its diagnosis accuracy is still uninvestigated in prodromal DLB (MCI-LB) in which the typical DLB metabolic pattern may be difficultly recognized at the individual level. Semiquantitative analysis is thought to enhance accuracy especially in moderately-skilled readers, but its incremental value with respect to visual assessment in this peculiar DLB stage is still unknown.

Methods: We assessed the diagnostic accuracy of visual assessment of 18F-FDG PET by six expert readers, blind to diagnosis, in discriminating two matched groups of patients (40 with prodromal AD, MCI-AD, and 39 with MCI-LB), both confirmed by in vivo biomarkers of either amyloidosis or dopamine transporter (DAT)-SPECT impairment, respectively. After two months, the readers were asked to re-evaluate the scans having for each patient also the T-maps obtained by the single-subject semiquantitative analysis (SPM-12) with respect to a control group of 40 age- and sex-matched healthy subjects.

Results: Mean diagnostic accuracy of visual assessment was 76.8±5.0% (range 68.4–83.5%) and did not significantly benefit from adding the semiquantitative analysis (77.4±8.3%, range 63.3–87.3%), regardless of the readers' years of expertise. Inter-rater reliability was good in both conditions (ICC 0.81[0.74–0.87] and 0.83[0.76–0.88], respectively).

Conclusion: We found a moderate diagnostic accuracy of 18-FDG PET in distinguishing between MCI-AD and MCI-LB patients which seems valuable considering the limited accuracy of DAT-SPECT in prodromal DLB. We also provided evidence of the poor utility of adding semiquantitative tools to visual assessment, both in moderately and highly expert readers

Disclosure: Nothing to disclose.

Cognitive Neurology/Neuropsychology

OPR-047

Remote white matter integrity improves prediction of cognitive outcome after ischemic stroke

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Background and aims: Cognitive impairment after ischemic stroke is frequent, especially after middle cerebral artery occlusion. Beyond clinical measures, advanced imaging modalities such as diffusion tensor imaging (DTI) and resting-state functional connectivity (rsFC) have been shown to improve prediction of post-stroke motor outcome over and above conventional imaging parameters. However, comparable studies on cognitive outcome are scarce.

Methods: We investigated patients with MRI-confirmed middle cerebral artery infarction and healthy controls. Cognitive outcome was determined using the Symbol Digit Modalities Test (SDMT), measuring processing speed. Associations between acute fractional anisotropy (FA) and rsFC with cognitive outcome were examined, and regression analyses were performed to predict post-stroke cognitive outcome further considering demographics (age, education), clinical measures (NIHSS at baseline), as well as extent and location of infarction and white matter hyperintensities (WMH).

Results: 36 patients (mean age=64.7 years, 33.3% female, median admission NIHSS=9.0) were investigated at the acute stage and three months post-stroke. 15 healthy controls (mean age=57.3 years, 53.3% female) were also assessed at two time-points. Patients showed decreased FA and rsFC three months post-stroke compared to healthy controls. Also, acute FA and rsFC correlated with processing speed three months post-stroke in patients. FA of corpus callosum body, splenium and forceps major at the acute stage predicted processing speed three months post-stroke independently from demographics, NIHSS at baseline, stroke location and volume and WMH, explaining 28% of additional variance (overall variance 56%).

Conclusion: Remote white matter integrity at the acute stage improves prediction of cognitive outcome beyond clinical measures, stroke location and volume.

Disclosure: Nothing to disclose.

OPR-048

Altered resting state dynamic functional connectivity of the precuneus contributes to cognition and depression in NMOSD

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Background and aims: In neuromyelitis optica spectrum disorders (NMOSD), cognitive impairment (CI) is frequent, but its substrates are unclear. Functional MRI (fMRI) studies disclosed an association between CI and damage of the precuneus (PCUN) in several neurological conditions. Dynamic changes of resting-state (RS) functional connectivity (FC) might contribute to brain functional reorganization.

Methods: In this 3.0 T RS fMRI study, 27 aquaporin-4 (AQP4)-positive NMOSD patients and 30 age- and sex-matched healthy controls (HC) underwent a neuropsychological evaluation including Rao's battery and Beck Depression Inventory II scores. A cognitive impairment index (CII) was derived. Dynamic FC (DFC) of bilateral PCUN was assessed by means of sliding-window seed-voxel correlation analysis and its standard deviation across windows used as a measure of dynamicity (the higher the better). Age- and sex-adjusted between-group dFC comparisons and correlations with cognitive scores were assessed using full-factorial models.

Results: Compared to HC, patients had reduced PCUN-dFC with rectus/olfactory bulb, post-central gyrus, superior temporal gyrus, inferior occipital/fusiform gyri and the caudate nucleus. Conversely, increased dFC within the PCUN and between PCUN and middle temporal gyrus, thalamus, insula, putamen, and cerebellar crus-1 was observed. 63% of patients had depressive symptoms, whose burden correlated with intra-PCUN-dFC and with PCUN-dFC with insula and cerebellar crus-1. 48t% of patients had CI and global CII correlated with intra-PCUN-dFC and with PCUN-dFC with the insula and the middle temporal gyrus.

Conclusion: In NMOSD, PCUN-dFC abnormalities contribute to neuropsychological performance. Higher dynamic connections with the temporal lobe and limbic/cerebellar regions were detrimental for cognition and depression, respectively.

Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

OPR-049

RISCOP – Cognitive Profile in a Portuguese cohort of Radiological Isolated Syndrome patients: a case-control study

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Background and aims: Radiologically isolated syndrome (RIS) refers to the incidental discovery of white matter lesions suggestive of MS, on brain MRI, in asymptomatic patients. Recent studies suggest similar features of cognitive impairment between RIS and MS patients. Also, lower levels of health-related quality of life (QOL) and fatigue are reported. We aimed to characterize the cognitive profile of a multicentric Portuguese cohort of RIS patients and compare with a control group.

Methods: Multicentric comparative study of a cohort of RIS adult patients, with age and gender-matched controls. We conducted participants interviews, collected clinical data and applied the BICAMS battery and self-reported questionnaires (HADS, MFIS, MSQOL-54).

Results: 61 RIS patients (median age 46 years, IQR [33–52], 72% women) and 19 controls (median age 32 years, IQR [28–48], 71% women) were included. Prevalence of cognitive impairment did not differ between groups (16% RIS Vs. 10% controls, p=0.579). We found no differences on the BICAMS tests between groups, although the California Verbal Learning Test (CVLT-II) score results trended to significance, with a lower value on the RIS group (53.9 vs. 59.3, p=0.066). There were no significant differences regarding fatigue, QOL, anxiety/depression scores.

Conclusion: This is the first Portuguese study assessing cognitive profile with BICAMS on a cohort of RIS patients. A non-neglectable part of our cohort presented cognitive impairment. Our findings suggest that a more pronounced impairment of verbal memory and learning, evaluated by CVLT-II, might be present in RIS patients compared to controls. BICAMS should be assessed on future studies with larger cohorts.

Disclosure: Nothing to disclose.

OPR-050

NODDI microstructural abnormalities in normal-appearing gray and white matter contribute to cognitive impairment in MS

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Background and aims: Heterogeneous processes contribute to cognitive impairment in multiple sclerosis (MS). Using neurite orientation dispersion and density imaging (NODDI), we explored the associations between microarchitecture abnormalities of focal lesions and normal-appearing (NA) tissues and cognitive impairment in patients with MS (PwMS).

Methods: 152 PwMS and 48 healthy controls (HC) underwent a brain 3T acquisition. PwMS with one abnormal test in two domains were defined as cognitively impaired (CI). A cognitive impairment index (CII) was also derived. Using NODDI, intracellular (ICV_f) and extracellular volume fractions (ECV_f) and orientation dispersion index (ODI) were assessed in cortical and white matter (WM) lesions, thalamus, NA-cortex and NAWM.

Results: 52 (34.2%) PwMS were CI. Compared to HC, both CI and cognitively preserved (CP) PwMS showed significantly decreased NA-cortex, thalamic and NAWM ICV_f (p<0.001) and NA-cortex ODI (p=0.003), and increased NAWM ECV_f (p<0.001). CI PwMS showed also a significantly decreased thalamic ODI (p=0.018) and increased NAWM ODI (p=0.005). CI vs CP PwMS had significantly decreased NA-cortex, thalamic and NAWM ICV_f (p=0.016) and thalamic ECV_f (p=0.009), and increased NAWM ECV_f and ODI (p=0.001). No cortical and WM lesion microstructural differences were found in CI vs CP PwMS. NA-cortex ICV_f and NAWM ICV_f and ODI were significantly correlated with CII (r from -0.24 to 0.30 p from 0.006 to 0.047).

Conclusion: NA-cortex, thalamic and NAWM neuro-axonal loss, together with NAWM inflammation, gliosis and loss of tissue coherence, are associated with cognitive impairment in MS. NODDI could disentangle in vivo the complex processes determining cognitive dysfunctions.

Disclosure: This study was supported by Fondazione Italiana Sclerosi Multipla with a senior research fellowship (FISM2019/BS/009) and a research grant from (FISM2018/R/16), and financed or co-financed with the '5 per mille' public funding.

OPR-051

Consciousness in Neurocritical Care Cohort Study Using fMRI and EEG (CONNECT-ME)

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Background and aims: Patients with acute brain injury who appear clinically unresponsive may show signs of covert consciousness when examined by functional MRI (fMRI) or electroencephalography (EEG). The main objective of this ongoing multimodal study is to facilitate individualized assessment of unresponsive patients with disorders of consciousness (DOC) in the ICU for signs of preserved consciousness.

Methods: We assess acute brain-injured ICU patients for preserved consciousness by clinical and multimodal evaluation using active, passive and resting state fMRI and EEG paradigms (Figure 1). EEG and fMRI data are correlated to clinical consciousness level at time of inclusion, discharge and long-term follow-up. EEG data is analyzed visually by two board-certified neurophysiologists and with automated EEG measures, previously validated on patients with chronic DOC. Automated EEG measures are utilized to calculate the probability of being in a consciousness level above unresponsive wakefulness state (P-MCS).
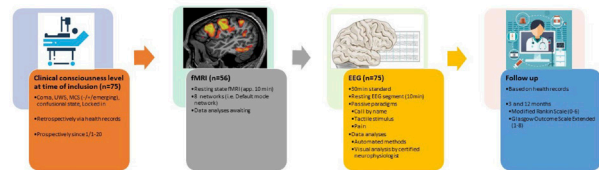

Figure 1: Flow of the first 75 patients through the study. All patients were clinically evaluated at time of inclusion followed by fMRI and EEG. Follow-up data was registered at 3 and 12 months after discharge from ICU.
Abbreviations: UWS: Unresponsiveness wakefulness state, MCS: Minimal conscious state, fMRI: functional MRI, EEG: Electroencephalography

Figure 1

Results: As of Dec. 2020, 102 patients have been included. The following results are from the first 75 patients (Table 1 and Figure 2). No significant correlation was found between P-MCS>50% and clinical consciousness level at time of inclusion, discharge and 3-month follow-up. We found significant correlation (p-value<0.05) between P-MCS >50% and long-term favorable follow-up outcome at 12 months. fMRI and visual EEG data analysis are ongoing.

Table 1: Characteristics of study population				
Characteristics	All patients (N = 75)	≥MCS (N = 30)	≤UWS, (N = 45)	p- value
Age – Yr				
Mean (SD)	50.1 (19.2)	46.6 (16.7)	52.4 (20.6)	0.2031
Gender – no. (%)				
Male	43 (57.3)	15 (50)	28 (62.2)	0.6112
mRS prior to admission – no. (%)				
0-2	67 (89.3)	27 (90.0)	30 (88.9)	1.000
>2	8 (10.7)	3 (10.0)	5 (11.1)	-
Comorbidity prior to admission (any), no. (%) [a]	54 (73.3)	20 (66.7)	34 (75.6)	0.440
Cardiopulmonary	30 (40.0)	9 (30.0)	20 (46.7)	0.235
Diabetes	9 (12.0)	3 (10.0)	6 (20.0)	0.733
Neurology, cerebrovascular	9 (12.0)	4 (13.3)	5 (16.7)	1.000
Neurology, Epilepsy	6 (8.0)	4 (13.3)	2 (4.4)	0.210
Neurology, other	16 (21.3)	7 (23.3)	9 (20.0)	0.779
Psychiatry, any	12 (16.0)	6 (20.0)	6 (13.3)	0.526
Other comorbidities	33 (44.0)	11 (36.7)	21 (48.9)	0.477
Cause of ICU admission, no. (%)				
Traumatic brain injury	22 (29.3)	7 (23.3)	15 (33.3)	0.441
Ischemic stroke	11 (14.7)	4 (13.3)	7 (15.6)	1.000
Subarachnoid or intracerebral hemorrhage	8 (10.7)	6 (20.0)	2 (4.4)	0.053*
Cardiac arrest	10 (13.3)	0 (0)	10 (22.2)	0.005*
Other causes	24 (32.0)	13 (43.3)	11 (24.4)	0.129
Cerebral scan findings during admission, no. (%)				
Normal	7 (0.9)	4 (13.3)	3 (6.7)	0.210
Focal or mild bilateral lesions	12 (1.6)	6 (20.0)	6 (13.3)	0.526
Diffuse severe bilateral, DAI or brainstem lesion	48 (64.0)	20 (66.7)	28 (62.2)	0.808
Anoxic brain damage	9 (12.0)	0 (0)	9 (20.0)	0.009*
GCS score at ICU admission, no. (%)				
Median (Min - Max)	6 (3 – 14)	9 (4 – 14)	5 (3 – 9)	<<0.001**
FOUR score at ICU admission, no. (%)				
Median (Min – Max)	8 (0 – 16)	11 (5 – 16)	6 (0 – 10)	<<0.001**
Time from ICU admission to index EEG, days				
Mean (SD)	15.9 (29.4)	18.17 (11.4)	14.4 (14.3)	0.209
Duration of ICU admission, days				
Mean (SD)	31.9 (24.8)	36.1 (29.4)	29.1 (21.0)	0.2339
Death during ICU admission – no. (%)	28 (37.3)	2 (6.7)	26 (57.8)	<<0.001 **
WLST due to poor prognosis	26 (34.7)	1 (3.3)	25 (55.6)	0.140§
Other causes (sudden clinical deterioration)	2 (2.7)	1 (3.3)	1 (2.2)	-

[a] Percentage of comorbidities do not add up to 100 as patients could have multiple comorbidities.
[§] n.o. total in this calculation is total number of deaths (28) and not the full population of 75.
*Indicates p-value < 0.05
**Indicates p-value < 0.001
Abbreviations: SD; Standard Deviation, mRS; Modified Rankin Scale, ICU; Intensive Care Unit, DAI; Diffus Axonal Injury, GCS; Glasgow Coma Scale, FOUR; Full Outline of UnResposivness, WLST: Withdrawal of Life-Sustaining Therapy
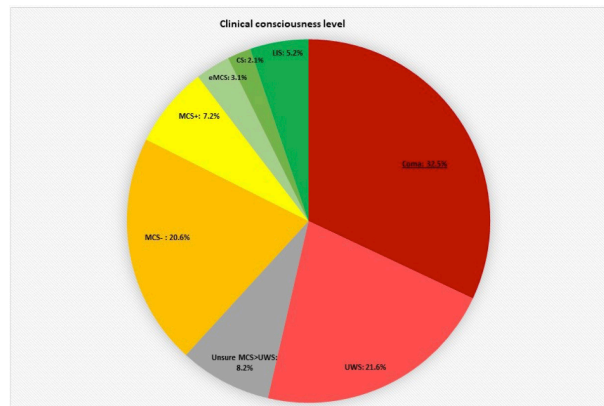
Table 1

Figure 2: Distribution of study population according to clinical consciousness level at time of inclusion.
Abbreviations: UWS; Unresponsive wakefulness state, MCS; Minimal conscious state, MCS-; Minimal conscious state minus, MCS+; Minimal conscious state plus, eMCS; Emerging from Minimal conscious state, CS; Confusional state, LIS; Locked -in syndrome

Figure 2

Conclusion: In acute brain-injured patients with DOC previously thought of as unconscious, a multimodal approach, including automated EEG measures, may help detect covert consciousness, thereby contributing personalized prognostication.
Disclosure: Nothing to disclose.

OPR-052

Unravelling the neural basis of spatial delusions after stroke

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Background and aims: Knowing explicitly where we are is an interpretation of our spatial representations. Spatial delusions are disrupting syndromes in which patients present a resilient belief of spatial mislocation. Here, we studied the largest sample of patients with spatial delusions after stroke to shed light on their neurobiology.

Methods: In a prospective, cumulative, case-control study, we screened 400 patients with acute right hemispheric stroke. We included 64 cases presenting spatial delusions and 233 controls. first, lesions were delimited and normalized. Then, we computed structural and functional disconnection maps using methods of lesion-track and network-mapping. The maps were compared, controlling for nuisance variables. 2nd, we built a multivariate logistic model including clinical, behavioural and neuroimaging data. Finally, we performed a nested cross-validation of the model with a support-vector machine analysis.

Results: We found a structural disconnection map that was significantly associated with spatial delusions. It was the strongest predictor of the syndrome and included two distinct streams, connecting right fronto-thalamic and right occipito-temporal structures. Significant functional disconnection was observed in the right precuneus, and a functional-structural link was demonstrated. In the multivariate model, the independent predictors of spatial delusions were the structural disconnection map, lesion sparing of right dorsal fronto-parietal regions, age and anosognosia. Good discrimination accuracy was demonstrated (median area under the curve=0.80, interquartile range 0.75–0.85).

Conclusion: Our results revealed the circuits associated with the abnormal spatial-emotional binding and the defective updating of spatial representations underlying spatial delusions. This novel data may contribute to better understand the pathophysiology of delusional syndromes after stroke.

Disclosure: Nothing to report.

COVID-19

OPR-053

Multiparametric analysis reveal no intrathecal inflammation in COVID-19 associated neurological syndromes

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Background and aims: Coronavirus disease (COVID-19) has been associated with a large variety of neurological disorders. However the mechanisms underlying these neurological complications remain elusive. In this study we aimed at determining whether neurological symptoms were caused by SARS-CoV-2 direct infection of by pro-inflammatory mediators.

Methods: We checked for SARS-CoV-2 RNA by RT-qPCR, SARS-CoV-2-specific antibodies and for 48 cytokines/ chemokines/growth factors (by Luminex) in the cerebrospinal fluids (CSF) ± sera of a cohort of 17 COVID-19 patients with neurological presentation and 55 neurological control patients (inflammatory [IND], non inflammatory [NIND], multiple sclerosis [MS]).

Results: We found SARS-CoV-2 RNA and antibodies specific for this virus in the CSF of 0/17 and 8/16 COVID-19 patients, respectively. The presence of SARS-CoV-2 antibodies was explained by a rupture of the blood brain barrier (passive transfer) in 6/16 (38%). An intrathecal synthesis of SARS-CoV2-specific antibodies was present in 2/16 patients. Of the four categories of tested patients, the CSF of IND exhibited the highest level of chemokines (CCL4, CCL5, CXCL8, CXCL10, CXCL12, and CXCL13), followed by the CSF of MS patients (CXCL12, and CXCL13). There was no significant difference between COVID-19 and NIND patients, even if some chemokines (CCL4, CCL5, CXCL8, andCXCL10) tended to be higher in the former. Interestingly, among COVD-19 patients, the CSF of those with a severe disease (encephalitis/ encephalopathy) contained higher levels CXCL8 and CXCL10 than those with other neurological presentations.
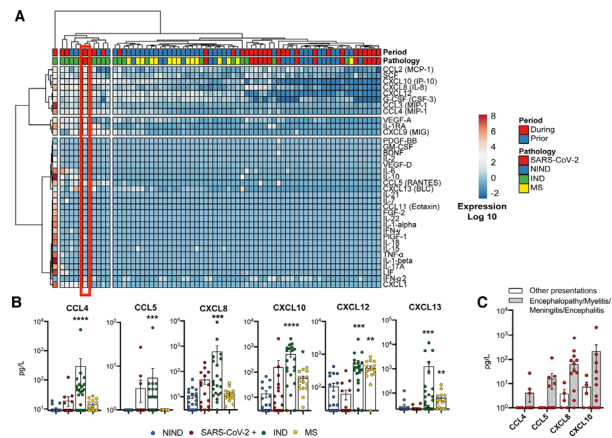
Cytokines/Chemokines/Growth factor in the CSF of patients with neurological presentation of SARS-CoV-2

Conclusion: Our results do not show obvious SARS-CoV-2 infection of the central nervous system, but point to a mild inflammatory reaction reflecting an astrocytic reaction.

Disclosure: Nothing to disclose.

OPR-054

Brainstem damage in COVID-19

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Background and aims: It has recently been proposed that SARS-CoV-2 might spread through the nervous system in a prion-like way, reaching respiratory centers in the brainstem. Here, we evaluated neuropathologically, neurophysiologically and clinically the brainstem involvement in COVID-19.

Methods: Neuropathological data were acquired from patients died for COVID-19 and COVID-19 negative; neuronal damage and the number of corpora amylacea (CA)/mm^2 were assessed. The expression of the "nuclear protein" of SARS-Cov-2 was also evaluated. To clarify whether neuropathological findings had a functional correlate, we studied the blink reflex (BR) in 11 COVID-19 patients, admitted to our Intensive Care Unit (ICU), and compared data both with healthy subjects and non COVID-19 ICU patients. An extensive neurological examination, comprising the corneal and glabellar reflexes, was also performed.

Results: Autopsies showed a high percentage of neuronal damage and a higher number of CA in the medulla oblongata of COVID-19 patients; immunohistochemistry revealed the presence of SARS-Cov-2 virus in the brainstem. Neurophysiologically, the RII component of the BR was selectively impaired in COVID-19 and, clinically, the glabellar reflex reduced or absent.
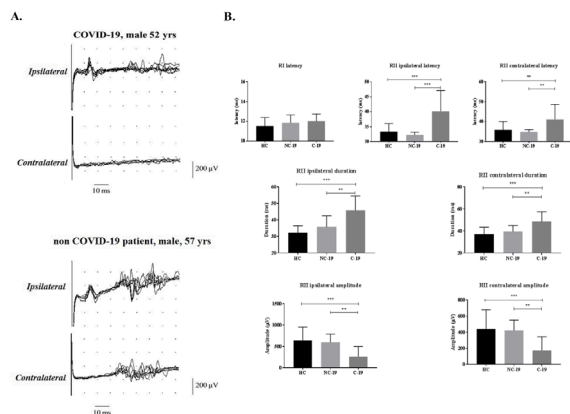
Neurophysiological findings. Note that the medullary RII response of the supraorbital blink reflex (BR) is impaired in COVID patients, compared both to controls and non-COVID ICU patients

Conclusion: Our findings provide the first combined neuropathological, neurophysiological and clinical evidence of SARS-Cov-2-related brainstem involvement, especially at the medullary level, suggesting a neurogenic component of respiratory failure.

**Disclosure:** The Authors have no conflicts to declare.

OPR-055

Neurological manifestations after COVID-19 illness: Observations in one of the largest COVID-19 centers in México.

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Background and aims: Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in 2019, that causes human coronavirus disease 2019 (COVID-19), persistent symptoms among COVID-19 survivors have been described. Our objective is to report neurological sequelae in hospitalized COVID-19 survivors.

Methods: Our study included the neurological sequalae observed in 238 patients that were admitted at a single medical center with acute respiratory distress syndrome (ARDS) due to COVID-19. Three months after their hospital discharge, a complete neurological examination and a cognitive screening Montreal Cognitive Assessment (MoCA) test was applied by two neurologists in Mexico City, from August 31, 2020, to January 8, 2021.

Results: All patients were positive for SARS-CoV-2, tested via reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assays of nasopharyngeal samples. The mean age of the cohort was 51 years. 97 patients (68.3%) needed mechanical ventilatory support. 52% patients exhibited a periphery oxygen saturation of less than 70% at admission. 10.6% were health care workers and eight patients had previous neurological disorders. The main neurological sequels found were sensory-motor neuropathy (66.4%), myopathic pain (43.9%), and cognitive complaints (59.7%) with an average MoCA score of 25.5 (46.6%). Furthermore, five patients were diagnosed with ischemic cerebral vascular disease, five patients presented seizures, 108 (45.6%) exhibited affective symptoms, and 52.2% patient reported a modified Rankin Scale score of less than 2.
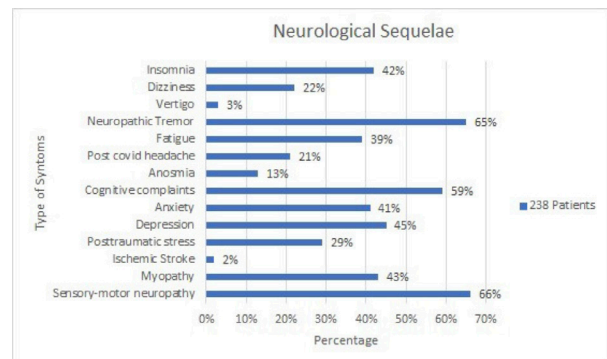
Main neurological sequelae found in the 238 patients three months after their hospitalization.

Main comorbidities found in the 238 patients three months after their hospital discharge.
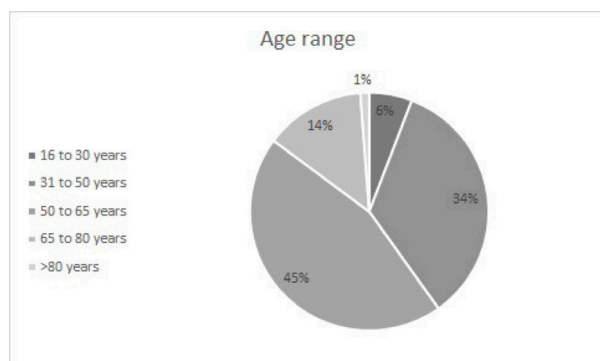
Age range of the 238 patients evaluated

Conclusion: The under-recognition of neurological sequelae may lead to an increase in the burden of COVID-19. Therefore having a multidisciplinary long-term follow-up is advisable in order to optimize treatment and to improve prognosis.

Disclosure: Nothing to disclose.

OPR-056

Neurological implications of COVID-19 – results of the LEOSS registry

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Background and aims: Register studies and cohort analyses of clinical data are essential to study neurological manifestations of COVID-19 at a large scale.

Methods: We analyzed neurological manifestations in COVID-19 patients, diagnosed before Aug 25th 2020, and registered in the European multinational LEOSS registry.

Results: Of the 3127 COVID-19 patients, 95.2% were hospitalized. In 54.4% at least one neurological symptom, and in 3.3% a new neurological complication occurred. Pre-existing neurological comorbidities were reported in 18.1% of the patients. Neurological symptoms were excessive tiredness (27.6%), headache (15.3%), nausea/emesis (14.0%), muscular weakness (13.2%), smell (6.9%), taste disorder (8.3%) and delirium (6.3%). Intracerebral bleeding occurred in 1.2%, ischemic stroke in 0.5%, and meningitis/encephalitis 0.4%. Overall, the death rate was 17.5%. It was higher in patients with the following neurological comorbidities: dementia 38.0%, movement disorders 32.8%, and prior cerebrovascular disease 32.3%. A multivariable logistic regression model found age (OR 1.53), cardiovascular diseases (OR 1.74), muscle weakness (OR 1.40), pulmonary diseases (1.49) and male gender (OR 1.52) to be associated with a significantly increased risk for a critical COVID-19 disease course, failed recovery, and death.

Conclusion: The neurological manifestations revealed in COVID-19 patients of this study are mostly in agreement with previously published data. Several neurological conditions, such as prior cerebrovascular diseases or dementia appeared to be associated with a higher risk in unadjusted analyses, which was not confirmed in a multivariable analysis adjusting for confounding variables such as age and sex. These findings contrast previously published studies and stress the importance of considering putative confounds in medical statistics carefully.

Disclosure: Nothing to disclose.

OPR-057

COVID-19 and Guillain-Barré syndrome in early pandemia in Lombardia: increased incidence or increased seroprevalence?

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Background and aims: Several studies reported increased incidence of Guillain-Barre' Syndrome (GBS) after Zika epidemic, SARS-CoV and MERS, and more recently SARS-CoV-2 infection. We estimate incidence and describe clinical characteristics and outcome of GBS in COVID-19 patients in one of the most affected regions by COVID-19 of the world, Lombardia.

Methods: A multi-center observational study on neurological complications in COVID-19 patients was conducted in 20 Neurology Units by the Italian society of Hospital Neuroscience (SNO). Adult patients admitted to Neurological units between February-April 2020 with COVID19-GBS were included.

Results: 38 COVID19-GBS patients had mean age of 60.7 years and male frequency of 86.8%. Mean interval between COVID-19 onset and GBS onset was 15.1 days. CSF albuminocytologic dissociation was detected in 71.4% of cases, PCR for SARS-CoV-2 negative in all 15 tested patients, and anti-ganglioside antibodies positive in 43.7%. Based on neurophysiology, 81.8% of patients had a diagnosis of AIDP diagnosis, 12.1% AMSAN and 6% AMAN. 29 patients have been treated with intravenous Immunoglobulin (IVIg), two with plasma exchange (PE), two with PE followed by IVIg and five untreated. The course was favorable in 76.3% of patients, stable in 10.5%, while 13.1% worsened, of which three died. The estimated occurrence rate in Lombardia is 0.5 GBS cases per 1000 COVID-19 infections.

Conclusion: We detected an increased incidence of GBS in COVID-19 patients which can reflect higher risk of GBS in COVID-19 patients or be secondary to an increase of prevalence of prior infection in that period.

Disclosure: Nothing to disclose

OPR-058

Clinical, neurophysiological and neuroradiological characteristics of SARS-Cov-2 encephalitis in Lombardia

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Background and aims: The number of cases of encephalitis in COVID-19 is increasing. We describe characteristics and outcome of encephalitis in COVID-19 (COV-ENC) patients in one of the most affected regions by COVID-19 of the world, Lombardia.

Methods: A multi-center observational study on neurological complications in COVID-19 patients was conducted by the Italian society of Hospital Neuroscience (SNO). Adult patients admitted to 20 Neurological units in Lombardia between February-April 2020 with COV-ENC have been included.

Results: 30 COV-ENC patients had a mean age of 66.5 years and male frequency of 56.6%. Altered consciousness was characterized by confusion in 86%, coma in 30%, delirium in 37.9% and alteration of personality trait in 27.6%. Epileptic seizures occurred in 74% of cases. One third of cases had hyperproteinorrachia, 1/3rd pleocytosis/hyperproteinorrachia, and left third had normal CSF. PCR for SARS-CoV-2 was negative in all tested patients. EEG was altered in 82.7% of patients. Brain CT and MRI were normal in nine patients, among abnormal findings nine patients had mesial temporal lesions, one of which confirmed with PET imaging. The course was favorable in 39.2% of patients, sequelae were few in 26.6% and moderate in 19.2%, while 20% of patients died.

Conclusion: The outcome tends to be worse in male patients. PCR negativity seems to confirm an autoimmune etiology more than a direct invasion of the virus. However, temporal lobe involvement, detected in 30% of patients with COV-ENC, suggest usual site of encephalitis due to herpes virus.

Disclosure: Nothing to disclose

Epilepsy: Quality of life, pregnancy and developmental outcomes

OPR-059

Epilepsy and depression – a bidirectional relationship

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Background and aims: Epilepsy and depression are two serious brain disorders that often co-occur, and the relationship between them has been suggested to be bidirectional; however, studies have provided ambiguous results, and the nature of the association between these two disorders remains to be fully understood.

Methods: In a nation-wide register-based cohort study, we identified all individuals who received a first diagnosis of epilepsy or depression from 1 Jan 1980 to 31 Dec 2016. For each person with epilepsy and depression we matched five persons without epilepsy and depression on age and sex at time of first diagnosis in the index person. We used Cox-regression to estimate the risk of epilepsy after depression and the risk of depression after epilepsy, adjusting for Charlson Comorbidity Index, substance abuse, and calendar time.

Results: In a population of 8,685,430 individuals, we identified 143,482 persons with epilepsy (54% males) with a median age at diagnosis of 42 years (interquartile range 17–65 years), and 226,149 persons with depression (37% males) with a median age at diagnosis of 43 years (interquartile range 29–60 years). The adjusted HR of depression after an epilepsy diagnosis was 1.91 (95% CI: 1.85–1.98) compared to persons without epilepsy, and the adjusted HR of epilepsy after a depression diagnosis was 2.37 (95% CI: 2.29–2.47) compared to persons without depression.

Conclusion: The risk of epilepsy is increased in persons with depression and the risk of depression is increased in persons with epilepsy. The results suggest a bidirectional association between depression and epilepsy and warrant further studies.

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OPR-064

Longitudinal reduction of quality of life in patients with epilepsy and no seizure increase during the COVID-19 pandemic

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Background and aims: In early 2020, the novel coronavirus disease (COVID-19) pandemic has impaired medical care of chronic neurological diseases, including epilepsy. The objective of this study is to evaluate the impact of the COVID-19 pandemic in the levels of anxiety, depression, somnolence and quality of life using validated scales in patients with epilepsy in real-life clinical practice.

Methods: Self-administered scales of anxiety disorders (GAD-7), depression (NDDI-E), somnolence (Epworth Sleepiness Scale; ESS) and quality of life (QOLIE-31-P) in patients with epilepsy treated in the Refractory Epilepsy Unit of a tertiary hospital were longitudinally analyzed with Generalized Linear Mixed Models. Data were collected before the beginning (December 2019–March 2020) and during the COVID-19 pandemic (September 2020–January 2021).

Results: 37 patients, 45.0±17.3 years of age, 43.2% women, epilepsy duration 23.0±14.9 years, number of anti-epileptic drugs 2.1±1.4, answered in the two periods. Significant longitudinal reduction of QOLIE-31-P scores (from 58.9±19.7 to 56.2±16.2, p=0.035) was identified. No statistically significant longitudinal changes in NDDI-E (from 12.3±4.3 to 13.4±4.4, p=0.293) or the number of seizures (from 0.9±1.9 to 2.5±6.2, p=0.125) were found. Significant higher ESS (from 4.9±3.7 to 7.4±4.9, p=0.001) and lower GAD-7 scores (from 8.8±6.2 to 8.3±5.9, corrected p=0.024 adjusted by refractory epilepsy and sleep disturbance) were found during the COVID-19 pandemic.

Conclusion: During the COVID-19 pandemic, quality of life was lower in patients with epilepsy, levels of anxiety were reduced and sleepiness levels were raised, without seizure change. Additional studies would be useful to adequately manage these comorbidities.

Disclosure: There is no disclosure.

OPR-151

Impact of fatigue on health-related quality of life in patients with drug-resistant focal epilepsy

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Background and aims: Improvement of health-related quality of life (HRQoL) is considered a main goal of treatment of drug-resistant focal epilepsy (DRFE). HRQoL is believed to be a complex parameter with multiple disease- and patient-specific determinants.

Methods: 111 adult patients with DRFE were included in the study. HRQoL was measured using the "Quality Of Life In Patients with Epilepsy – 31" questionnaire (QOLIE-31). The severity the disease (frequency and subjective assessment of the severity of attacks), the effect of pharmacotherapy (drug load and composition of the treatment regimen), the social status of patients, comorbidities (anxiety, depression, fatigue) were assessed.

Results: The median of the final score for QOLIE-31 was 65.4 (interquartile range – 53.0–72.6 points). A statistically significant decrease in HRQoL was found in subgroups of patients with seizures during the previous three months, taking carbamazepine or barbiturates, suffering from anxiety and depressive disorders, with fatigue, as well as in unemployed patients ($p > 0.05$). A multiple linear regression model ($R2 = 0.66$) was developed, which included the following determinants: Fatigue Severity Scale (=-0.612), Liverpool Seizure Severity Scale (=-0.159), and the risk of depression according to the NNDI-E questionnaire (=-0.174).

Conclusion: Pathological fatigue has a large negative impact on HRQoL along with seizure severity perception and depression. These factors need to be addressed in clinical practice in order to improve HRQoL.

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OPR-154

Prenatal antiseizure medication exposure and risk of autism and intellectual disability.SCAN-AED: a Nordic cohort study

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Background and aims: The objective of this study was to investigate the risk of autism spectrum disorder (ASD) and intellectual disability (ID) after prenatal exposure to antiseizure medication (ASM).

Methods: We carried out a population-based cohort study (www.scanaed.org) of singleton births using linked health and social register data from Denmark, Finland, Iceland, Norway, and Sweden. We defined prenatal exposure by ASMs prescription fills from 90 days before pregnancy to birth and child outcomes by ICD-10 codes from specialist healthcare. Cox regression provided hazard ratios (HR) for ASD and ID in children after prenatal exposure to the 10 most common ASM monotherapies We adjusted for potential confounders using fine strata propensity score weighting.

Results: We identified 4,493,377 singleton births with a median

follow up of eight years (interquartile range 4.0–12.1. Background characteristics Table 1). Compared with unexposed children, ASM exposed children (0.7%) had an increased risk of ASD and ID with highest estimates for valproate and topiramate. For valproate (n=3,042) the adjusted HR (95% confidence intervals) was 2.9 (1.5-5.7) for ASD, and 4.3 (3.5–5.3) for ID. For topiramate (n=879) the adjusted HRs were 2.8 (1.9–4.2) and 3.3 (2.3–4.6) respectively. The associations between prenatal exposure to other ASMs and neurodevelopmental outcomes were weaker and disappeared when we accounted for maternal disease by comparing exposed and unexposed children among mothers with epilepsy.

Table 1: Characteristics of study population according to prenatal exposure to antiseizure medication (ASM)[1]

	No ASM	Any ASM
Pregnancies, n	4 462 358	31 019
Characteristics of mothers		
Maternal age, mean (sd)	30.2 (5.2)	30.2 (5.4)
Parity, n (%)		
0	1 920 451 (43.0)	14 532 (46.9)
1	1 599 692 (35.9)	9 562 (30.8)
≥ 2	919 501 (20.6)	6 723 (21.7)
Missing	22 713 (0.5)	202 (0.65)
Married/cohabiting, n (%)		
no	329 965 (7.4)	4 418 (14.2)
yes	4 052 347 (90.8)	26 030 (83.9)
Missing	80 045 (1.6)	80 (0.3)
Education, n (%)		
Compulsory	611 126 (13.7)	7 618 (24.6)
Secondary/Pre-university	2 073 541 (46.5)	14 901 (48.0)
Bachelor	978 623 (21.9)	5 111 (16.5)
Master/PhD	614 053 (13.8)	2369 (7.6)
Missing	185 014 (4.2)	1 020 (3.3)
Antidepressants LMP-90 to birth, n (%)	156 881 (3.5)	7 842 (25.3)
Opioids LMP-90 to birth, n (%)	165 503 (3.7)	4 839 (15.6)
Epilepsy[2], n (%)	8862 (0.2)	15 750 (50.8)
Depression, n (%)	59 023 (1.3)	3 378 (10.9)
Anxiety, n (%)	96 178 (2.2)	4 176 (13.5)
Personality disorder, n (%)	14 148 (0.3)	19 57 (6.3)
Bipolar disorder[2], n (%)	5 956 (0.1)	3079 (9.9)
Number of chronic somatic diseases[4], n (%)		
0	4 118 321 (92.3)	27 014 (87.1)
1	321 213 (7.2)	3 567 (11.5)
≥ 2	22 824 (0.5)	438 (1.4)
Number of pre-pregnancy hospitalizations the last year before pregnancy[5], n (%)		
0	3 785 855 (84.8)	23 223 (74.9)
1	558 191 (12.5)	4 922 (15.9)
≥ 2	118 312 (2.7)	2 874 (9.3)
Characteristics of children		
Male, n (%)	2 290 256 (51.3)	15 911 (51.3)

1) Exposure to antiseizure medication (ASM) defined as filling ASM prescriptions between 90 days before last menstrual period to delivery. 2) Diagnosis in the prescription -and birth registers and/or in records from specialist heath care the last year be

Conclusion: In this very large nationwide study from five Nordic countries, prenatal valproate and topiramate exposure were associated with increased risk of autism and intellectual disability.

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OPR-185
Prenatal exposure to antiseizure medication and the full spectrum of diagnosed psychiatric disorders: A SCAN-AED study

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Background and aims: We examined the association between prenatal exposure to antiseizure medication (ASM) with psychiatric disorders among children of mothers with epilepsy.

Methods: We carried out a prospective population-based register study within the SCAN-AED project (www.scanaed.org), based on children born in Denmark, Finland, Iceland, Norway and Sweden between 1996 and 2016. Maternal use of ASM in pregnancy was defined as any redeemed prescription of ASM from 90 days before pregnancy to birth and assessment of psychiatric disorders in children was based on ICD-10 diagnoses (F10-F99) from specialized care. Maternal epilepsy was defined as any hospital contact with epilepsy or use of ASM with epilepsy as indication from one year before pregnancy to birth. Adjusted hazard ratios (aHR) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models.

Results: From the overall SCAN-AED population consisting of 4,490,152 live-born singletons, we identified 25,288 (0.6%) children of mothers with epilepsy, of whom 15,899 (62.9%) were prenatally exposed to ASM. Compared with children of mothers with epilepsy who did not use ASM during pregnancy, we found an increased risk of psychiatric disorders with prenatal exposure to valproate (aHR=1.85, 95% CI: 1.62–2.13) and topiramate (aHR= 1.43, 1.00–2.05), but not with lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, clonazepam, and gabapentin. Prenatal valproate exposure was associated with increased risks of neurodevelopmental- and attachment disorders, but not with e.g. anxiety-, mood- and schizophrenia spectrum disorders.

Conclusion: In pregnant women with epilepsy, treatment with valproate and topiramate was associated with an increased risk of early-onset psychiatric disorders in the child.

OPR-187

Evaluation of Clinical Support and Medication Adherence of Women with Epilepsy During Pregnancy

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Background and aims: Women with epilepsy (WWE) have higher rates of mortality and morbidity during pregnancy. Reasons are unclear but a reduction in anti-seizure medication (ASM) levels and poor adherence to ASMs are likely relevant. This study aims to evaluate adherence to ASMs and access to specialist care for WWE during pregnancy.

Methods: Pregnant WWE within NHS Greater Glasgow and Clyde health-board were identified from the National Obstetric Register between June 2019–June 2020. A manual review of electronic patient records was undertaken to ensure diagnostic accuracy. Contact with epilepsy services was recorded. Medication dispensing records were obtained and a medication possession ratio to ASMs, six months before and after midwifery booking date, calculated.

Results: 87 WWE were identified: 43 with generalised (49.4%), 34 focal (39.1%) and 10 unclassified (11.5%) epilepsy. 42/87 WWE (48.3%) had input from epilepsy services within a year of conception. As of December 2020, 65/87 (74.7%) had antenatal input from epilepsy services, with 4/87 (4.6%) reviewed post-partum. One was pending review. No review was planned for 17/87 (19.5%). Of those reviewed, 21/65 (32.3%) were seen in the first trimester, 29/65 (44.6%) in the second and 15/65 (23.1%) in the third. Only 71/87 WWE were on ASMs. 32/71 (45.1%) had poor adherence to at least one of their ASMs before booking and 29/71 (40.8%) after booking.

Conclusion: National electronic databases demonstrate high incidence of non-adherence prior to and during pregnancy. Access to routine health-data and early review by specialist epilepsy services will provide opportunity to improve adherence and pregnancy-related outcomes in WWE.

Headache and Pain 1

OPR-065

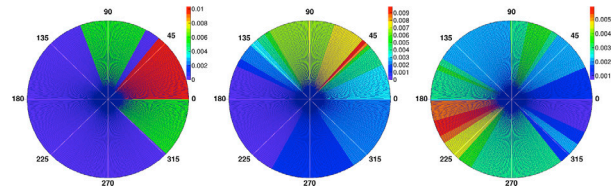### Vascular Compression in Trigeminal Neuralgia discloses Trigeminal root somatotopic organization

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E. Ripiccini [2], P. Falco [1], C. Leone [1], M. Fiorelli [1],
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Background and aims: In Trigeminal Neuralgia pain is localized in the distribution of one or more branches of the trigeminal nerve. A hallmark of TN is the presence of discrete skin areas able to trigger pain attacks when touched. In classical TN trigeminal reflexes are normal but it is possible to recognize a vascular compression with morphological changes of trigeminal nerve root.

Methods: We enrolled 53 patients with clinically defined TN, normal trigeminal reflexes testing, and evidence of neurovascular compression at 3-Tesla MRI. From MRI images we measured the polar coordinates of the impacting vessel on the trigeminal root circumference and then correlate it with pain distribution, trigger zones and latencies of the early components of the trigeminal reflexes.
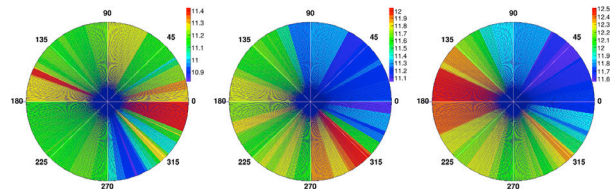
Results: Pain in V1, V2 and V3 is associated, respectively, with vascular compression in the medial, superior and lateral aspect of the nerve (p<0.05). Cutaneous trigger zones are associated with corresponding region of the circumference (p<0.05). Increased latency of the R1 component of the blink reflex is associated with medial compression, while increased latency of the SP1 component of the masseter inhibitory reflex is associated with inferomedial compression when the reflex is evoked from the infraorbital nerve, and with lateral compression when it is evoked from the mental nerve (p<0.05).

Preliminary data of location of neurovascular compression along the root circumference as derived by MRI data of 25 TN patients with pain limited to one trigeminal division, three with pain in V1, 10 with pain in V2 and 12 with pain in V3. Patients with pain
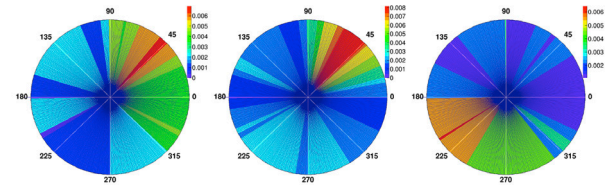
Preliminary data of location of neurovascular compression along the root circumference as derived by MRI data of 31 TN patients reporting as cutaneous trigger zones forehead, cheek or jaw. Polar coordinates are expressed in degrees, with 0 corresponding t

Preliminary data of location of neurovascular compression along the root circumference as derived by MRI data of 45 TN patients that underwent complete trigeminal reflex testing. Polar coordinates are expressed in degrees, with 0 corresponding to the medi

Conclusion: Our study showing that pain distribution, trigger zones and increased latencies of the early components of the trigeminal reflexes are correlated with specific sites of neurovascular compression along trigeminal root circumference discloses its somatotopic organization.

Disclosure: Nothing to disclose.

OPR-066

Migraine in pregnancy and post partum-epidemiological and clinical characteristics

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Background and aims: Migraine is one of the most prevalent and disabling neurological disorders. The aim of our study was to assess whether women suffering from migraine are at increased risk of developing pregnancy and postpartum complications, and to evaluate their characteristics and medical needs.

Methods: Pregnancy and delivery records from a database of "Clalit" Health Medical Organization, Israel were reviewed. The diagnosis of migraine was based on the International Headache society criteria and ICD-9 codes. The study included a total of 161,574 women who gave birth during a time period of five years (2014–2019). The information collected included: demographic data, mode of delivery, medical and obstetric complications in each pregnancy trimester, use of medications and repeated medical consultations.

Results: 8,723 women had a diagnosis of migraine. The control group included the remaining 152,851 women. The risk of obstetric complications and postpartum depression were higher in migraine patients compared with the control group. Migraine pregnancies had increased risk of preeclampsia and stroke. There was an increased incidence of cesarean section (20.5% vs 18.1%) and epidural anesthesia (43.6% vs 36.5%). Women with migraine showed tendency to seek more medical consultations and use more medications during pregnancy and post-partum.

Conclusion: Pregnant women with migraine were at increased risk of having obstetric and medical complications compared with unaffected women, therefore should be included in a high-risk pregnancy protocol of care throughout pregnancy. We recommend a neurological follow-up during the pregnancy and post-partum period.

Disclosure: Nothing to disclose.

OPR-067

Occipital nerve stimulation in drug-resistant chronic cluster headache: a third-level hospital experience

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Background and aims: Occipital nerve stimulation (ONS) is a surgical treatment proposed for drug-resistant chronic cluster headache (drCCH). Long-term series assessing its efficacy are scarce.

Methods: We designed a retrospective observational study with consecutive sampling, evaluating the follow-up of 22 drCCH patients who underwent ONS. Our endpoint was the weekly attacks reduction. We also evaluated the pain intensity scored by the Visual Analogue Scale (VAS), patient overall perceived improvement and decrease in oral medication intake.

Results: After a median follow-up of 5.0 years, patients decreased from a median of 30 weekly attacks to 22.5 at three months [p=0.012], 7.5 at one year [p=0.006] and 15.0 at the end of follow-up [p=0.023]. The VAS decreased from a median of 10.0 to 9.0 at three months [p=0.011] and 7.0 at one year [p=0.002] and at the end of follow-up [p=0.002]. 23.5% had an overall perceived improvement of 70% at three months, 41.2% at one year and 27.8% at the end of follow-up. Reducing prophylactic oral medication was possible in 59.1% and it was stopped in 13.6%. Triptan use decreased in all the responder patients and 13.6% stopped its intake. 40.9% presented mild adverse events.
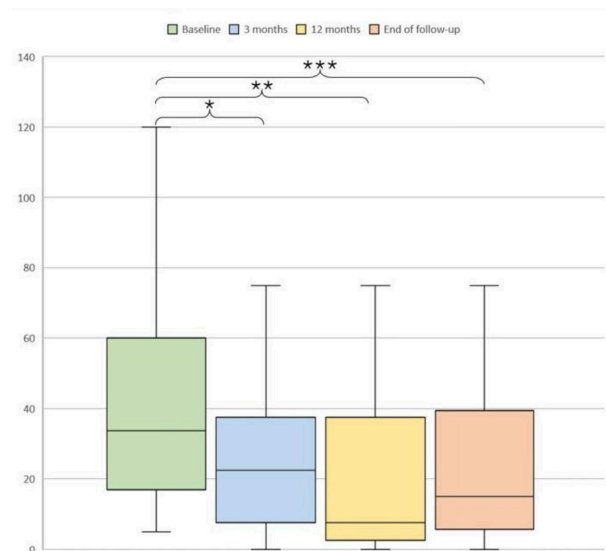
Evolution of weekly number of cluster headache attacks at baseline and after occipital nerve stimulation. Median and ranges are shown. *: p=0.012, **: p=0.006, ***: p=0.023

Conclusion: Our long-term experience shows that ONS is a beneficial treatment which does not entail serious harm and should be offered as the first option for drCCH management.

Disclosure: Financial support for medical writing were provided by Boston Scientific. The funder was not involved in the study design, collection, analysis or interpretation of data.

OPR-068

The effects of great occipital nerve block over photophobia in migraine patients

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Background and aims: To study the effect of greater occipital nerve (GON) block over photophobia in patients with migraine.

Methods: This is an observational prospective case-control study. Patients with migraine and photophobia attending the Headache Unit of a third-level hospital were recruited. Cases were defined as patients receiving GON block, which was performed at visit 1 (V1). All patients were evaluated with the Hospital Anxiety and Depression Scale, the Migraine Specific Quality of Life Questionnaire, the Utah Photophobia Symptom Impact Scale (UPSIS-12) and the Korean Photophobia Questionnaire (KUMC-8); both in V1 and one week after (V2).

Results: 41 patients were recruited; 28 cases and 13 controls. At V1, there were not significant differences in UPSIS (mean±SD): cases 29.4±8.3 vs controls 27.8±8.1, p=0.558) and KUMC-8 (cases 6.7±1.2 vs controls 6.2±1.7, p=0.323. At V2, cases experimented a significant improvement in photophobia impact scales compared to controls (UPSIS-12: reduction of 6.0±6.5 points, p<0.001; KUMC-8: reduction of 1.2±1.8 points, p=0.002). The other used scales did not show significant variation. Lesser improvement was seen in migraine with aura, but this was not statistically significant (reduction of 4.4±4.1 vs 8.5±8.7, p=0.101).

Conclusion: GON block has a beneficial effect over photophobia in migraine patients, measured with UPSIS-12 and KUMC-8. Patients without aura may have a greater improvement. GON block could be a useful therapeutic technique for photophobia in migraine.

Disclosure: The authors declare no conflict of interests.

OPR-069

Potential migraine "protectors": factors associated with decreased attack risk in individuals

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Background and aims: In the management of migraine, potential protective factors have been widely ignored even though they are probably as important as trigger factors. Therefore, the objective of this study was to identify factors associated with decreased migraine attack risk in individuals with migraine.

Methods: Individuals with migraine registered to use N1-Headache® and for 90 days entered daily data about potential attack risk factors (diet, mood etc), as well as migraine symptoms when these occurred. Univariate associations between each factor and migraine events were evaluated using Cox Proportional Hazards models. A factor was defined as a potential "protector" if significantly associated with a decreased risk of migraine attack (unadjusted hazard ratio <1; p-value <0.05).

Results: Out of 672 individuals included in this study (88% female; mean (SD) 8.8 (5.5) migraine days/month; 83% episodic migraine), no "protectors" were found in 211 (31.4%); 443 individuals (65.9%) had between one and eight "protectors"; and 18 (2.7%) had nine "protectors" or more. In a Day -1 analysis (excluding factor data on the day headache starts) fewer "protectors" were found: none in 314 individuals (46.7%), between one and five "protectors" in 339 (50.4%), and 19 had six "protectors". The most common "protectors" were waking feeling refreshed, feeling happy, good sleep quality, being relaxed and coffee/caffeine.

Conclusion: In two-thirds of individuals with migraine, at least one factor associated with decreased migraine attack risk could be identified. Knowledge of these factors may help individuals adopt behavioural changes that may, ultimately, decrease migraine attack risk.

Disclosure: SD, MV-M and GB are consultants to and hold stock options in Curelator Inc., AM is CEO of Curelator Inc. and holds stock and stock options in Curelator Inc., CW is a paid consultant to Curelator Inc.

OPR-070

Triptans and vascular comorbidity in over-fifties: Findings from a nationwide insurance database

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Background and aims: Beyond the age of 50, migraine is still common, and the incidence of vascular disorders increases. Triptans, specific drugs for acute migraine attacks, are vasoconstrictive and contraindicated in persons with vascular disorders. We aimed to gather the prescription of triptans and to evaluate whether vascular comorbidity differs in users and non-users of triptans over the age of 50.
Methods: Based on a nationwide insurance database from 2011, we compared the prescription of vascular drugs, vascular diagnoses (based on ATC-codes and ICD-10) and hospitalizations between triptan users >50 years and a control-group matched for age, sex, and place of residency.
Results: Of 3,116000 persons over 50, 13,833 (0.44%, 81% female) had at least one triptan prescription. 30% of the triptan users were over 50. In triptan-users, prescriptions of cardiac therapies and betablockers were significantly more common and prescriptions of calcium channel blockers and renin/angiotensin inhibitors were significantly less common. The prescriptions of antihypertensive, diuretic, and antilipidemic drugs, of platelet inhibitors and vitamin-K-antagonists, the frequency of vascular diagnoses, the number of hospital stays and of days in hospital did not differ significantly between the two groups.
Conclusion: In over-fifties, prescription of triptans is common. Even though triptans are contraindicated in vascular disorders, vascular comorbidity does not differ in users and non-users of triptans. Triptan users over the age of 50 should regularly be evaluated for vascular disorders and risk factors for such disorders. Future studies should assess the risk of triptan use in patients with vascular disorders.
Disclosure: Nothing to disclose.

OPR-071

Resting State Functional Connectivity Changes of the Pons in Migraine Patients: A Cross-Sectional and Longitudinal Study

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Background and aims: Previous studies support a key role of the dorsal pons in in migraine pathophysiology. In this study, we aimed to explore cross-sectional and longitudinal resting state functional connectivity (RS FC) changes of the pons in migraine patients.
Methods: Using a 3.0 Tesla scanner, RS functional magnetic resonance imaging (MRI) and 3D T1-weighted scans were acquired from 91 headache-free episodic migraine patients and 73 controls. Twenty-three migraineurs and 23 controls were reexamined after four years. RS FC analysis was performed using a seed-region correlation approach and SPM12.
Results: At baseline, compared to controls, migraine patients showed a decreased RS FC between the left pons and ipsilateral lingual gyrus and bilateral cerebellum. The left pons had also an increased RS FC with the left precuneus and bilateral orbitofrontal cortex. While, the right pons had a decreased RS FC with the left cerebellum, right fusiform and right inferior temporal gyrus. After four years, compared to controls, migraine patients developed a decreased FC between the left pons and the bilateral precuneus. The decreased RS FC between the left pons and ipsilateral cerebellum was associated to less severe and less frequent migraine attacks over the years.
Conclusion: Migraine patients experience altered functional interactions between the pons, pain and visual processing areas. A decreased RS FC between the pons and cerebellum might reduce the frequency and severity of migraine attacks over time. RS FC between the pons and precuneus, a region known to play a role in sensory integration, is initially strengthen, but weaken over time.
Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Movement disorders: Neuroimaging

OPR-073

Motor cerebro-cerebellar networks breakdown among different subtypes of Parkinson's disease

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Background and aims: To investigate functional alterations in the cerebro-cerebellar system in two Parkinson's disease (PD) clinical phenotypes (tremor-dominant [TD] and postural instability and gait disorder [PIGD]) using stepwise functional connectivity (SFC).

Methods: 58 PD patients performed clinical and cognitive evaluations and resting-state functional MRI (fMRI). PD cohort was divided into two groups: 32 patients with TD (PD-TD) and 26 with PIGD (PD-PIGD). 60 age- and sex-matched healthy controls were also enrolled. SFC analysis aims to characterize regions that connect to specific seed brain areas at different levels of link-step distances. The cerebellar seed-region was identified using motor task-based fMRI in 23 controls. For each of the SFC maps, whole-brain two-sample t-test comparisons between groups were performed.

Results: The performance of the motor task during fMRI was associated with activation of the lobule VI and vermis of the cerebellum. SFC analysis at one-link step distance showed, in both PD subtypes, a decreased regional–local connectivity between seed region and thalamus and parietal lobe relative to controls; across intermediate link-steps, a reduced connectivity was observed with frontal, parietal and occipital lobes. Only PD-PIGD patients showed lower connectivity at intermediate link-step distances between the seed-cerebellar region and sensorimotor areas. In addition, SFC pattern identified different localization of functional overconnectivity in frontal lobe in both PD groups: in inferior frontal gyrus and insula in PD-PIGD, and in orbitofrontal gyrus in PD-TD.

Conclusion: These findings highlight subtype-specific PD changes in cerebellar functional connectivity, providing novel insights into the pathophysiological mechanism potentially underlying different motor phenotypes.

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

OPR-077

Longitudinal clinical, cognitive and neuroanatomical changes over five years in GBA-positive PD patients

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Background and aims: To study the 5-year disease course of Parkinson's disease (PD) patients with glucocerebrosidase mutation (GBA-positive) at diagnosis compared to PD noncarriers (GBA-negative), evaluating changes in clinical/cognitive outcomes, and structural MRI.

Methods: 10 GBA-positive and 20 GBA-negative PD at diagnosis underwent clinical, neuropsychological and brain MRI assessments at study entry and once a year for five years. At baseline and at the last visit, each group of patients was compared in terms of cortical thickness and subcortical volumes to a group of 22 age-matched healthy controls (HC). Clinical, cognitive and MRI features were compared between groups at baseline and over time.

Results: At baseline, GBA-positive and GBA-negative patients had similar clinical and cognitive profiles. Compared to GBA-negative and HC, GBA-positive patients showed cortical thinning of left temporal, parietal and occipital gyri. Over time, compared to GBA-negative, GBA-positive worsened significantly in motor and cognitive symptoms, and showed a greater pattern of bilateral cortical thinning involving also frontal cortices. After 60 months, compared to HC, GBA-negative PD patients showed a pattern of cortical thinning similar to that shown by GBA-positive at baseline. The two groups of patients showed similar patterns of subcortical volume loss over time.

Conclusion: Compared to GBA-negative patients, GBA-positive PD showed a greater and earlier cortical thinning which worsened over time. GBA-negative PD patients reached the pattern of cortical thinning of GBA-positive at the baseline only after five years, reflecting a slower disease progression. This study highlights the importance of the early detection of GBA mutation in PD patients.

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OPR-103

Associations between grey matter metabolism and dopaminergic and serotonergic systems degeneration in de novo PD

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Background and aims: Degeneration of the nigrostriatal dopaminergic (DA) and the raphe-thalamic serotonergic (SE) systems due to alpha-synuclein accumulation in the brainstem is one among the earliest changes observed in Parkinson's disease.

Methods: We assessed in 96 drug-naïve de novo Parkinson's disease patients (age 71.9±7.5; 59 males) the association between cortical metabolism and DA-SE deafferentation of either striatum or thalamus, and then we explored whether this association was mediated by either striatum or thalamus metabolism. We acquired brain FDG-PET images as a marker of neurodegeneration and 123I-Ioflupane Single Photon Emission Computed Tomography (123I-FP-CIT-SPECT, as a marker of dopaminergic impairment in the striatum as well as a proxy marker of serotoninergic deafferentation in the thalamus).

Results: We found that 123I-FP-CIT specific-to-non displaceable binding ratio (SBR) and glucose metabolism positively correlated one another in bilateral caudate, bilateral putamen and bilateral thalami. Moreover, using a voxel-wise approach, we observed a direct correlation between temporo-parietal cortical metabolism and caudate DA innervation, as well as a direct correlation between prefrontal metabolism and thalamus SE innervation. Lastly, we found that the effect of caudate 123I-FP-CIT SBR values on temporo-parietal metabolism was mediated by caudate metabolic values (percentage mediated 91%, p-value= 0.008), as well as that the effect of thalamus 123I-FP-CIT SBR values on prefrontal metabolism was fully mediated by thalamus metabolic values (p<0.001).

Conclusion: These data shed light on the impact of diffuse projection systems degeneration on cortical metabolism in Parkinson's disease as well as on their regional specificity.

Disclosure: MP: fees from Novartis, Merck and Biogen. DA: fees from Fidia SM: speaker Honoraria from Ge Healthcare. FN: fees from Roche Bial e G.E. Healthcare. All other authors report no conflicts of interest.

OPR-105

Functional MRI connectivity of the primary motor cortex in functional dystonia patients

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Background and aims: This study explores the functional connectivity (FC) of the primary motor (M1) cortex in functional dystonia (FD) patients relative to healthy controls, with a focus on different clinical phenotypes.

Methods: 40 FD patients (12 fixed [FixFD]; 28 mobile [MobFD]) and 43 healthy controls (14 young FixFD-age-matched [yHC]; 29 old MobFD-age-matched [oHC]) underwent resting state fMRI. A seed-based FC analysis was performed using bilateral M1 as regions of interest.

Results: Compared to controls, FD patients showed reduced FC between left M1 and left dorsal anterior cingulate cortex, and between right M1 and left M1, premotor/supplementary motor area (SMA), dorsal posterior cingulate cortex (PCC), and bilateral precuneus. Relative to yHC, FixFD patients showed reduced FC between M1 and precuneus bilaterally. Compared to oHC, MobFD patients revealed reduced FC between right M1 and left M1, premotor/SMA, dorsal-PCC, bilateral primary sensory cortices and parieto-occipital areas, and increased FC of right M1 with right associative visual cortex and bilateral ventral-PCC. FixFD patients, relative to MobFD, showed lower FC between the right M1 and right associative visual area, and bilateral precuneus and ventral-PCC.

Conclusion: This study suggests an altered brain FC of the motor circuit with areas involved in emotional processes and sense of agency in FD. FixFD patients showed FC abnormalities mainly in areas related to sense of agency, while MobFD in regions involved in sensorimotor functions (reduced FC) and emotional processing (increased FC).

Disclosure: Ministry of Education, Science, and Technological Development of the Republic of Serbia (project #175090).

OPR-107

Cortical sensorimotor representations remain normal in musicians' dystonia despite global deficit in dexterity

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Background and aims: Musicians' dystonia presents with a persistent loss of motor control during musical performance. The predominant hypothesis is that this loss of motor control is underpinned by maladaptive neural changes to the somatotopic organization of finger representations in primary somatosensory cortex.

Methods: Here, we tested this hypothesis by investigating the finger-specific activity patterns in the primary somatosensory (S1) and motor cortex (M1) using functional magnetic resonance imaging with state-of-the art multivariate analyses in 11 musicians with dystonia and nine healthy musicians. We also characterized their dexterous finger control to investigate whether the deficit is strictly limited to musical performance or also generalizes to a non-musical task.

Results: We report two key findings. 1st, during the production of individuated finger presses, musicians with dystonia showed a small, but robust loss of motor control. This deficit was characterized by both a reduction in finger individuation ability, and an exaggeration of mirror movements primarily during use of the clinically identified symptomatic hand, but also to a lesser extent during asymptomatic hand use. 2nd, we found no evidence of disease-related changes in the corresponding finger representations in S1/M1.
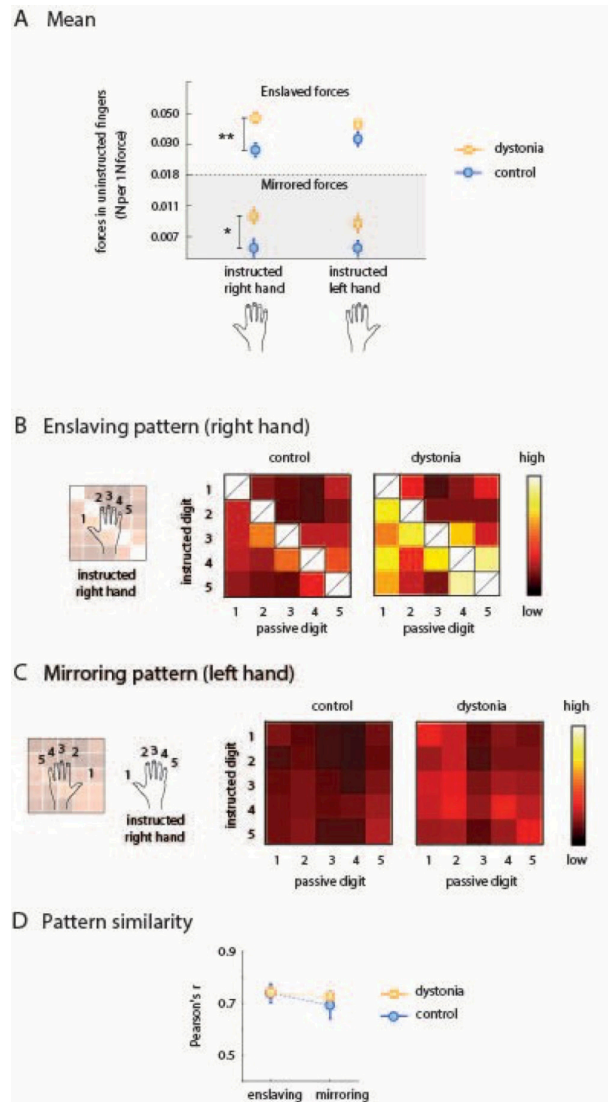
Finger individuation was reduced in musicians with dystonia.
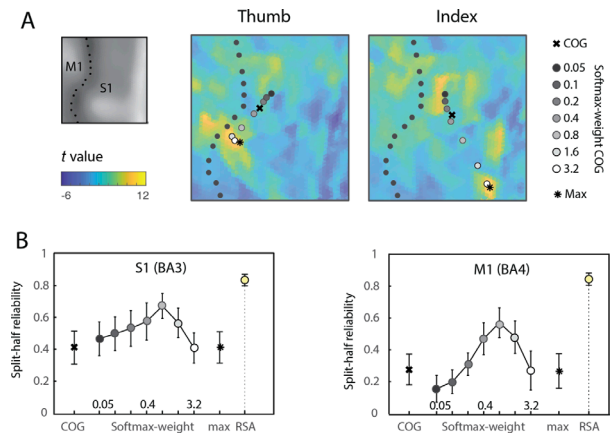
Comparison of different methods to characterize the spatial layout of digit representations.
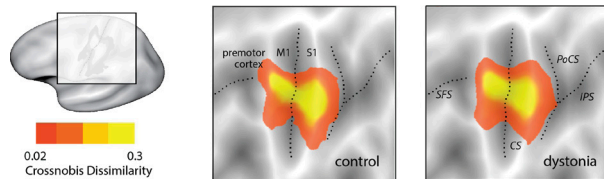
Extent and location of digit representations for healthy musicians (controls) and musicians with dystonia.

Conclusion: Our results contradict the view that abnormalities in sensorimotor finger representations play a role in the pathophysiology of musicians' dystonia. Our behavioral results also suggest that the loss of finger dexterity in musicians' dystonia expresses along a spectrum with subtle abnormalities in motor control evident during ordinary dexterous tasks.

Disclosure: Nothing to declare.

OPR-146

The role of white matter hyperintensities in Parkinson's disease progression and outcome

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Background and aims: We aimed to investigate the influence of white matter hyperintensities (WMH) on the longitudinal progression and outcome in Parkinson's disease (PD).

Methods: 154 PD patients underwent clinical assessment, neuropsychological evaluation and Magnetic Resonance Imaging (MRI) scan once a year up to 48 months. WMH were identified on T2-weighted scans and WMH total volume was computed for each scan at baseline. Then PD patients were divided in subgroups: low (lowH, 25th quartile, n=45), intermediate (mediumH, between 25th and 75th quartile, n=77) and high (highH, 75th quartile, n=32) baseline WMH burden. Analysis of variance was used to compare groups at baseline and age-corrected linear regression models for longitudinal data. Influence of WMH on the progression to Hoehn & Yahr (H&Y) three and dementia was investigated with Kaplan-Meier estimator analysis (KM).

Results: Subjects in PD highH showed significantly lower scores in Mini Mental State Examination and Addenbrooke's Cognitive Examination compared to lowH, Longitudinally, the highH group showed a significant worsening in motor and non-motor variables (p<0.001) compared to lowH and mediumH, independent of the effect of age. The KM analysis showed lower rates of progression to dementia (p=0.03) and to H&Y score 3 (p=0.02) in the lowH group.

Conclusion: Our study showed that higher WMH volumes are associated with a worse progression of both motor and non-motor symptoms, independently from age. Moreover, PD patients with high WMH volumes are more likely to progress to dementia and to advanced disease stages in the following four years.

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

OPR-149

Striatal Dopamine Transporter Imaging measures and CD4+ T cells profile in Parkinson's disease drug-naïve patients

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Background and aims: In Parkinson's disease (PD) there is a complex interplay between peripheral immunity and dopaminergic neural death in the nigrostriatal pathway. It has been found that in circulating CD4+ T lymphocytes from PD patients there are lower levels of Th2, Th17, and Treg subpopulations, with a relative increase of Th1, determining a pro-inflammatory bias. Nevertheless, no correlation with the quantitative assessment of dopaminergic neural loss in the striatal nuclei has been proved thus far.

Methods: 19 drug-naïve PD patients were enrolled, aged 65.84 ± 7.8 years and with a mean UPDRS-III score of 11.38 ± 4.7. A brain SPECT with [I-123]Ioflupane was performed, and automatic extraction of uptake at caudate and putamen level was conducted through the BasGan software. Within four weeks, a peripheral blood venous sample was obtained for CD4+T lymphocytes assessment. Th1, Th2, Th17, and Treg subsets were quantified using flow cytometry analysis. Expression of transcription factors genes TBX21, STAT1, STAT3, STAT4, STAT6, RORC, GATA3, FOXP3, and NR4A2 was measured by Real-Time PCR.

Results: In the most affected hemisphere an inverse correlation between putaminal uptake and percentage of CD4+ ($r=-0.581$, $p=0.018$) and Treg ($r=-0.560$, $p=0.024$) was found. Total putamen-to-caudate ratio and striatal binding ratio showed respectively a direct correlation with percentage of Th1 ($r=0.576$, $p=0.02$) and an inverse correlation with percentage of CD4+ ($r=-0.682$, $p=0.01$).
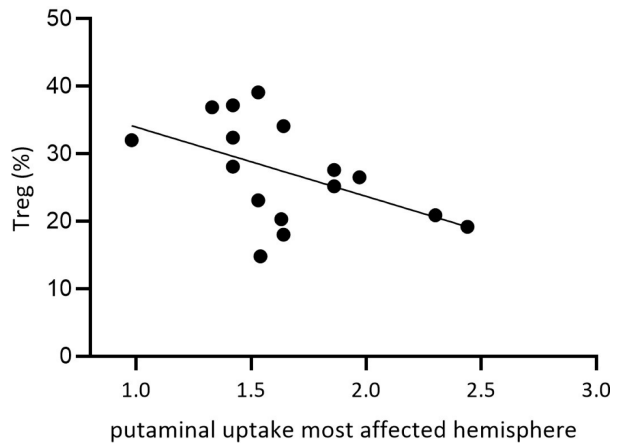
Inverse correlation between putaminal uptake and Treg (%)

Direct correlation between total putamen-to-caudate ratio and Th1 (%)

Conclusion: To our knowledge, this is the first evidence highlighting a possible relationship between CD4+ T cells profile and DaTscan measures. Unbalanced levels of circulating Th1 and Treg subpopulations may be involved in the early stages of PD.

Disclosure: Nothing to disclose.

Miscellaneous: Infectious Diseases and Neuro-oncology

OPR-079

Anti-PD-L1 Treatment for Progressive Multifocal Leukoencephalopathy: Lessons from Two Cases

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Background and aims: Progressive multifocal leukoencephalopathy (PML) is a brain infectious disease caused by JC virus (JCV) in the course of cellular immunodeficiency. There is no effective anti-viral treatment for PML but immune restoration using immune checkpoint inhibitors (ICIs) recently emerged as a therapeutic hope.

Methods: We administrated atezolizumab, an anti-programmed death-ligand 1 antibody, at the dosage of 1,200 milligrams every three weeks to two patients with PML hospitalized at Liège University Hospital (Belgium). Follow-up consisted in weekly physical examination, cerebral magnetic resonance imaging (cMRI) and JCV polymerase chain reaction in the cerebrospinal fluid (CSF) every three weeks.

Results: Characteristics of both patients at baseline are summarized in Tab. 1. Patient 1 showed remarkable clinical improvement following treatment initiation, recovering the ability to walk with assistance and speak simple sentences. CSF JCV load reduced from 17,564 to 1,870 copies/ml (Fig. 1). Lesions visualized with cMRI stopped progressing (Fig. 2). After initial clinical and virological improvement (Fig. 1), patient two developed life-threatening immune reconstitution inflammatory syndrome (IRIS) with brutal clinical deterioration and status epilepticus. She received prolonged high-dose intravenous methylprednisolone resulting first in IRIS resolution but then in slow PML progression.

Fig. 1: Evolution of the JC viral load in the CSF during atezolizumab treatment
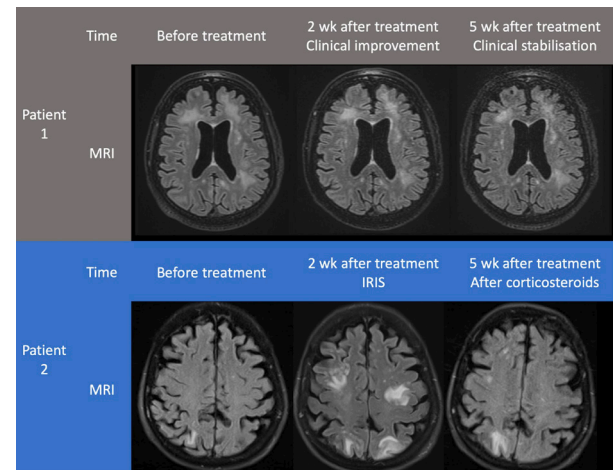
Fig. 2: Evolution of cerebral MRI scans (T2-fluid attenuated inversion recovery-weighted imaging) during atezolizumab treatment. Wk denotes weeks.

Conclusion: Atezolizumab successfully reinvigorated anti-JCV immunity in our two patients. It was also responsible for life-threatening IRIS in one patient. Since corticosteroids impair JCV-specific T-cell response and mitigate beneficial ICIs effects, methylprednisolone probably resulted in treatment resistance. ICI-associated PML-IRIS represents a particularly complex clinical situation during which deleterious consequences of IRIS have to be balanced with potential loss of treatment efficiency due to iatrogenic immunosuppression.

Disclosure: Atezolizumab was supplied by Roche on a compassionate use basis.

Patient	Sex	Age (yo)	Etiology of immune deficiency	CD4+; CD8+; CD19+ counts (number/mm³)	Clinical characteristics	JVC in CSF (copies /ml)
1	Man	66	o Lung adenocarcinoma o Alcoholic liver disease o No previous iatrogenic immunosuppression	140; 210; 100	o Global aphasia; no usable speech o Severe cerebellar ataxia o Right hemiparesis o Bedridden	17,564
2	Woman	77	o B-cell chronic lymphocytic leukemia o Previous treatment with rituximab and chlorambucil	280; 80; 30	o Motor aphasia; fragmentary expression o Cognitive impairment o Cerebellar ataxia o Bedridden	733,845

Tab. 1: Patients characteristics at baseline. M denotes man, W woman, yo year-old, JCV JC virus, CSF cerebrospinal fluid.
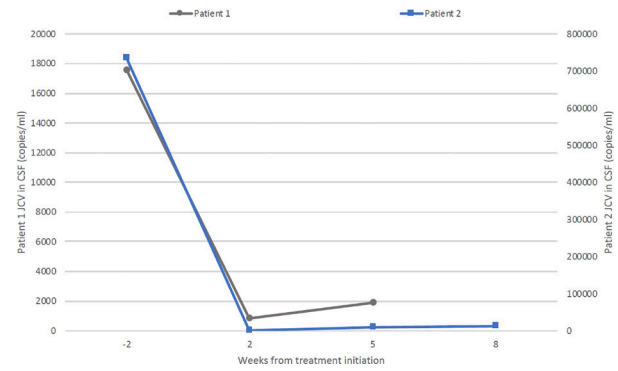
OPR-080

Neurofilament light chain in central nervous system infections: a prospective study of diagnostic accuracy

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Background and aims: Patients with suspected central nervous system (CNS) infections are often a diagnostic challenge. Neurofilament light chain (NfL), a component of the axonal cytoskeleton and an identified marker of neuronal damage, might be of diagnostic relevance for the diagnosis of CNS infections

Methods: We analyzed patients from a prospective cohort in the Netherlands in whom a lumbar puncture was performed for suspected CNS infection. The index test was NfL in CSF and the reference standard the final clinical and/ or confirmed diagnosis.

Results: We included 273 patients, with a median age of 50 years (IQR 35-65) and 52% (n=142) were women. Patients were diagnosed with a CNS infection (26%, n=70), CNS inflammatory disease (7%, n=20), systemic infection without CNS involvement (32%, n=87), non-infectious or -inflammatory neurological disorders (33%, n=90) and other systemic diseases (2%, n=6). The median level of NfL was 593 pg/ml (IQR 249–1,569) and did not discriminate between diagnostic categories or CNS infection subcategories. The AUC for diagnosing a CNS infection was 0.50 (95% CI 0.42–0.59). The AUC for differentiating bacterial meningitis from a viral CNS infection was 0.65 (95% CI 0.50–0.81). Patients presenting with seizures, focal neurological deficits or altered mental status had higher NfL levels compared to other patients. NfL was associated with mortality and unfavorable outcome (odds ratio 1.16 [95% CI 1.08–1.24] and 1.14 [95% CI 1.06–1.22] per 1,000pg/ml).

Conclusion: NfL has no diagnostic value in patients suspected of CNS infections to discriminate between causes. High concentrations of NfL are associated with severe neurological disease and unfavorable outcome.

Disclosure: Nothing to disclose.

OPR-081

Abstract withdrawn

OPR-082

ABTR-SANO Real-World Pattern of Care Study on Glioblastoma in the Austrian Population. Update 2020.

S. Oberndorfer [1], A. Woehrer [2], C. Marosi [3], T. Urbanic-Purkart [4], M. Nowosielski [5], S. Iglseder [5], G. Stockhammer [5], W. Kleindienst [6], M. Stultschnig [7], B. Surböck [2], J. Pichler [8], S. Weiss [9], M. Hutterer [6], A. Hager [10], L. Seebrecht [11], T. Rötzer [11], A. Hainfellner [11], J. Hainfellner [2]
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Background and aims: The Austrian ABTR-SANO Glioblastoma Registry is the first population-based assessment of patterns of care for patients with Glioblastoma across Austrian healthcare institutions. The primary aim is to assess the real world effectiveness of administered therapies.

Methods: Clinical data are collected via a common web-based IT platform "ABTR-SANO Net" since 2014. The database and the ongoing evaluation of clinical parameters, as well as interims analysis are provided in cooperation with a review board.

Results: 11 centers across Austria are involved, which collect the information of now over 1,600 patients (m/f ratio: 1,3 – median age: 66 years). The proportion of patients with cross total resection increased gradually since 2014 from 36% to 56% in 2020. Almost all patients were MGMT testet in 2020, whereas in 2014 only half of patients underwent MGMT testing. Analysis of median time from clinical presentation to diagnostic scan (overall: nine days), time from diagnostic scan to surgery (overall: 10 days), and time from surgery to the beginning of first line treatment (overall: 31 days) was stable throughout the years. First overall survival data show a median survival of Austrian Glioblastoma patients of 12 months.

Conclusion: One defined set of clinical parameters results in excellent phenotypic annotation of the patient cohort from 2014 ongoing. Pattern of care characteristics show a different picture with respect to treatment, as we used to see in RCT. The first outcome analysis comparing different Austrian centers is available since 2020.

Disclosure: The project is funded by the Austrian Society of Neurology (ÖGN), ROCHE © and AbbVie©.

Multiple Sclerosis: Clinical studies

OPR-083

Safety of Ocrelizumab in Patients With RRMS With Suboptimal Response to Prior DMTs: Data From the CASTING Study

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Background and aims: Patients with relapsing-remitting multiple sclerosis (RRMS) often experience disease activity despite receiving a disease-modifying therapy (DMT). The Phase IIIb CASTING study (NCT02861014) evaluated the efficacy and safety of ocrelizumab in patients with RRMS who had a suboptimal response to ≥6 months' treatment with one or two prior DMTs. Here we evaluate CASTING 2-year safety outcomes by subgroups, including age and prior DMT.

Methods: Patients (n=680; Expanded Disability Status Scale score ≤4.0; discontinued prior DMT due to suboptimal response) received intravenous ocrelizumab 600mg every 24 weeks for 96 weeks. Safety outcomes included adverse events (AEs), serious AEs (SAEs), AEs ≥Grade 3, discontinuations for AEs, infections, serious infections (SIs), and lymphocyte count.

Results: Safety outcomes were comparable between subgroups by age or prior DMT (Tab. 1, 2). No haematological abnormalities were seen in patients treated with ocrelizumab, regardless of previous DMTs or age. A single death occurred in the study; this was suicide (not related) and occurred in a patient who had one prior DMT (teriflunomide), aged >40 years.

Conclusion: The safety profile was comparable between subgroups, including age and number/type of prior DMTs. No new safety signals were identified.

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

Table 1.

	One prior DMT (n=411)	Two prior DMTs (n=269)	Age <=40 years (n=511)	Age >40 years (n=169)
Percentage of patients with event				
AEs	89.3%	88.8%	88.8%	89.9%
SAEs	7.5%	6.7%	7.4%	6.5%
Infections	67.6%	65.8%	66.3%	68.6%
SIs	1.9%	1.1%	1.8%	1.2%
Discontinuations for AEs	1.2%	0.7%	1.4%	0
AEs >=Grade 3	11.9%	11.9%	11.4%	13.6%
Lymphocytes (x10⁹/L), median (range) at Week 96	1.60 (0.39–3.60)	1.57 (0.69–3.51)	1.60 (0.69–3.60)	1.50 (0.39–3.07)

Tab. 1

Table 2.

	Last DMT				
	Interferons (n=198)	Glatiramer acetate (n=116)	Dimethyl fumarate (n=168)	Teriflunomide (n=65)	Fingolimod (n=129)
Percentage of patients with event					
AEs	87.4%	89.7%	91.7%	92.3%	86.0%
SAEs	8.1%	9.5%	3.6%	12.3%	6.2%
Infections	66.2%	68.1%	69.0%	67.7%	62.8%
SIs	2.0%	0.9%	1.8%	3.1%	0.8%
Discontinuations for AEs	1.0%	1.7%	1.2%	1.5%	0
AEs >=Grade 3	11.6%	11.2%	11.9%	18.5%	10.1%
Lymphocytes (x10⁹/L), median (range) at Week 96	1.64 (0.39–3.30)	1.63 (0.70–3.60)	1.58 (0.70–2.97)	1.71 (0.80–3.51)	1.34 (0.69–3.60)

Tab. 2

OPR-084

Determination of a clinically effective evobrutinib dose: exposure-response analyses of a phase II MS study

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Background and aims: The pharmacometric analysis of this double-blind, randomised, phase II trial (NCT02975349) investigating the safety and efficacy of evobrutinib, explored exposure-response relationships and suitable dosing regimens of evobrutinib, a highly selective Bruton's tyrosine kinase (BTK) inhibitor, for relapsing multiple sclerosis.

Methods: Population pharmacokinetic (PK)/pharmacodynamic (PD) modelling was performed on data from fasted patients treated with placebo or evobrutinib (25mg once daily (QD), 75mg QD, or 75mg twice daily (BID)) for 24 weeks (W), followed by a 24W blinded extension (placebo patients switched to evobrutinib 25mg QD). Model-based exposures for PK and BTK occupancy (BTKO) were used for cross-sectional exposure-response analyses (maximum n=207). Alternative dosing regimens were simulated.

Results: Exposure-response modelling indicated a relationship between evobrutinib exposure and clinical response for total T1 Gd+ and new/enlarging T2 lesions at W12 to 24, and annualized relapse rate (ARR) at W48. A steady state (SS) area under the curve over 24 hr of 468 and 400ng/mL*hr or higher appeared to be associated with lesion reduction and ARR improvement, respectively. These exposures were associated with SS predose BTKO of 95%. Based on PK and BTKO profile simulations, evobrutinib 75mg BID without food is predicted to maintain predose BTKO at SS of >95% in 92% of patients. Evobrutinib 45mg BID with food is predicted to achieve similar exposure as 75mg BID without food and provide predose BTKO of >95% in 93% of patients.

Conclusion: An evobrutinib dose of 45mg BID with food will be pharmacologically effective and is appropriate for clinical use in phase III multiple sclerosis trials.

Disclosure: This research was funded by Merck KGaA, Darmstadt, Germany.

OPR-085

Effect of Ocrelizumab on Cerebellar Atrophy in RMS and PPMS: Results from OPERA I/OPERA II and ORATORIO

D. Arnold [1], H. Assemlal [2], A. Traboulsee [3], S. Kolind [3], T. Sprenger [4], A. Bar-Or [5], J. Wolinsky [6], L. Kappos [7], M. Inglese [8], H. Schneble [9], S. Magon [9], H. Koendgen [9], C. Bernasconi [9], L. Gaetano [9]
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Background and aims: In multiple sclerosis (MS), the cerebellum is affected by lesions and secondary degeneration of connections with supratentorial brain and spinal cord. However, temporal cerebellar atrophy dynamics and treatment impact remain unclear. The aim is to assess ocrelizumab (OCR) effect versus interferon beta-1a (IFN)/placebo (PBO) on cerebellar atrophy in relapsing MS (RMS)/primary progressive MS (PPMS), in the phase III OPERA (NCT01247324/NCT01412333) and ORATORIO (NCT01194570) trials, respectively.

Methods: During the double-blind and open-label extension (OLE, all patients on OCR) periods of OPERA and ORATORIO, changes in cerebellar volume from baseline were computed using Jacobian integration and analysed using a mixed-effect repeated measurement model, adjusted for baseline volume, age, region (US vs rest of the world), Expanded Disability Status Scale category (<4, >=4), week, treatment, treatment-by-time interaction, treatment-by-baseline-volume interaction, gadolinium-enhancing lesions (presence/absence) and T2 lesion volume.

Results: In OPERA, changes in cerebellar volume (%) at Weeks 24, 48, 96, OLE Weeks 46, 94, 142, 190 and 238 were: -0.42/-0.27 ($p<0.001$), -0.58/-0.46 (p=0.007), -0.92/-0.63 ($p<0.001$), -1.08/-0.81 ($p<0.001$), -1.32/-1.02 ($p<0.001$), -1.48/-1.21 ($p<0.001$), -1.61/-1.34 (p=0.004) and -1.83/-1.63 (p=0.05) for IFN/OCR patients, respectively. In ORATORIO, changes (%) in cerebellar volume at Week 24, 48, 120, OLE Day 1, Week 48, 96, and 144 were: -0.24/-0.12 (p=0.042), -0.33/-0.29 (p=0.493), -0.83/-0.72 (p=0.207), -1.23/-1.06 (p=0.150), -1.58/-1.23 (p=0.010), -1.82/-1.53 (p=0.064) and -2.12/-1.77 (p=0.043) for PBO/OCR patients, respectively.

Conclusion: Compared with IFN, ocrelizumab reduced cerebellar atrophy in RMS. During the OLE, patients initially randomized to ocrelizumab maintained lower cerebellar volume loss relative to baseline in both RMS and PPMS.

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

OPR-086

Ublituximab versus teriflunomide in relapsing multiple sclerosis (RMS): Results of the Phase 3 ULTIMATE I and II trials

L. Steinman [1], E. Fox [2], H. Hartung [3], E. Alvarez [4], P. Qian [5], S. Wray [6], D. Robertson [7], D. Huang [8], K. Selmay [9], D. Wynn [10], M. Weiss [11], J. Bosco [11], S. Power [11], K. Mok [11], B. Cree [12]

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Background and aims: Ublituximab (UTX) is a novel monoclonal antibody targeting a unique epitope on the CD20 antigen and is glycoengineered for enhanced B-cell depletion through antibody-dependent cellular cytotoxicity (ADCC). The increased ADCC may offer benefit over available anti-CD20 agents in terms of lower doses and shorter infusion times.

Methods: Patients were randomized (1:1) to receive either 450mg UTX via a one-hour intravenous infusion every 24 weeks (following day one infusion of 150mg) or 14mg oral teriflunomide once-daily, throughout a 96-week treatment period. Eligible patients had diagnosis of RMS (McDonald Criteria 2010), Expanded Disability Status Scale (EDSS) score of 0–5.5, and age of 18–55 years. The primary endpoint was annualized relapse rate (ARR). Key secondary endpoints include MRI, no evidence of disease activity (NEDA), confirmed disability progression and safety/tolerability

Results: Overall, 1,094 patients were randomized in 10 countries (ULTIMATE I, N=549; ULTIMATE II, N=545). Both studies met their primary endpoint of significantly reduced ARR ($p<0.005$ in each study) with UTX demonstrating an ARR of <0.10 in each of the studies. Reductions of approximately 60% and 50% in ARR over teriflunomide were observed in ULTIMATE I & II, respectively.

Conclusion: ULTIMATE I&II significantly reduced ARR ($p<0.005$ in each study) with UTX demorating an ARR of <0.10 in each of the studies, utilizing a one-hour 450mg ublituximab infusion every six months after the first cycle infusions in RMS. Additional efficacy/safety results will be presented at the meeting.

Disclosure: Authors have received compensation from Pharma companies for speaking, consulting and contracted research.

OPR-087

GFAP as a Marker of Disease in Relapsing Multiple Sclerosis: Post Hoc Analysis of the Phase 3 Ozanimod SUNBEAM Trial

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Background and aims: Glial fibrillary acidic protein (GFAP), an intermediate filament expressed by astrocytes, is involved in central nervous system (CNS) cell communication and blood-brain barrier function. GFAP may be a biomarker in various CNS conditions, including multiple sclerosis. This post hoc analysis explored relationships between baseline plasma GFAP concentration and patient and disease characteristics in the SUNBEAM trial (NCT02294058) of ozanimod in relapsing multiple sclerosis (RMS).

Methods: This randomised, double-blind trial compared oral ozanimod 0.92 or 0.46 mg/day with intramuscular interferon beta-1a 30 µg/week for 12 months in adults with RMS. GFAP was measured using Simoa® GFAP Assay (Quanterix, Billerica, MA). Using regression analysis, we investigated relationships between baseline GFAP and demographic and disease characteristics at baseline and month 12.

Results: Of 1,346 participants randomised, 1,117 had baseline GFAP assessments (median 113.03pg/mL). Men had lower baseline GFAP concentration than women ($R2=1.5\%$ for GFAP relationship with sex; $p=0.0002$). GFAP and age had a U-shaped relationship ($r2=1.3\%$; $p=0.0018$). GFAP related positively to plasma neurofilament light chain (NfL) concentration ($r2=19.8\%$) and inversely to body mass index (BMI) ($R2=5.5\%$; both $p<0.0001$). Baseline GFAP was unrelated to pretreatment relapse but higher in those with more relapses through month 12 ($r2=5.7\%$; $p<0.0001$). Baseline GFAP positively related to T2 and gadolinium-enhancing lesion counts and inversely related to whole brain volume (WBV) at baseline ($R2=4.7\%9.2\%$) and month 12 ($R2=5.0\%8.5\%$) (all $P<0.0001$).

Conclusion: We found significant but weak relationships between baseline GFAP and sex; age, BMI, and NfL concentration at baseline; lesion counts and WBV at baseline and on treatment; and on-treatment relapse.

Disclosure: This study was supported by Bristol Myers Squibb, Princeton, NJ.

OPR-088

Whole Brain, Cortical Grey Matter, and Thalamic Volume Changes During 3 to five Years of Ozanimod in Relapsing MS

<u>D. Arnold</u> [1], J. Sheffield [2], X. Montalban [3], B. Cree [4], L. Kappos [5], G. Comi [6], H. Hartung [7], H. Liu [8], C. Pachai [9], D. Silva [10], J. Cohen [11]

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Background and aims: Ozanimod reduced whole brain volume (WBV), cortical grey matter volume (CGMV), and thalamic volume (TV) loss vs interferon beta-1a (IFN) in phase 3 SUNBEAM (NCT02294058) and RADIANCE (NCT02047734) trials. We evaluated brain volume loss among SUNBEAM/RADIANCE participants who entered an ongoing extension trial (DAYBREAK, NCT02576717).
Methods: The two randomised, double-blind trials compared oral ozanimod 0.92 and 0.46mg/day with intramuscular IFN 30 µg/week in adults with relapsing MS. Completers were eligible to receive open-label ozanimod 0.92mg/day in DAYBREAK. MRI was performed at months six (SUNBEAM), 12 (SUNBEAM/RADIANCE), and 24 (RADIANCE), then every 12 months (DAYBREAK). Baseline WBV and CGMV were measured using SienaX, and TV using ThalamicVolume software; percentage change in WBV, CGMV, and TV was quantified using Jacobian integration. Data are reported through DAYBREAK month 36.
Results: DAYBREAK includes 2257 SUNBEAM/ RADIANCE participants. Loss of WBV (Fig 1A), CGMV (Fig 1B), and TV (Fig 1C) was less on ozanimod than IFN and remained less after switching from IFN to ozanimod, especially for WBV (Fig 1A) and TV (Fig 1C). CGMV was lost to a much greater extent while on IFN, and recovered substantially, but not completely, upon switching to ozanimod (Fig 1B).
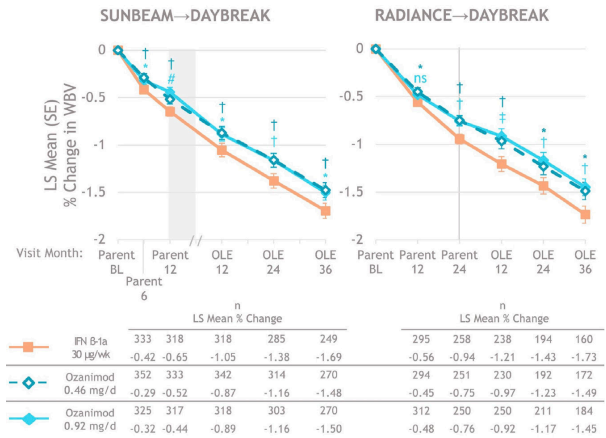
Figure 1. Mean (SE) Percentage Change From Baseline in (A) Whole Brain Volume, (B) Cortical Grey Matter Volume, and (C) Thalamic Volume; (A) WBV
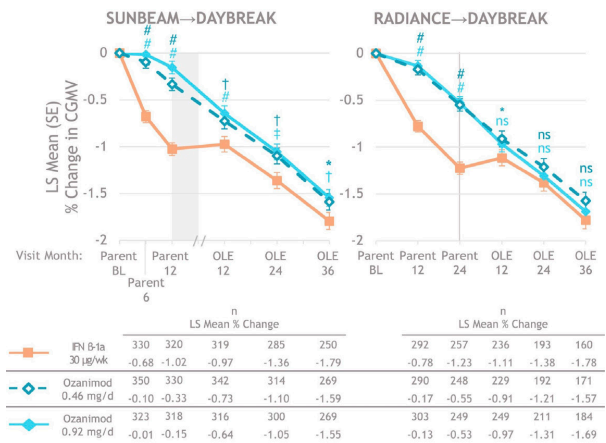
Figure 1 (B) CGMV
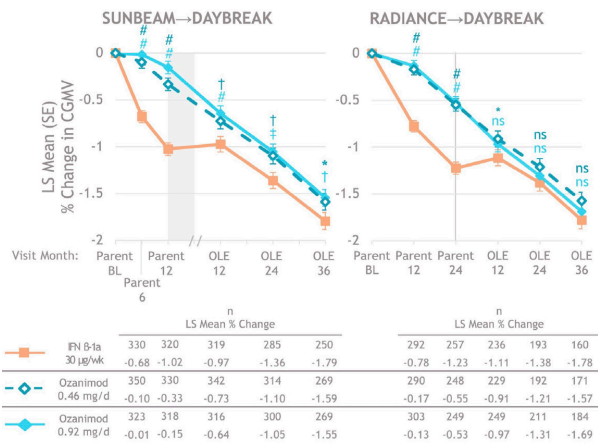
Figure 1 (C) TV

Conclusion: Switching from IFN to ozanimod reduced the rate of WBV, CGMV, and TV loss. Global and regional brain volume loss after 4–5 years of follow-up remained higher in participants who started on IFN than in continuous ozanimod users. These results support early treatment with ozanimod.

Disclosure: This study was supported by Bristol Myers Squibb, Princeton, NJ.

Sunday, June 20 2021

Movement Disorders: Biomarkers and Experimental

OPR-072

Functional connectivity as an early marker of indication for deep brain stimulation treatment in Parkinson's disease

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Background and aims: To identify early neuroimaging biomarkers for deep brain stimulation (DBS) in patients with Parkinson's disease (PD).

Methods: A cohort of PD patients prospectively recruited underwent clinical and cognitive evaluations and resting-state functional MRI (RS-fMRI) at baseline and every year for a maximum of four years. Patients were divided into two groups: 19 patients eligible for DBS (PD-DBS) over the 48-month follow-up and 41 patients who did not meet the criteria to undergo DBS surgery (PD-noDBS). Sixty age- and sex-matched controls performed baseline assessments. Graph analysis and connectomics assessed global and local topological network properties and regional functional connectivity (FC) at baseline and at time intervals.

Results: Lobar network analysis showed a significantly higher mean nodal strength, local efficiency and clustering coefficient of the occipital areas in PD-DBS relative to both controls and PD-noDBS at baseline. These results were then confirmed by regional analysis. A significantly decreased FC between sensorimotor/frontal and basal ganglia networks was found in PD-DBS compared to PD-noDBS patients at baseline. Referring to longitudinal analysis, PD-DBS patients showed a progressive decreased FC within occipital networks compared to PD-noDBS (stable over time). Progressively, increased FC between sensorimotor/frontal and basal ganglia networks occurred in PD-DBS compared to PD-noDBS (stable over time). At correlation analysis, FC within the occipital network were positively related to tremor in PD-DBS patients at baseline and over time.

Conclusion: RS-fMRI analysis might represent an early biomarker to help clinicians to establish the indication for DBS in PD patients.

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

OPR-074

### New Investigational DBS Lead and Burr Hole Device Improves Stability in Sheep Model

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Background and aims: A market-released DBS lead and burr hole device (BHD, together the "control" system) has traditionally stabilized DBS leads with ring electrodes. Since newer segmented electrodes cluster at the center of the array and offer more programmability, improved chronic stability may ensure segmented electrodes remain near the stimulation target. A sheep study with a new DBS system ("investigational" and not commercially approved) tested the hypothesis that design changes improved lead stability compared to control.

Methods: 17 sheep were implanted contralaterally with control and investigational DBS systems. Implant and termination CT scans were segmented, processed, and registered. Distal electrode displacements were measured to assess chronic lead migration. A one-way analysis of variance assessed stability differences between the two systems and a line plot illustrated lead migration differences.

Results: Implant durations were 13.4±2.1 (SD) weeks. DBS lead tip displacements were 2.2±1.3mm for the control system and 1.0±0.5mm for the investigational system (p=0.002). As own in the line plot, a majority of leads experienced large differences in tip displacement while several differences were slight, suggesting that lead stability differences in some animals were too small to be reliably measured with CT scans.
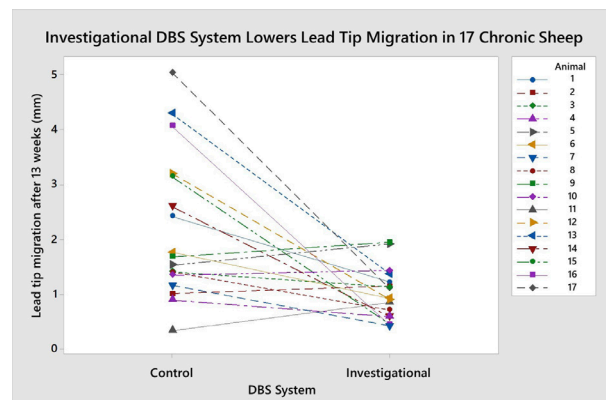
Conclusion: The investigational DBS system demonstrated a statistically significant 55% improvement in chronic lead tip stability compared to the control DBS system in 17 sheep. These results suggest that design changes incorporated into the investigational DBS system can further stabilize the lead tip, potentially leading to better programmability and therapy optimization.

Disclosure: Walt Baxter, Ph.D.: Medtronic PLC: salary/employee/shareholder, Kelly Salb, M.S.: Medtronic PLC: salary/employee/shareholder.

OPR-076

Competing endogenous RNA networks and circular RNAs in peripheral blood cells of patients with Parkinson's disease

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Background and aims: New noninvasive and affordable molecular approaches that will complement current practices and increase the accuracy of PD diagnosis are urgently needed. CircRNAs are highly stable non-coding RNAs that accumulate with aging in neurons and are increasingly shown to regulate all aspects of neuronal development and function.he aims of the present study were to identify differentially expressed circular RNAs in peripheral blood mononuclear cells (PBMCs) of idiopathic PD patients and explore the competing endogenous RNA networks affected.

Methods: 87 circRNAs were initially selected based on relatively high gene expression in the human brain. Over half of these were readily detectable in PBMCsusing RT-qPCR. Comparative expression analysis was then performed in PBMCs from sixty controls and 60 idiopathic subjects with PD.

Results: Six circRNAs derived from MAPK9, HOMER1, SLAIN1, DOP1B, REPS1, and PSEN1 transcripts were significantly downregulated in PD patients. The classifier that best distinguished PD consisted of four circRNAs with an AUC of 0.84. Cross-linking immunoprecipitation-sequencing data revealed that the RNA-binding proteins bound by most of the deregulated circular RNAs include the neurodegeneration-associated FUS, TDP43, FMR1 and ATXN2. MicroRNAs predicted to be sequestered by most deregulated circular RNAs have the gene ontology categories 'protein modification' and 'transcription factor activity' mostly enriched.

Conclusion: This is the first study that identifies specific circular RNAs that may serve as diagnostic biomarkers for PD. Since they are highly expressed in the brain and are derived from genes with essential brain functions, they may also hint on the PD pathways affected.

Disclosure: Nothing to disclose.

OPR-090

The in-vivo diagnosis of synucleinopathies: a comparative study of skin biopsy and RT-QuIC

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Background and aims: The in-vivo diagnosis of synucleinopathies is particularly challenging. The aim of this study is to determine whether: 1) the immunofluorescence (IF) is a reproducible technique in detecting misfolded -synuclein (-syn) in skin nerves; and subsequently 2) IF and RT-QuIC (both in skin and CSF) show a comparable in-vivo diagnostic accuracy in distinguish synucleinopathies (SOPs) from non-synucleinopathies (non-SOPs) in a large cohort of patients

Methods: We prospectively recruited 90 patients fulfilling clinical and instrumental diagnostic criteria for all SOPs variants and non-SOPs (mainly including Alzheimer´s disease, tauopathies, and vascular parkinsonism or dementia). 24 patients with mainly peripheral neuropathies were used as controls. Patients underwent skin biopsy for IF and RT-QuIC whereas CSF was performed in patients who underwent lumbar puncture for diagnostic purposes. IF and RT-QuIC analysis were made blinded to the clinical diagnosis

Results: IF showed reproducible results between two pairs of neighbouring skin samples. Furthermore, both IF and RT-QuIC showed high sensitivity and specificity in discriminating SOPs from non-SOPs and controls but IF presented the highest diagnostic accuracy. IF presented a good level of agreement with RT-QuIC both skin and CSF in SOPs

Conclusion: 1) Both IF and RT-QuIC showed a high diagnostic accuracy although IF displayed the better value as well as an optimal reproducibility; 2) they presented a good level of agreement in SOPs supporting the use of a less invasive tests such as skin IF or RT-QuIC instead of CSF RT-QuIC as diagnostic tool for synucleinopathies

Disclosure: Nothing to disclose.

OPR-091

Optical coherence tomography: a potential biomarker of neurodegeneration in patients with Wilson's disease?

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Background and aims: WIlson's disease (WD) is an autosomal recessive disorder that leads to copper accumulation and deposition in different organs, frequently affecting visual pathways. Recent studies have detected morphological changes of retina in patients with WD using optical coherence tomography (OCT). The aim of this study was to evaluate the relationship between OCT parameters and form of the disease, therapy and symptoms duration, as well as severity of neurological impairment.

Methods: Study comprised 52 patients with WD and 52 healthy controls (HC). All the patients were on regular and stable chelation therapy and/or zinc salts. According to the main affected system, patients were divided in two groups, with neurological (NWD) or hepatic form of the disease (HWD). OCT was performed to assess the thickness of the RNFL (RNFLT).

Results: The intraocular pressure and the RNFLT were significantly lower in patients with WD when compared to HC. There were no differences between NWD and HWD in any of the ophthalmologically tested parameters. No significant correlations were found between clinical features and parameters of retinal thickness. The stratification of the cohort according to the disease duration showed that disease duration does not influence RFNL thickness.
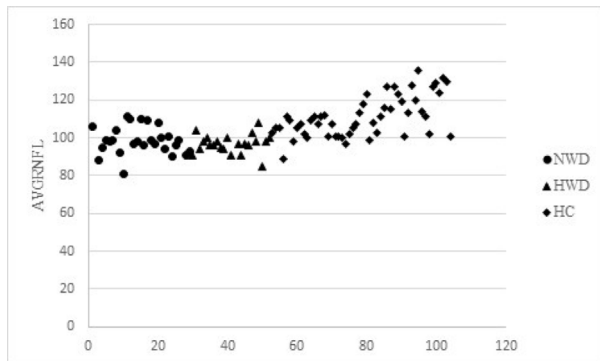
Figure 1. Values of average RNFL thickness in the superior and inferior segments in NWD and HWD patients and healthy control subjects
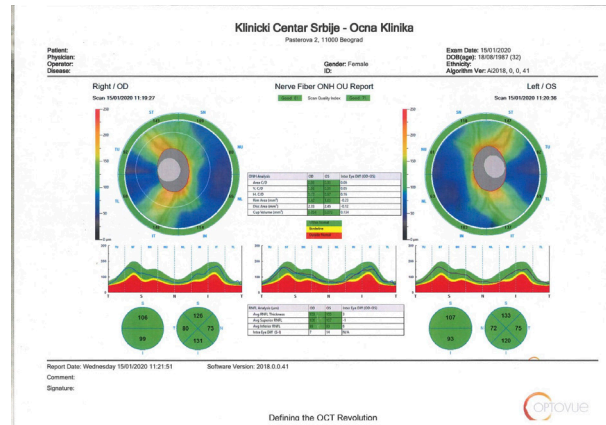
Figure 2: MS, right and left eye OCT, 32yrs, hepatic form

Conclusion: We found that involvement of retina represented subclinical finding in neurologically intact patients in HWD group. The value of the OCT as a biomarker for assessing clinical course and progression of WD still stays uncertain.

Disclosure: Nothing to disclose.

OPR-094

Characterising the role of alpha-synuclein in Ferroptosis in the context of Parkinson's disease

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Background and aims: Iron accumulation and intracellular inclusion of aggregated alpha synuclein (a-syn) are two main hallmarks in Parkinson's disease (PD). Iron deposition in the brain tightly correlates with a-syn deposition in the dorsal substantia nigra and cortex. Despite the involvement of alpha synuclein (a-syn) in Parkinson's disease (PD) pathology, the exact function of this protein and the mechanisms involved in the neuropathology remain unclear. Recently, we have shown that a novel regulated cell death pathway termed ferroptosis is predominant in pro-oxidant models of PD. Here we aim to demonstrate a pivotal interplay between a-syn, iron metabolism and ferroptosis in PD.

Methods: Via CRISPR/Cas 9 we have modulated endogenous a-syn and created stable human dopaminergic neuronal cell lines. Cell death in response to two different ferroptosis inducers was measured by resazurin assay. Levels of lipid peroxidation were equally assessed with C11-BODIPY by flow cytomery

Results: We observed that the absence of wild type a-syn conferred a protection against two ferroptosis inducers-Erastin and RSL3. This difference in cell viability was specific to ferroptosis since no difference was observed when inducing apoptosis or autophagic cell death. Levels of lipid peroxidation in response to Erastin or RSL3 were significantly less in the dopaminergic neurons lacking wild type asyn.

Conclusion: For several years, anti-apoptotic drugs have failed to afford any improvement in neuroprotection. For the first time, ferroptosis could represent the missing part to the puzzle in explaining the vicious circle between synucleinopathy, iron accumulation and subsequent cell death in Parkinson's disease.

Disclosure: The authors have nothing to declare.

Autonomic Nervous System Disorders

OPR-095

Heart-rate variability measured with wearable sensors is associated with disability status in multiple sclerosis

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Background and aims: New developments in sensor technology in recent years, facilitate novel approaches to assess neurological symptoms outside the clinic. Autonomic dysfunction is common in patients with multiple sclerosis (pwMS), but its role in the disease and its association with neurologic impairment is poorly understood. Therefore, we aim to assess the feasibility of studying heart rate variability (HRV), as a measure of autonomic dysfunction using wearable sensors and to correlate it with clinical measures of disease activity.

Methods: We studied 29 people with multiple sclerosis over the course of two weeks. Participants were continuously monitored with a wearable sensor. The data were subsequently cleaned and common HRV metrics were calculated and compared to the COMPASS-31 questionnaire.

Results: Of the calculated metrics most show a significant correlation with the COMPASS-31 and the EDSS. We compared the classification of the COMPASS-31 across the day. The best results are produced in the early morning hours by the normalized HF (AUC 0.84, CI: 0.69 to 0.99), normalized LF (AUC 0.84, CI: 0.69 to 0.99), pnn50 (AUC 0.78, CI: 0.61 to 0.95) and RMSSD (AUC 0.77, CI: 0.59 to 0.95).

Conclusion: Using a wearable to calculate HRV is feasible, reliable and poses a distinct advantage over standard ECG based methods. Our data suggests that early morning hours are the best time window to quantify autonomic dysfunction, when using a continuous measurement with a wearable sensor. Wearable sensors are a useful tool to assess and follow longitudinal changes in pwMS to study the impact of autonomic dysfunction in the disease.

Disclosure: No disclosures.

OPR-096

Cardiovascular autonomic neuropathy in type 2 diabetic patients

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Background and aims: Cardiovascular autonomic neuropathy is a common complication in type 2 diabetes mellitus (DM2) and is typically evaluated with measures of parasympathetic nerve fibre function. Few studies have assessed the sympathetic branch of the autonomic nervous system. Sympathetic neuropathy is associated with increased morbidity and mortality, and identification hereof is therefore imperative as conservative and/or pharmacological treatments are available. This study assessed sympathetic function in DM2 patients through standardized quantitative clinical testing.

Methods: 40 DM2 patients and 40 age- and gender-matched healthy controls (HC) were examined using Ewings autonomic test-battery, 24-hour blood pressure (24h-BP) profiling and self-reported COMPASS 31-questionaires.

Results: DM2 patients showed reduced parasympathetic activity with reduced inspiratory:expiratory-ratio (median [IQR] in DM2 1.11 [1.08-1–18] vs HC 1.18 [1.11–1.25] (p=0.01)) for deep breathing, and reduced heart rate variability measures in the time domain (p<0.05). No difference in cardiovascular sympathetic markers measured through the Valsalva manoeuvre was found (p>0.05) despite DM2 reporting more symptoms in the orthostatic domain of COMPASS-31 (p=0.04). 24h-BP showed reduced night-time systolic BP drop in DM2 (9.77%±8.84 vs. HC 15.72%±7.77 (p<0.01)) with an increased proportion of patients showing reverse dipping (9 DM2 vs. 1 HC p=0.03).

Conclusion: DM2 patients showed reduced parasympathetic activity, which is a known complication in DM2. No difference was found in short-term regulatory sympathetic markers, suggesting preserved cardiovascular sympathetic function. DM2 patients had altered circadian BP regulation, and reported more symptoms of orthostatic intolerance, indicating COMPASS-31 reported orthostatic intolerance and circadian BP regulation may not be sensitive markers of cardiovascular sympathetic neuronal dysfunction.

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OPR-097

Orthostatic muscle excitability changes in neuropathic postural tachycardia syndrome

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Background and aims: The postural tachycardia syndrome (POTS) is a form of dysautonomia, characterized by chronic symptoms of orthostatic intolerance. 56–69% of patients report pain and muscle weakness in the lower extremities when upright, which is often accompanied by acrocyanosis. Muscle velocity recovery cycles (MVRCs) of muscle action potentials can be used to assess changes of muscle membrane potential. The present study examined muscle properties depending on body position in patients with neuropathic POTS and healthy controls.

Methods: In 10 patients and 10 control subjects repeated MVRCs of the left tibialis anterior muscle were recorded in the supine position and during 10 minutes of head-up tilt (HUT). Outcome measures included early supernormality, late supernormality and relative refractory period. Additionally, circumferences of the lower leg and experienced pain levels were assessed.

Results: Measurements of early supernormality and relative refractory period showed hyperpolarized muscle fibres in patients in the supine position, which depolarized faster during HUT compared to control subjects. Late supernormality revealed no significant changes. In parallel, the leg circumference increased during HUT significantly in patients only. Pain ratings were significantly higher in patients after five and 10 minutes of HUT.

Conclusion: The present results indicate postural changes in muscle membrane properties in patients with POTS. These alterations may be a consequence of inadequate perfusion of the muscles due to excessive pooling in the lower extremities.

Disclosure: The present study did not receive any funding and there are no conflicts of interest.

OPR-098

Compromised cardiovascular autonomic modulation in patient with acute ischemic stroke improves after three & six months

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Background and aims: Previous studies showed that patients with ischemic stroke have impaired cardiovascular autonomic modulation (CAM) with reduced parasympathetic and augmented sympathetic modulation. It is unclear whether CAM improves after several months. Therefore, we compared CAM of ischemic stroke patients in the acute phase, and three and six months after stroke.

Methods: In 82 ischemic stroke patients [33 women, 64.88 ± 8.87 years], we recorded RR-intervals (RRI), systolic, diastolic blood-pressure (BPsys, BPdia), and respiration (RESP) at rest, during the first week, three and six months after stroke-onset. We calculated parameters reflecting total CAM [RRI-standard-deviation (RRI-SD), RRI-total-powers], sympathetic [RRI-low-frequency-powers (RRI-LF), BPsys-LF-powers] and parasympathetic CAM [Root-Mean-Square-of-Successive-RRI-Differences (RMSSD), RRI high-frequency powers (RRI-HF-powers)], and baroreflex-sensitivity (BRS). Patient-data were compared to data of 30 age-matched controls using repeated measurements of ANOVA Friedman-test with post-hoc analyses ($p<0.05$).

Results: In the first week, values of RRI, RRI-SD, RRI-total-powers, RRI-HF-powers, and BRS were significantly lower while BPsys-LF-powers were significantly higher in patients than controls. After three and six months, patients had significantly higher values of RRI, RRI-SD, RRI-total-powers, RMSSD, RRI-HF-powers, and BRS but lower values of BPsys-LF-powers than in the first week; RMSSDs and RRI-HF-powers no longer differed between patients and controls. However, after six months, RRIs, RRI-SD, and BRS were still lower in patients than controls.

Conclusion: In our patients, acute ischemic stroke caused cardiovascular autonomic dysregulation with decreased cardiovagal modulation and baroreflex sensitivity but increased sympathetic modulation. After three and six months, the initial autonomic impairment recovered but still showed minor autonomic imbalance with higher heart rates and lower baroreflex sensitivity.

Disclosure: The authors declare that there is nothing to disclose related to the study.

Child Neurology

OPR-099

Age at disease onset influences gray matter and white matter integrity in multiple sclerosis

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Background and aims: To investigate whether age at onset influences brain gray matter volume (GMV) and white matter (WM) microstructural abnormalities in adult multiple sclerosis (MS) patients, given its influence on clinical phenotype and disease course.

Methods: This hypothesis-driven cross-sectional study included 67 pediatric-onset MS (POMS) patients and 143 sex- and disease duration (DD)-matched randomly-selected adult-onset MS (AOMS) patients, together with 208 healthy controls. All subjects underwent neurological evaluation and 3T MRI acquisition. MRI variables were standardized based on healthy controls, to remove effects of age and sex. Associations with DD in POMS and AOMS patients were studied with linear models. Time to reach clinical and MRI milestones was assessed with product-limit approach.

Results: At DD=1 year, GMV and WM fractional anisotropy (FA) were abnormal in AOMS but not in POMS patients. Significant interaction of age at onset (POMS vs AOMS) into the association with DD was found for GMV and WM FA. The crossing point of regression lines in POMS and AOMS patients was at 19 years of DD for GMV and 15 for WM FA. For POMS and AOMS patients, median DD was 29 and 19 years to reach Expanded Disability Status Scale=3 ($p<0.001$), 31 and 26 years to reach abnormal Paced Auditory Serial Addition Task-3 ($p=0.01$), 24 and 19 years to reach abnormal GMV ($p=0.04$), and 19 and 17 years to reach abnormal WM FA ($p=0.31$).

Conclusion: Younger patients are initially resilient to MS-related damage. Then, compensatory mechanisms start failing with loss of WM integrity, followed by GM atrophy and finally disability.

OPR-100

Outcomes in 51 patients with cerebral ALD from two studies of elivaldogene autotemcel (eli-cel; Lenti-D) gene therapy

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Background and aims: Elivaldogene autotemcel (eli-cel; Lenti-D) gene therapy is being investigated in patients with cerebral adrenoleukodystrophy (CALD) in two open-label studies: ALD-102 and ALD-104.

Methods: Post-myeloablation, boys with CALD (≤17 years) received eli-cel (autologous CD34+ cells transduced with Lenti-D lentiviral vector encoding ABCD1 cDNA). After initial 2-year follow-up in ALD-102/ALD-104, monitoring will continue for 13 years in LTF-304. Data are median (minmax) as of October 2020 (ALD-102/ALD-104) and November 2020 (LTF-304).

Results: In ALD-102/LTF-304 (N=32), follow-up was 38.6 (13.4–82.7) months. The primary endpoint of major functional disabilities (MFDs)-free survival at Month 24 was met in 27/30 (90%) evaluable patients; two withdrew and one died after rapid disease progression. Of 28 patients still in ALD-102/LTF-304, none had MFDs through follow-up. Figure 1 shows neurologic function scores and Loes scores over time. At last visit, gadolinium enhancement resolved in 25/28 patients. Given limited follow-up in ALD-104 (N=19), only safety data as of 8.6 (0.1–16.8) months

are included. The safety/tolerability profile of treatment regimen in both studies primarily reflected known effects of mobilization/aphaeresis and myeloablation. Eli-cel-related adverse events included BK viral cystitis (n=1, SAE) and vomiting (n=2) in ALD-102, and pancytopenia (n=2, SAEs) in ALD-104. One ALD-104 patient experienced a transverse myelitis SAE (aetiology unknown), with ongoing ambulation issues and incontinence post-steroids/plasmapheresis. There was no graft failure, graft-versus-host disease, replication-competent lentivirus, or insertional oncogenesis.
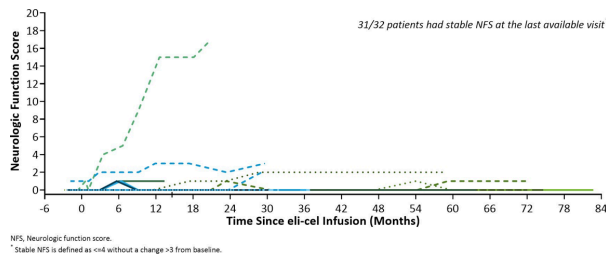

31/32 patients had stable NFS at the last available visit

NFS, Neurologic function score.
* Stable NFS is defined as <=4 without a change >3 from baseline.

Figure 1A. Neurologic Function Score Over Time in ALD-102/LTF-304

21/32 patients had stable Loes score at the last available visit

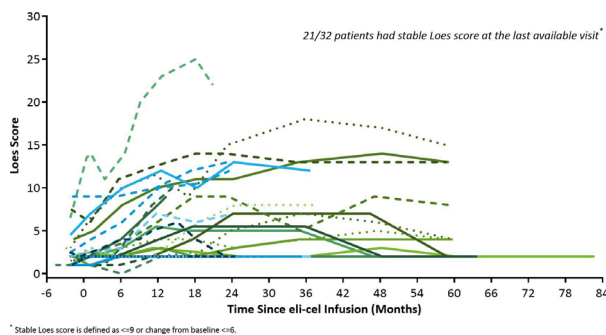* Stable Loes score is defined as <=9 or change from baseline <=6.

Figure 1B. Loes Score Over Time in ALD-102/LTF-304

Conclusion: As of October 2020, 51 eli-cel-treated patients were followed for up to 83 months with favourable safety profile. Neurologic function stabilised in ALD-102/LTF-304 and continues to be evaluated in ALD-104.

Disclosure: Sevin, Caroline: Consultant (bluebird bio, Inc.)

OPR-101

Association of prenatal exposure to antidepressants with standardized tests scores among Danish school-aged children

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Background and aims: This study evaluates whether prenatal exposure to antidepressants is associated with standardized test scores in Danish School Children.

Methods: Population-based cohort study of children born in Denmark between January 1, 1997 and December 31, 2009 who participated in the Danish National Test Program for public schoolchildren attending grades 2, 3, 4, 6, and 8 between January 1, 2010 and December 31, 2018 (n= 575,369 children with 2,178,923 test results). Primary outcomes were pooled test scores in mathematics and language. Test scores ranged from 1–100. Linear regression models with robust standard errors were used to estimate the difference in mean test scores between the exposure groups, while adjusting for potential confounders.

Results: Among the 575,369 children included in this study, 10,198 (1.77%) children were prenatally exposed to antidepressants. The overall mean score in mathematics and language was 56.79 (SD 24.44) and the mean score in mathematics was 57.26 (SD 25.02) and in language 56.53 (SD 24.11). When compared to unexposed children, prenatal exposure to antidepressants was associated with worse performance in the pooled score (difference: -0.90 (95% CI: -1.34; -0.45). The difference could only be observed in mathematics (-2.17, 95% CI: -2.71 to -1.63) but not in language (-0.16, 95% CI: -0.62 to 0.31).

Conclusion: Maternal use of antidepressants in pregnancy was associated with worse performance in mathematics but not in language tests among Danish school-aged children. The findings raise concern about potential long-term neurodevelopmental consequences of prenatal exposure to antidepressants.

Disclosure: Jakob Christensen received honoraria from serving on the scientific advisory board of UCB Nordic and Eisai AB, received honoraria from giving lectures from UCB Nordic and Eisai AB, and received funding for a trip from UCB Nordic.

OPR-102

Epilepsy and Psychiatric Disorders in Children with Congenital Disorders in the Danish Neonatal Screening Program.

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Background and aims: This study describes the long-term outcome of children with phenylketonuria (PKU) and congenital primary hypothyroidism (CH) – the two most frequent disorders included in the Danish Neonatal Screening Program.

Methods: We identified all children born in Denmark between 1 May 1981 and 31 December 2016 (n=2,218,308). We used the Danish National Hospital Register and the Psychiatric Central Research Register to identify children hospitalised with epilepsy and psychiatric disorders by 31 December 2016. Hazard ratios (HR) and corresponding 95% confidence intervals (95% CIs) were estimated using Cox Proportional Hazard Models adjusted for sex and calendar year.

Results: Among the overall study population, we identified 129 children with PKU (median age at diagnosis 0.4 years, males 51.2%) and 1,039 with CH (median age at diagnosis 14 days, males 35.7%). Among children diagnosed with PKU, 19 (14.7%) developed psychiatric disorders, and six (4.7%) developed epilepsy. Among children diagnosed with CH, 151 (14.5%) developed psychiatric disorders, and 39 (3.8%) developed epilepsy. Compared to children without PKU and CH, the risk of psychiatric disorders in children with PKU was HR=1.71 (95% CI: 1.09–2.68), and the risk of epilepsy was 3.46 (95% CI: 1.55–7.70). Compared to children without PKU and CH, the risk of psychiatric disorders in children with CH was 1.50 (95% CI: 1.28–1.76), and the risk of the risk of epilepsy was 2.56 (95% CI: 1.86–3.52).

Conclusion: The two major diseases included in the Danish Neonatal Screening Program (PKU and CM) were associated with increased risks of psychiatric disorders and epilepsy.

Movement Disorders: Treatment

OPR-078

Neurological manifestations of Wilson disease in treatment-naive patients and in patients receiving standard of care

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Background and aims: There is a lack of large cohort datasets presenting the neurological patients with Wilson disease (WD). An ongoing phase 3 study (NCT03403205) will assess the efficacy and safety of ALXN1840, a novel copper-binding agent in patients with WD. This interim analysis focuses on baseline neurological signs and symptoms of WD in this study.

Methods: The study includes two patient cohorts: Cohort 1; chronically treated patients who had previously received standard of care (SoC) for >28 days, Cohort 2; treatment naïve patients who could have previously received SoC from 0 to 28 days, prior to study enrollment. Eligible patients were 12 years of age with a diagnosis of WD confirmed by a Leipzig-Score 4. Patients could have a hepatic, extra-hepatic and/or neurologic phenotype. Neurological disease parameters were assessed at baseline using the Unified Wilson Disease Rating Scale (UWDRS) Part I (level of consciousness), II (disability) and III (neurologic examination) and were analyzed using descriptive statistics.

Results: 182 patients were enrolled between March 9, 2018 and January 30, 2020. Baseline UWDRS Part II, Part III and total score are shown by cohort and overall [Table 1]. Figure 1 shows the percentage of patients with abnormal UWDRS scores at baseline (i.e. a score >0). The most common neurological manifestations in Cohort 1 were tremors, impaired speech, finger taps and dysdiadokinesia and in Cohort 2 were tremor, salivation and impaired speech.

Table 1. UWDRS score at baseline

	Cohort 1 (Treated >28 days) N = 130	Cohort 2 (Treated 0-28 days) N = 52	All Patients N = 182
UWDRS Part II			
n	128	48	176
Mean (SD)	3.88 (7.342)	3.88 (7.019)	3.88 (7.235)
Median (IQR)	0.00 (3.00)	0.00 (4.00)	0.00 (3.00)
Q1, Q3	0.00, 3.00	0.00, 4.00	0.00, 3.00
Min, Max	0.0, 36.0	0.0, 25.0	0.0, 36.0
Patients with score >0, n	60	22	82
UWDRS Part III			
n	127	47	174
Mean (SD)	15.81 (20.293)	12.79 (18.158)	15.00 (19.733)
Median (IQR)	8.00 (20.00)	4.00 (18.00)	6.50 (19.00)
Q1, Q3	1.00, 21.00	1.00, 19.00	1.00, 20.00
Min, Max	0.0, 91.0	0.0, 71.0	0.0, 91.0
Patients with score >0, n	101	36	137
UWDRS Total Score			
n	125	47	172
Mean (SD)	19.93 (26.766)	16.79 (24.418)	19.07 (26.112)
Median (IQR)	9.00 (27.00)	5.00 (24.00)	8.00 (27.00)
Q1, Q3	1.00, 28.00	1.00, 25.00	1.00, 28.00
Min, Max	0.0, 127.0	0.0, 88.0	0.0, 127.0
Patients with score >0, n	100	37	137

Baseline is defined as last non-missing value on or before first study drug administration. SD = standard deviation; IQR = interquartile range; Q1, Q3 = 1st and 3rd quartile. UWDRS Part II, is patient/caregiver-rated and can range from 0 to 40 and Part III is clinician rated and can range from 0 to 175. Higher scores indicate worse disease rating. 'n' represents number of patients with non-missing values

Figure 1. Percentage of Patients with Abnormal UWDRS Scores at Baseline
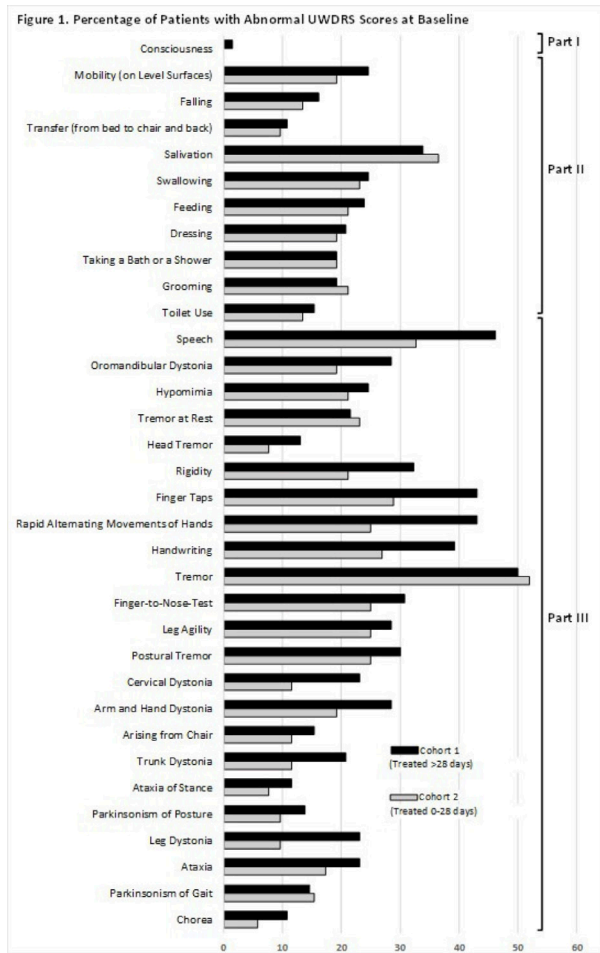
Conclusion: Tremor and speech disturbances are the most common neurological symptoms in patients with WD in these cohorts.

Disclosure: AP, PH, DB, JB, DN, AC: investigators to Alexion Pharmaceuticals: AP, PH, AC: adviser to Alexion. AP: advisor to Vivet Therapeutics, Univar BV and GMP-Orphan Ltd. DB: adviser to Ultragenyx. CL: Alexion employee. DB: adviser to Ultragenyx.

OPR-089

Sialorrhea in advanced Parkinson's disease is associated to speech and swallowing disturbances

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Background and aims: Sialorrhea is an under recognised non-motor symptom of Parkinson's disease (PD) which has been associated to facial hypomimia. Aim of this study was to investigate whether sialorrhea in advanced PD might be related to speech and swallowing dysfunction and more severe motor and non-motor signs.

Methods: We collected the following demographic and clinical data from consecutive advanced PD patients: gender, age, age at onset, disease duration, total levodopa equivalent daily dose (LEDD) and LEDD dopamine agonists (D-Ag), Unified Parkinson's disease Rating Scale (UPDRS), Non-Motor Symptoms Scale (NMSS), SCOPA-autonomic questionnaire (SCOPA-AUT) and Parkinson's disease questionnaire-39 items (PDQ-39). Orofacial symptoms were measured using the Radboud Oral Motor Inventory for PD (ROMP), a self-administered questionnaire evaluating speech, swallowing disturbances, and drooling of saliva. PD with and without sialorrhea (PD-droolers, PD-non-droolers) were compared for all variables. We defined PD-droolers those scoring >1 at UPDRS-II item 6.

Results: We included 101 PD patients, of which sixty-five (64.4%) were classified as PD-"droolers" and 36 (35.6%) as PD-"non-droolers". UPDRS-III was more severe in the OFF (p=0.03) and ON medication state (p=0.002) in PD-droolers, who also had lesser improvement at the levodopa challenge test (p=0.007). At ROMP, PD-droolers had more severe speech (p<0.0001) and swallowing (p<0.05) dysfunction. NMSS (p=0.0008) and SCOPA-AUT (p=0.003) scored higher in PD-droolers. Quality of life by PDQ-39 (p=0.049) was poorer in PD-droolers.

Conclusion: Sialorrhea in PD is associated to more severe motor and non-motor symptoms, speech and swallowing dysfunction and significant burden of non-motor and autonomic symptoms.

Disclosure: No disclosures.

OPR-106

Quantifying the incremental economic burden of Advanced Parkinson's disease: Real-world Evidence from EU5 countries

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Background and aims: Parkinson's disease (PD) is among world's fastest growing neurodegenerative disorders. Recent efforts to quantify the burden of PD have identified the need for further understanding of the incremental economic burden in higher disease severity.

Methods: We conducted a cross-sectional analysis of the Adelphi Parkinson's disease Specific Programme™ (2017–2019). The study evaluated real-world Persons with PD (PwP) receiving care in EU5 (Spain, Italy, UK, France, Germany). Patients were grouped according to physician judgement of PD severity (early, intermediate, advanced). The economic burden was measured based on annual healthcare resource utilization (HCRU) including direct medical and indirect costs. Annual costs were based on 2017-2018 UK reference and converted to Euros using 2020 currency rate. Binary and generalized linear models were computed to estimate costs across disease severity (adjusted for country, age, sex, and Charlson comorbidity index).

Results: We included 3,486 PwP (Age: 69.4±10.4 years; Time since diagnosis: 5.1±5.1 years) with 18% classified as advanced PD. Compared to early PD, Advanced PD patients were considerably more likely to utilize comprehensive care such as professional care (29.9x higher), non-professional care (18.6x higher), and hospitalizations (14.4x higher) [Table 1]. Overall annual mean HCRU costs increased significantly with advancing PD severity (Early: €2,110, intermediate: €11,431, Advanced: €38,625) [Table 2]. Key drivers for high annual HCRU costs among advanced PD patients included professional care (€20,300), respite care (€ 11,972), and hospitalizations (€ 3,225).

12-Month Healthcare Resource Utilization	Intermediate PD (n=1433)		Advanced PD (n=631)	
	OR [a]	(95% CI) [a]	OR [a]	(95% CI) [a]
Overall Utilization	1.34	(0.93, 1.94)	1.35	(0.79, 2.30)
Hospitalizations	5.02	(3.62, 6.95)	14.43	(10.11, 20.61)
Emergency Room Visits	3.08	(2.21, 4.29)	5.83	(4.07, 8.37)
Consultations [b]	1.45	(1.10, 1.91)	0.95	(0.67, 1.35)
Scans [c]	0.65	(0.55, 0.76)	0.50	(0.40, 0.63)
Professional care [d]	7.31	(4.23, 12.63)	29.91	(17.26, 51.84)
Respite care	5.21	(3.30, 8.21)	14.98	(9.33, 24.05)
Non-professional Care [e]	6.12	(3.31, 11.30)	18.63	(9.80, 35.42)

Abbreviations: OR: Odds ratio; CI: Confidence Interval. **Notes:** a: Logistic regression model estimating odds of any utilization with Early PD as reference and adjusted for country, patients age, sex, and Charlson comorbidity index; b: Consultations include visits to any of the following: GP/PCP, consultant, and/or PD nurse; c: Scans include any of the following: MRI, CT, SPECT, fMRI, DaT, and/or PET; d: Professional care include any of the following: district nurse, nursing home staff, home help, psychiatric nurse, physiotherapist, speech therapist, social worker, and/or other; e: Non-professional care is based on reduction in weekly working hours due to caregiving as incurred by non-professional caregivers (i.e. spouse, adult son/daughter, other relative, friend, other).

Table 1: Annual healthcare resource utilization of patients with Parkinson's disease

12-Month Healthcare Costs	Early PD (n=1422)		Intermediate PD (n=1433)		Advanced PD (n=631)	
	Mean [a]	(95% CI) [a]	Mean [a]	(95% CI) [a]	Mean [a]	(95% CI) [a]
Overall Costs (Euro) [b]	2110	(1014, 4843)	11431	(6327, 20567)	38625	(23797, 61935)
Hospitalizations	184	(97, 340)	1057	(693, 1580)	3225	(2247, 4529)
Emergency Room Visits	9	(5, 15)	36	(23, 53)	95	(65, 136)
Consultations [c]	270	(233, 311)	350	(304, 399)	471	(393, 557)
Scans [d]	239	(185, 308)	149	(111, 198)	105	(72, 149)
Professional care [e]	317	(102, 936)	4130	(2312, 7227)	20300	(13009, 31223)
Respite care	872	(311, 2376)	4774	(2396, 9370)	11972	(6676, 21018)
Non-Professional Care [f]	220	(82, 557)	936	(487, 1738)	2458	(1335, 4323)

Abbreviations: CI: Confidence Interval. **Notes:** a: Two-part regression model including probit and generalized linear models (inverse Gaussian with log link function) estimating predicted mean costs and adjusted for patients country, age, sex, and Charlson comorbidity index; b: Unit costs are based on 2017-2018 UK reference costs and were converted to euros based on 2020 currency exchange rate (1 GBP=1.1237 EUR); c: Consultations include visits to any of the following: GP/PCP, consultant, and/or PD nurse; d: Scans include any of the following: MRI, CT, SPECT, fMRI, DaT, and/or PET; e: Professional care include any of the following: district nurse, nursing home staff, home help, psychiatric nurse, physiotherapist, speech therapist, social worker, and/or other; f: Non-professional care is based on reduction in weekly working hours due to caregiving as incurred by non-professional caregivers (i.e. spouse, adult son/daughter, other relative, friend, other).

Table 2: Annual healthcare costs of patients with Parkinson's disease

Conclusion: PwP experience substantial and incrementally higher economic burden with advancing PD. Future intervention to alleviate PD symptom burden and delay progression may reduce future economic burden.

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OPR-145

Falls Predict Acute Hospitalization in Parkinson´s Disease

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Background and aims: The aim of the present study was to identify predictors of acute unplanned hospitalization in Parkinson´s disease (PD).

Methods: PD patients recruited from 35 centers of Spain from the COPPADIS cohort from January 2016, to November 2017, were included in the study. Patient baseline evaluation included motor assessment, non-motor symptoms (NMS), cognition, mood and neuropsychiatric symptoms, disability, and quality of life. Kaplan-Meier estimates were obtained and Cox regression performed on time to hospital encounter 1-year after the baseline visit.

Results: Thirty-five out of 605 (5.8%) PD patients (62.5 ± 8.9 years old; 59.8% males) presented an acute unplanned hospitalization during the 1-year follow-up after the baseline visit. Traumatic falls (9 events) represented the most frequent cause of admission, being 56.3% of all indirect PD-related morbidity causes and 23.7% and 18.4% of all acute unplanned (38 events) and all hospitalizations (49 events), respectively. To suffer from motor fluctuations (HR [hazard ratio] 2.461; 95% CI, 1.065–5.678; p=0.035), a very severe NMS burden (HR [hazard ratio] 2.828; 95% CI, 1.319–6.063; p=0.008), falls (HR 3.966; 95% CI 1.757–8.470; p=0.001), and dysphagia (HR 2.356; 95% CI 1.124–4.941; p=0.023) was associated with acute hospitalization after adjustment to age, gender, disease duration, levodopa equivalent daily dose, total number of non-antiparkinsonian drugs, and UPDRS-III-OFF. Of the previous variables, only falls (HR 2.998; 95% CI 1.080–8.322; p=0.035) was an independent predictor of acute hospitalization.

Conclusion: Falls is an independent predictor of acute unplanned hospitalization in PD patients.

Disclosure: Nothing to disclose.

OPR-147

Clinical and imaging features of idiopathic cerebellar ataxia with anti-cerebellar antibodies

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Background and aims: Idiopathic cerebellar ataxia (IDCA) is the clinical-based term for sporadic cerebellar ataxia with insidious onset and a slowly progressive course. Despite a heterogeneous pathogenesis, diagnostic criteria for IDCA were recently proposed on the basis of those for sporadic adult-onset cerebellar ataxia of unknown etiology, albeit with slight modifications. The purpose of this study was to determine whether autoimmunity can account for some cases of IDCA.

Methods: Using tissue-based immunofluorescence assay (TBA), we examined the expression of anti-cerebellar antibodies (ACAs) in serum samples from 47 patients who met the IDCA diagnostic criteria and control subjects, including 20 patients with multiple system atrophy (MSA), 13 with hereditary ataxia (HA), and 17 healthy subjects. Clinical and imaging features were compared between ACA-positive and ACA-negative IDCA patients.

Results: ACAs were detected in the serum samples of 34% patients with IDCA. This prevalence of ACAs was significantly higher than that of patients with MSA (10%, p=0.037), HA (0%, P = 0.010), or healthy subjects (6%, p=0.016). ACA-positive IDCA patients frequently showed asymmetrical cerebellar hypoperfusion on single-photon emission computed tomography (SPECT) and tended to show pure cerebellar ataxia. The progression of cerebellar ataxia in IDCA patients with neuropil staining of molecular layer is faster than that of patients with intracellular staining of Purkinje cell.

Conclusion: We detected ACAs in 34% of IDCA patients. Autoimmunity can account for some cases of IDCA. The characteristic clinical features of ACA-positive IDCA patients were asymmetrical cerebellar hypoperfusion on SPECT and pure cerebellar ataxia.

Disclosure: The authors declare that they have no competing interests.

OPR-148

Reliability and validity of passively measured gait, gestures from smartphones and smartwatches in Parkinson's disease

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Background and aims: Motor functioning in daily life is the most ecologically valid reflection of motor disease severity, but is difficult to quantify objectively. Smartphones and smartwatch sensors worn by patients enable the passive quantification of motor behavior in daily life, but it is unclear whether these metrics are reliable and clinically meaningful. Here we determined the reliability and clinical validity of such measures in individuals with early Parkinson's disease (PD).

Methods: Baseline PASADENA clinical trial (NCT03100149) data from 316 individuals with early PD were analyzed. Passive sensor features of gait and gestures were averaged over 14 days. Test-retest reliability was assessed by calculating intraclass correlation coefficients of sensor features over two consecutive fortnights. Spearman's rank order correlations tested for associations between sensor features and MDS-UPDRS scores.

Results: Test-retest reliabilities of passively monitored gait and gesture sensor feature were high (ICC's>0.7; p<0.001). Hand gesture features negatively correlated with MDS-UPDRS parts 1–3, bradykinesia and rigidity subscores (-0.37rs[df263]-0.17, p<0.05), and positively correlated with tremor subscores (0.17rs[df263]0.21, p<0.05). Gait measures negatively correlated with MDS-UPDRS parts 2, 3, bradykinesia, and postural stability subscores (-0.35rs[df264]-0.15, p<0.05), and positively with freezing of gait scores (rs[df264]=0.26, p<0.001). Regression analyses with MDS-UPDRS scores (outcomes) and sensor features (predictors) confirmed these results.

Conclusion: Gait and gestures in daily life, passively monitored with smartphones and smartwatches, were associated with physicians' ratings of motor symptom severity, even in this early population with overall mild symptom levels. These findings support the preliminary reliability and validity of passively monitored daily motor behavior with the Roche PD Mobile Application v2.

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Multiple Sclerosis: MRI in MS and related disease

OPR-109

Clinical Relevance of Multiparametric MRI Assessment of Cerebellar Damage in Multiple Sclerosis

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Background and aims: To explore cerebellar damage in multiple sclerosis (MS) with multiparametric MRI, and to identify MRI predictors of physical disability and cognitive impairment.

Methods: 164 MS patients (89 relapsing-remitting [RR] and 75 progressive MS [PMS]), and 68 age- and sex-matched healthy controls underwent brain and cervical spinal cord (CSC) 3T MRI with pulse sequences for assessing lesions and atrophy in the brain (separately for cerebellum, brainstem and supratentorial areas) and CSC; and microstructural damage (with diffusion-tensor metrics) of the cerebellar peduncles. Subjects underwent neurological examination, and neuropsychological assessment with the Brief Repeatable Battery. Domain-specific z-scores were averaged yielding a cognitive z-score. MRI predictors of clinical variables were identified with random forest models.

Results: In RRMS patients, predictors of higher Expanded Disability Status Scale (EDSS) score were: higher brainstem, CSC GM and middle cerebellar peduncle lesion volumes (LV), and CSC atrophy (out-of-bag [OOB]-R2=0.35). In PMS patients, predictors of higher EDSS score were: CSC and cerebellum lobule I-IV GM atrophy, and longer disease duration (OOB-R2=0.16). In RRMS patients, predictors of lower cognition z-score were: thalamic and brain atrophy, cerebellum lobule IX and Crus2 GM atrophy, supratentorial and superior cerebellar peduncle LV (OOB-R2=0.18). In PMS patients, predictors of cognition z-score were: brain GM, thalamic and cerebellum Crus2 GM atrophy, supratentorial LV (OOB-R2=0.22).

Conclusion: Atrophy of specific anatomo-functional sub-regions of the cerebellum conveys important predictive information for physical disability and cognitive impairment in MS patients. Lesions in the cerebellar peduncles also play a relevant role, particularly in RRMS.

Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

OPR-110

Relevance of NODDI to characterise microstructural abnormalities of MS cortex and cortical lesions in vivo: a 3T study

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Background and aims: Neurite orientation dispersion and density imaging (NODDI) could better evaluate multiple sclerosis (MS)-related damage to cortical microarchitecture. Using NODDI, we characterized the microstructural abnormalities of normal-appearing cortex (NA-cortex) and cortical lesions (CLs) and their relations with MS phenotypes and clinical disability.

Methods: One hundred and seventy-two patients with MS (PwMS) (101 relapsing-remitting [RR], 71 progressive [P]) and 62 healthy controls (HC) underwent a brain 3T acquisition. Brain cortex and CLs were segmented from 3D T1-weighted and double inversion recovery, respectively. Using NODDI on diffusion-weighted sequence, intracellular (ICV_f) and extracellular volume fractions (ECV_f) and orientation dispersion index (ODI) were assessed in NA-cortex and CLs.

Results: One hundred and seventeen (68.3%) PwMS had one CL. PwMS NA-cortex had a significant lower ICV_f vs HC NA-cortex (p=0.001). CLs showed a significant increased ECV_f (p<0.001) and decreased ICV_f and ODI vs NA-cortex of both HC and PwMS (p0.006). Compared to RRMS, PMS had a significant decreased NA-cortex ICV_f (p=0.03). Higher CL burdens were found in PMS vs RRMS (p<0.001), without microstructural differences. MS NA-cortex ICV_f, ECV_f and ODI were significantly correlated with disease duration, EDSS, white matter and CL burdens, and brain atrophy (r from -0.51 to 0.71, p from <0.001 to 0.02).

Conclusion: A significant neurite loss occurs in MS NA-cortex. CLs show a further neurite density reduction, an increased extracellular space, reflecting inflammation and gliosis, and a reduced ODI suggesting a simplification of neurite complexity. NODDI is relevant to investigate in vivo the heterogeneous pathology affecting MS cortex.

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OPR-111

Characterizing 1-year cervical cord atrophy progression in different MS phenotypes: a voxel-wise, multicenter analysis

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Background and aims: In multiple sclerosis (MS), the cervical spinal cord frequently shows irreversible tissue loss. Here, we evaluated voxel-wise distribution and changes over time of cervical cord atrophy in a MS dataset acquired at seven European sites.

Methods: Baseline and 1-year clinical and 3D T1-weighted cervical cord data were obtained from 54 healthy controls (HC) and 110 MS patients (13 clinically isolated syndrome [CIS], 75 relapsing-remitting [RR] and 22 progressive [P] MS). An optimized pipeline was used to assess voxel-wise differences of cervical cord atrophy, their longitudinal changes and correlations with clinical variables.

Results: MS patients exhibited significant (p<0.05, family-wise error [FWE] corrected) baseline cervical cord atrophy vs HC in C1/C2 anterior, posterior/lateral, and C4–C6 posterior cord. While CIS patients showed slight cord expansion vs HC at posterior C4, RRMS presented significant cord atrophy vs CIS at posterior/lateral C2–C4, and PMS showed widespread cord atrophy vs RRMS patients at C4–C5 and C7. During the follow-up, a significant cord atrophy progression (p<0.05, FWE) was detected in MS at posterior/lateral C2 and C4–C6. Such progression was driven by RRMS, while CIS did not show cord atrophy changes over time, and PMS patients showed circumscribed tissue loss at posterior C2-C6. Baseline clinical disability was strongly related (p<0.05, FWE) with baseline cord atrophy at posterior/lateral C2–C4. Also, baseline atrophy at lateral C3-C4 was able to explain clinical disability at 1-year follow-up.

Conclusion: Voxel-wise analysis of cervical atrophy characterized 1-year evolution of tissue loss across phenotypes. Cord atrophy was clinically relevant and contributed to explain follow-up disability.

OPR-112

Classifying and characterizing multiple sclerosis disease phenotypes with functional connectivity and machine learning

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Background and aims: Graph theoretical analysis is helping to shed light into brain functional reorganization in multiple sclerosis (MS). Here, we developed advanced machine-learning methods to analyse resting state (RS) functional connectivity (FC) data and classify MS patients according to their disease phenotype.

Methods: RS fMRI scans were obtained from 46 healthy controls (HC) and 113 MS patients (62 relapsing-remitting [RR]; 51 progressive [P]MS). Dominant sets clustering was used to group covariance-based RS FC matrices into clusters of subjects sharing some similarities in their network configuration. Support vector machines (SVMs) were then used to classify disease phenotypes exploiting a representation of networks based on their geodesic distance from cluster means. Finally, a sensitivity analysis on the trained classifier was used to identify clusters and connections more relevant for classification.

Results: The described machine-learning tool was able to classify RRMS patients from HC with an accuracy of 72.5%, PMS patients from HC with an accuracy of 84.1% and PMS from RRMS patients with an accuracy of 76%. The sensitivity analysis on trained SVMs found that increased connectivity within the basal ganglia sub-network and decreased RS FC within the temporal sub-network contributed to an accurate classification of both RRMS and PMS patients from HC. Moreover, decreased RS FC within the occipital and parietal sub-networks contributed to differentiate PMS patients from HC.

Conclusion: A combination of different machine learning principles allowed to classify MS patients with different clinical phenotypes from HC with a good accuracy. Distinct sub-networks abnormalities contributed to an accurate phenotype classification.

Disclosure: Partially supported from by a grant from Fondazione Italiana Sclerosi Multipla (FISM/2018/R/5) and financed or co-financed with the '5 per mille' public funding.

OPR-113

Choroid plexus enlargement characterizes inflammatory multiple sclerosis

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Background and aims: A role for choroid plexuses (CPs) was shown in experimental autoimmune encephalitis, but we lack in vivo evidence in patients with multiple sclerosis (MS).

Methods: 97 patients with MS (61 relapsing-remitting, RRMS, 36 progressive, PMS) and 44 healthy controls (HC) underwent 3T MRI; a subgroup of 37 patients and 19 HC underwent translocator protein (TSPO) 18F-DPA-714 PET to quantify neuroinflammation. Relapses and disability scores were collected at baseline and through a 2-year follow-up. CPs were manually segmented on 3DT1-weighted images. Whole brain, thalamus, normal-appearing white matter (NAWM), cortex, T2-hyperintense and gadolinium-enhancing lesions were additionally segmented. 18F-DPA-714 distribution volume ratio was quantified in parenchymal ROIs, whereas standardized uptake value was used to quantify inflammation in CPs. Multivariable linear regressions were fitted to assess: i) CP volumetric and inflammatory differences between patients and HC; ii) correlations between CP volume and lesion load, brain volumes, parenchymal inflammation and annualized relapse rate (ARR).

Results: CPs were 35% larger in MS compared to HC (p=0.004), particularly in RRMS (p=0.008, fig.1). CP enlargement was higher in patients with gadolinium-enhancing lesions (p<.001), and correlated with brain inflammation as reflected by WM lesion load (r:0.39; p<0.001), thalamic and NAWM 18F-DPA-714 binding (r:0.44; p=0.04, and r:0.5; p=0.005). Moreover, it correlated with ARR in RRMS (r:0.37;p=.005, fig.2). Finally, patients showed 17.5% higher CP 18F-DPA-714 uptake (p=.016, fig.3), which correlated with CP volume in RRMS (r:0.58; p=0.01).

Conclusion: CPs are enlarged and inflamed in MS, particularly in patients with RRMS with an inflammatory profile. CP volumetric analysis could represent a novel imaging marker in MS.

Disclosure: The authors declared no conflict of interest related to this work. V.A.G.R. reports fees for traveling from Novartis and Roche.
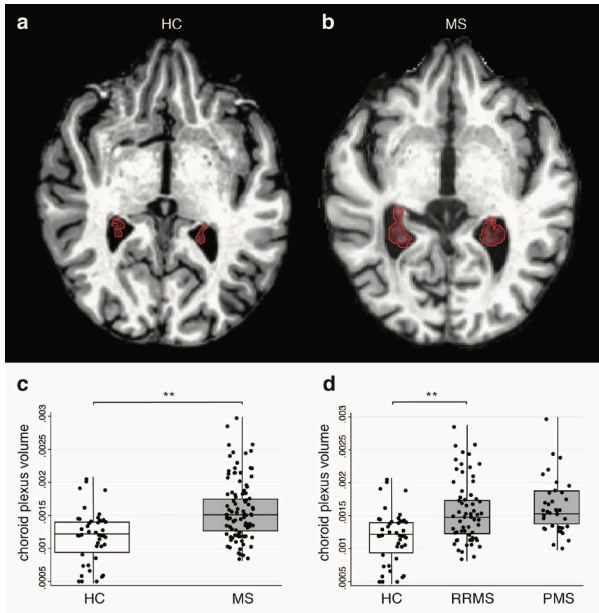
T1-w images showing the segmentation of the left and right choroid
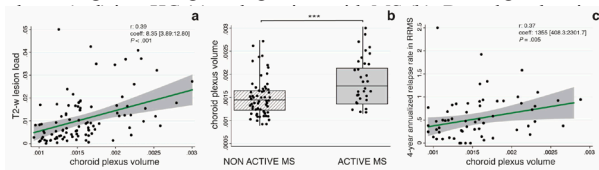
Scatter plots of the association of higher choroid plexus volume with greater T2 lesion load in MS patients (a) and with 4-year annualized relapse rate in RRMS (c). Box plot showing that MS with at least one gadolinium+ lesion had larger CPs (b).
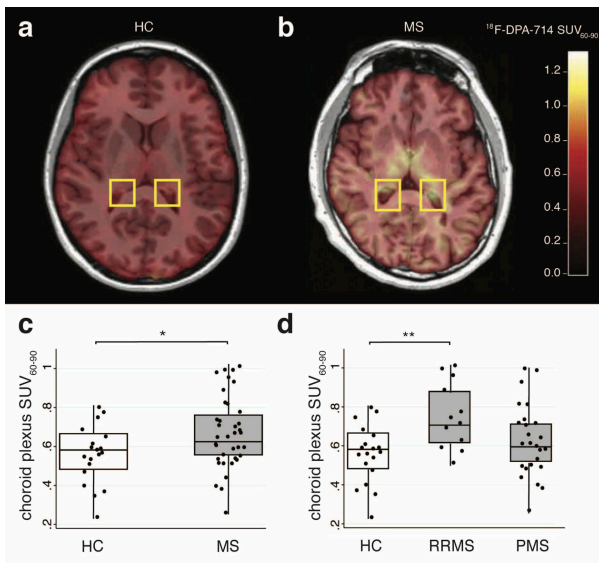
18F-DPA-714 standardized uptake value (SUV60-90) maps of a HAB HC (a) and a HAB patient with MS (b). Box plot showing greater CP inflammation, measured as 18F-DPA-714 SUV60-90, in the whole MS cohort vs HC (c), and in RRMS or PMS separately vs HC (d).

OPR-114

Leptomeningeal enhancement under anti-CD20 therapies – a monocentric retrospective cohort study of 70 patients

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Background and aims: Evaluate the evolution of leptomeningeal enhancement (LME) as a new imaging biomarker of disease activity under treatment with anti-CD20 therapies.

Methods: Retrospective analysis of clinical and MRI data regarding LME of 70 multiple sclerosis (MS) patients treated with ocrelizumab or rituximab in a tertiary neurological center in Switzerland.

Results: We evaluated 70 MS patients (mean age 47 years, range 24–81 years, 39 female); 17 (24%) with primary progressive (PP) and 53 (76%) with relapsing remitting (RR) MS. 18 (26%) patients were initially treated with rituximab (later switched to ocrelizumab) and 52 (74%) initially with ocrelizumab. 18 patients (26%) had no treatment before anti-CD20 therapies. Each patient had one MRI exam before initiation and at least one (range 1–8) during treatment (mean 4.7 MRI exams per patient). Mean observed treatment duration was 18 months (range 1–80 months). Mean disease duration was 126 months (range 24–456 months). 58 patients (83%; 43 RRMS, 15 PPMS) had no LME, seven patients (10%; six RRMS, one PPMS) had persistent LME, whereas five patients (7%; four RRMS, one PPMS) showed resolution of LME under anti-CD20 therapy (all under ocrelizumab).

LME UNDER ANTI-CD20

resolution of LME
5 patients (7%)

persistent LME
7 patients (10%)

no LME
58 patients 83%
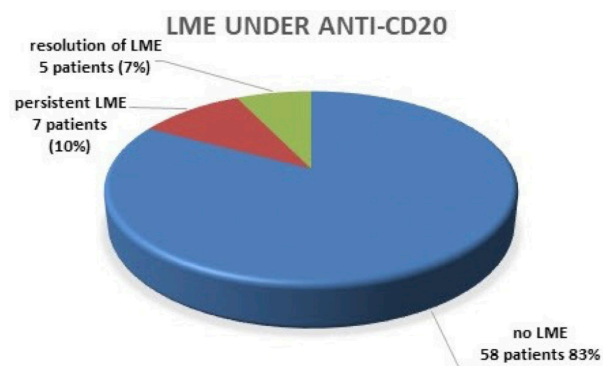
Conclusion: In our cohort of 70 patients, we detected resolution of LME in 7% of MS patients (both RR and PP) under treatment with anti-CD20 therapies, a finding that has not been described so far. As LME plays an important role in cerebral gray matter pathology, further investigations, correlation with clinical phenotypes and a comparison with other immunotherapies are needed.

Disclosure: No disclosures related to this manuscript.

Neurotraumatology

OPR-115

Automated pupillometry to uncover signs of consciousness in acute brain injury

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Background and aims: Cognitive and emotional processes evoke pupillary dilation and may act as surrogate marker for brain activity. Automated pupillometry has shown promising results in quantifying pupil motility and can easily be performed serially at the bedside at low-cost. As cognitive stimuli such as mental arithmetic or emotional stimuli generate pupil dilation, we hypothesize that automated pupillometry may have a role in assessment of consciousness in acute brain injuries if proven sensitive enough to detect responses to standardized stimuli.

Methods: We assess automated pupillometry in healthy volunteers, neurological patients suffering from acute brain injury and cardiac arrest patients in the ICU during and after sedation. Pupillary function is registered over time while subjects are shown their reflection in a mirror, hear auditive stimuli and are asked to perform mental arithmetic's.

Results: Pilot data have been collected on 22 healthy subjects (male 72%; median-age 62), as well as 29 patients with cardiac arrest (n=21) or other brain injury (n=8). 72% of healthy controls reacted with pupil dilation on two of the auditive stimuli, while only 18% responded to their own reflection. 10 subjects show at least 4/5 dilations in both difficulties of mental arithmetic's. Lowering the cut-off to a minimum of three dilations, the pilot data show respectively 64% (n=14) and 59% (n=13) succession rate, suggesting cognitive processing of mental tasks.

Table 1: Pilot data

Dilations	Mirror (n=22)	Music (n=22)	MA Medium (n=22)	MA Hard (n=22)
0	18	1	2	1
1	4	5	2	3
2	-	14	4	5
3	-	2	4	3
4	-	-	6	6
5	-	-	4	4
Success rate	18%	72%	45%	45%

Abbreviations: MA=Mental arithmetic; n=number of subjects

Dilations for each patient

Figure 2
This figure depicts results from pupillary measurements in control subjects. Healthy volunteers (n=22) were asked to focus on their reflection in a mirror, listened to an audio tape with three short sequences of music intermixed with silence, and perform series of mental arithmetic with different degrees of complexity (x-axis). Automated pupillometry was used to assess pupillary dilation as evidence of arousal (mirror, music) and sustained attention/command following (arithmetic). The y-axis reveals the number of pupillary dilations for individual subjects during each of the four tests, and the stars denote the maximal number of possible dilations during each task (i.e. from 1 dilation for the mirror task to 5 dilations for arithmetic). Successful command following was defined by ≥4 significant pupillary dilations during five mental arithmetic tasks. Subjects who were able to follow commands and successfully engage in both arithmetic tasks, as evidenced by pupillary dilations, are shown in red (n=6). Subjects able to do so in one of the two arithmetic tasks are shown in blue (n=11). Those who did not pass the threshold of 4/5 dilations in neither of the two tasks, suggesting that they were unable to sustain attention, are depicted in green (n=7).
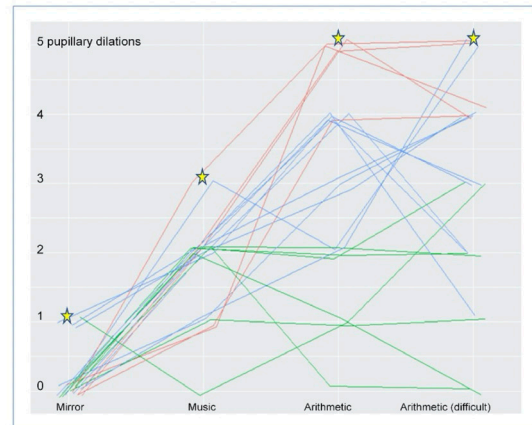
Conclusion: We suggest that automated pupillometry is worthy of further exploration in the assessment of consciousness following acute brain injuries. Applying this tool in the setting of ICU could help detect patients with covert consciousness.

Disclosure: Nothing to disclose..

OPR-116

Overexpression of miR-26a promotes neurite regeneration in the central nervous system in vitro

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Background and aims: The central nervous system (CNS) has an intrinsic low capacity for axon regeneration due to an imbalance in gene expression. Thus, investigating the role of molecules that control gene expression, such as microRNAs (miR), is an interesting strategy to promote regeneration. The miR-26a promotes neurite outgrowth and axonal regeneration in the peripheral nervous system, by targeting mRNAs that encode proteins related to regeneration pathways. However, the role of miR-26a in axon regeneration in the CNS is still unknown. We aim to test if the overexpression of miR-26a promotes axonal regeneration of CNS neurons.

Methods: We produced recombinant adeno-associated viral (rAAV) vectors expressing miR-26a (rAAV.miR-26a) or EGFP (rAAV.EGFP), as control, to transduce cortical neuron in vitro. Transduction efficiency and neurite regeneration after scratch lesion were evaluated. Then, we performed a bioinformatics evaluation for the mRNA targets of miR-26a.
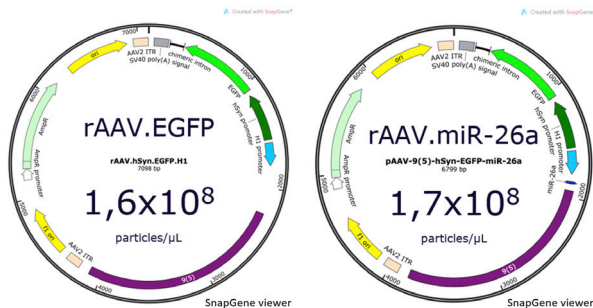
Recombinant adeno-associated viral (rAAV) vectors maps: EGFP (the control) on the left, and miR-26a on the right. Both vectors contains the sequence to express the fluorescent protein EGFP.

Results: Neurons were efficiently transduced with both vectors. Transduction with rAAV.miR-26a increases neurite length and the number of neurites crossing the distance of 200m from the scratch border. The bioinformatics evaluation showed 33 predicted mRNA targets and 30 validated targets of miRNA-26a. These results indicated that miR-26a improves neurite regeneration in vitro, however, further analysis are required to confirm this pro-regenerative effect in vivo.
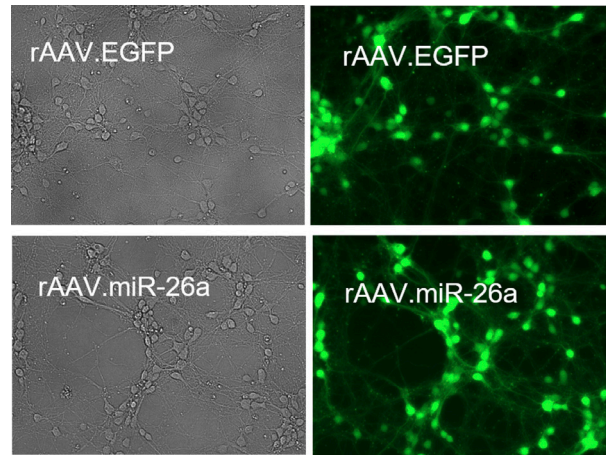
Transduction efficiency of viral vectors in vitro comparing different types of microscopic images: on the left for both vectors a bright-field light microscopic image and on the right a fluorescence light microscopic image. The vectors worked properly.
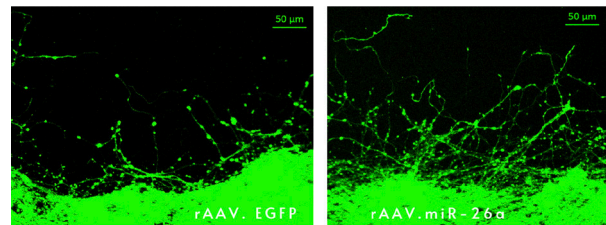
Scratch lesion essay: the group transduced with rAAV.miR-26a compared to rAAV.EGFP had an increase in neurite length and in the number of neurites crossing the distance of 200m from the scratch border.

Conclusion: This study could identify novel therapeutic targets to promote regeneration in the CNS.

Disclosure: The authors declare that they have no conflicts of interest.

OPR-117

Corticosterone in acute traumatic brain injury in rats: association with immediate seizures and neuroinflammation

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Background and aims: Corticosterone modulates hippocampal activity, neurogenesis, and plays critical role in susceptibility to seizures. We assessed corticosterone level in blood and hippocampus during acute period of traumatic brain injury (TBI) in rats, its relationships with immediate seizures and proinflammatory response in the blood and hippocampus.

Methods: The study was performed on 140 male Wistar rats. TBI was modelled using lateral fluid percussion brain injury. The duration of immediate posttraumatic seizures were analyzed. Interleukin (IL) -1beta, IL-6 and corticosterone in the blood and hippocampus of both hemispheres were measured on days 1, 3, 7, and 14 after TBI using ELISA.

Results: We revealed that time of day significantly affected the semiology of immediate seizures; tonic seizures were more frequent in the afternoon (close to the period of elevated corticosterone in rats). Corticosterone was elevated on days 1, 3, and 14 after TBI in blood and on day 3 in the hippocampus (bilaterally) as compared to sham-operated rats. IL-1beta raised in the ipsilateral hippocampus on day one and in the hippocampus bilaterally on day seven after TBI. Corticosterone in the blood and hippocampus correlated with immediate seizures duration and IL-1beta level in the contralateral hippocampus seven days after TBI.

Conclusion: Corticosterone-dependent mechanisms may be involved in neuroinflammation and late consequences of TBI, including epilepsy, depression and cognitive disturbances. However, immediate seizures may also be associated with glucocorticoid system and posttraumatic brain pathology.

Disclosure: Supported by RFBR, grant 19-015-00258

OPR-118

Effects of single-walled carbon nanotubes on the survival and release of cytokines from stretch-injured astrocytes

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Background and aims: Astrocytes are considered to have an important role in neuronal regeneration following brain injury. Here, we explored the potential of a nanomaterial on the survival and secretory function of astrocytes after trauma. We tested the effects of single-walled carbon nanotubes (SWCNTs), chemically functionalized with poly-m-aminobenzene sulfonic acids (PABS), in an in vitro model of severe traumatic brain injury (TBI).

Methods: Primary mouse astrocytes were severely injured by rapid stretching. Following injury, PABS-SWCNTs were added to the cell culture medium. Injured and non-injured untreated cells were used as the control TBI and sham-treated groups, respectively. Astrocytes' survival rate within the first 24 h and the effects of PABS-SWCNTSs were determined by lactate dehydrogenase (LDH) assay. Cytokine secretion profiles were evaluated at 24 h after stretch by a multiplex array.

Results: Severe injury triggered an increased release of LDH from the astrocytes. Application of PABS-SWCNTs did not alter the LDH levels compared to the results from the injured, untreated cells. Cell injury caused a decrease in the Eotaxin1 and an increase in the SDF-1 alpha levels in the culture medium compared to the non-injured cells. Application of PABS-SWCNTs induced increased secretion of RANTES from the injured astrocytes, related to non-injured and injured untreated cells.

Conclusion: Reported results indicate that PABS-SWCNTs do not affect the survival of astrocytes subjected to severe TBI within the first 24 h. An increase in the release of RANTES from the injured cells, caused by PABS-SWCNTs addition, points to possible effects of this nanomaterial on the function of injured astrocytes.

Disclosure: This research was fully supported by the Croatian Science Foundation grant UIP-2017-05-9517 to KP.

OPR-119

Lateral fluid percussion injury in the rat instigates early T-cell infiltration in the ipsilateral parietal cortex

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Background and aims: Traumatic brain injury (TBI) represents a burden to healthcare due to limited management options and as well as long-term consequences, which are underrepresented and contribute to naming TBI a "silent epidemic". Neuroinflammation appears to have a significant role in the development of secondary brain injury, involving processes affecting both resolution and persistence of inflammation. The purpose of this study was to elucidate the early activation of the immune cell-mediated response in an experimental model of TBI.

Methods: Lateral fluid percussion injury (LFPI), a TBI model causing both focal cortical lesion and diffuse cerebral damage, was induced in adult male Wistar rats that were sacrificed at 1, 3, or seven days following the procedure. For the control group, we used the animals sacrificed at one day after sham injury. Markers of the cellular arm of adaptive immunity were evaluated by quantitative and qualitative immunohistochemical analyses of the brain tissue.

Results: The results of this study demonstrated the invasion of CD3+, CD4+, and CD8+ cells in the ipsilateral cortices of injured animals. The number of CD3+ cells in this brain region was highest on day one after the trauma and decreased thereafter. CD4+ cells were most abundantly present in the cortex three days after the injury. Invasion of CD8+ cells was also noted in the cortex but also in the subpial space ipsilaterally.

Conclusion: Reported results show that LFPI elicits a cellular immune response within the first week following TBI, which could exacerbate secondary posttraumatic effects and determine recovery outcomes.

Disclosure: This work was supported by the University of Rijeka under the projects uniri-biomed-18-204 and 13.06.1.1.09 to GŽ.

OPR-120

Modulating Balance with Galvanic Vestibular Stimulation in Traumatic Brain Injury Patients

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Background and aims: Impaired balance, mainly a vestibular ataxia, affects 80% of patients with moderate-to-severe acute traumatic brain injury (TBI). Although vestibular ataxia improves over time post-TBI, no interventions have yet been shown to accelerate patient's balance recovery. Neuromodulation by galvanic vestibular stimulation (GVS) may itself or in conjunction with physical therapy, accelerate the balance recovery of TBI patients. We performed a mechanistic, randomised and double-blinded, sham-controlled study exploring the effect of GVS on imbalance in TBI patients.

Methods: We administered bipolar noisy GVS (frequency 0-30Hz) through anodes and cathodes placed on the mastoids of seven TBI patients and four healthy controls (HC). Subjects stood on a soft-foam surface, placed upon a 'balance' or force platform for 120 seconds, with eyes closed. Either anodal or sham stimulation was applied for the first and last 30 seconds of the balance task, in randomised order.

Results: The sway parameters of six TBI subjects reduced when compared to sham, with amplitudes between 100-300uA (n=4) and 500–600uA (n=2). The average sway RMS, path and 95% confidence ellipse area of the subject's movement reduced compared to sham by (Mean (± SEM; p-value) 28.86% (2.57; p<0.01), 4.24% (2.65; p>0.05) and 41.21% (5.07; p<0.05), respectively.

Conclusion: This is the first demonstration of noisy GVS in patients with TBI. Our work demonstrates GVS may have a role in balance modulation in TBI. Future work will assess possible brain mechanisms involved in noisy GVS upon patients' balance.

Disclosure: Nothing to disclose.

Cerebrovascular diseases

OPR-127

Etiology, functional outcome and recurrent events in non-traumatic intracerebral hemorrhage

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Background and aims: Knowledge about different etiologies of non-traumatic intracerebral hemorrhage (ICH) and their outcomes is scarce.

Methods: We assessed prevalence of pre-specified ICH etiologies and their association with outcomes in consecutive ICH patients enrolled in the prospective Swiss Stroke Registry (2014–2019).

Results: We included 2,650 patients (mean age 72 years (SD 14), 46.5% female, median NIHSS 8; IQR 3–15). Etiology was as follows: hypertension: 1,238 patients (46.7%); unknown: 566 patients (21.4%); antithrombotic therapy: 227 patients (8.6%); cerebral amyloid angiopathy (CAA): 217 patients (8.2%); vascular cause: 128 patients (4.8%); other determined etiology: 274 patients (10.3%). At three months, 880 patients (33.2%) were functionally independent and 664 had died (25.1%). ICH due to hypertension had a higher odds of functional independence (aOR 1.33, 95%CI 1.00–1.77, p=0.05) and lower mortality (aOR 0.64, 95%CI 0.47–0.86, p=0.003). ICH due to antithrombotic therapy had higher mortality (aOR 1.62, 95%CI 1.01–2.61, p=0.045). 4.2% of patients had cerebrovascular events within three months. The rate of ischemic stroke was higher than that of recurrent ICH in all etiologies but CAA and unknown etiology. CAA had high odds of recurrent ICH (aOR 3.38, 95%CI 1.48–7.69, p=0.004) while the odds was lower in ICH due to hypertension (aOR 0.42, 95%CI 0.19–0.93, p=0.031).

Conclusion: Although hypertension is the leading etiology of ICH, other etiologies are frequent. One third of ICH patients are functionally independent at three months. Except for patients with presumed CAA, the risk of stroke within three months of ICH was higher than the risk of recurrent hemorrhage.

OPR-128

Phenotypes of chronic covert brain infarction in first-ever ischemic stroke patients – a cohort study

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D. Seiffge [1], M. Heldner [1], M. Goeldlin [1], U. Prange [1],
U. Fischer [1], M. Arnold [1], S. Jung [1], J. Gralla [2],
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Background and aims: To assess the rate of chronic brain infarctions (CBI) in patients with acute ischemic stroke (AIS) and to describe their phenotypes and diagnostic value.

Methods: This is a single-center cohort study including 1546 consecutive patients with first-ever AIS on MRI imaging from 01/2015–12/2017. The main study outcomes were CBI phenotypes, their relative frequencies, location and association with vascular risk factors.
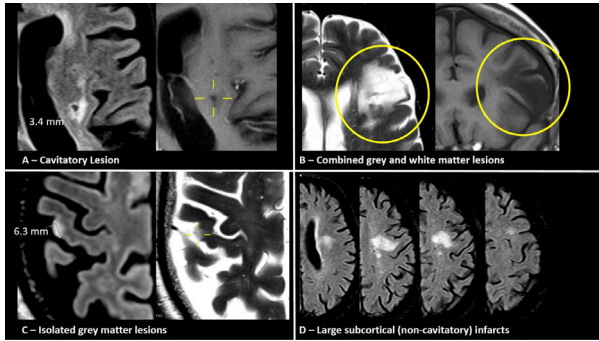
(A) Cavitatory lesions. (B) Combined gray and white matter lesions. (C) Isolated gray matter lesions. (D) Large subcortical (non-cavitatory) infarcts.

Results: Any CBI was present in 574/1546 (37%,95%CI 35–40%) of patients with a total of 950 CBI lesions. The most frequent locations of CBI were cerebellar in 295/950 (31%), subcortical supratentorial in 292/950 (31%), and cortical in 213/950 (24%). CBI phenotypes included cavitatory lesions (49%), combined gray and white matter lesions (30%), gray matter lesions (13%) and large subcortical infarcts (7%). Vascular risk profile and white matter hyperintensities severity (19% if no WMH, 63% in severe WMH, p<0.001) were associated with presence of any CBI. Atrial fibrillation was associated with cortical lesions (aOR 2.032, 95%CI 1.041–3.967)Median NIHSS scores on admission were higher in patients with an embolic CBI phenotype (median NIHSS 5,[2-10],p=0.025).
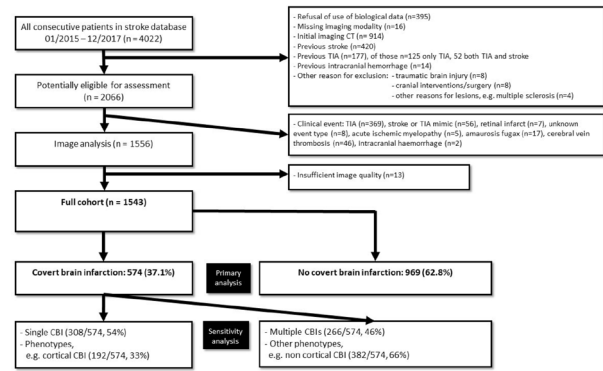
Study flow chart. TIA = transient ischemic attack, CBI = Covert brain infarction
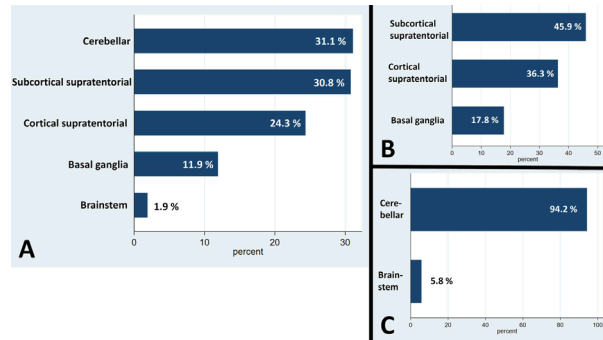
Conclusion: CBI were present in more than a 3rd of patients with 1st AIS. Their location and phenotypes as determined by MRI were different from previous studies using CT imaging. Among patients suffering AIS, those with additional CBI represent a vascular high-risk subgroup and the association of different phenotypes of CBIs with differing risk factor profiles potentially points towards discriminative AIS etiologies.

Disclosure: No disclosures

OPR-129

Dissociated deficits in the sensorimotor control of torques with the ipsilesional hand of chronic stroke patients

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Background and aims: To safely lift objects without tilting, arising torques due to asymmetric weight distributions must be anticipated and compensated already at lift-off. Previous studies showed that anticipatory force scaling even with the ipsilesional hand may be impaired after stroke. However, anticipatory torque control in object manipulation has not yet been studied in stroke survivors.

Methods: Here, we asked 13 patients with chronic left hemispheric stroke (SL group) and nine patients with right hemispheric stroke (SR group) to use their ipsilesional hand to grasp and lift an object whose center of mass (CoM) could be changed by either varying the position of a hidden weight (no cues condition) or the position of the grip-handle (visual cues condition). CoM changes either occurred after blocks of eight trials or randomly.

Anticipatory torque compensation of stroke survivors was compared with control groups using the same hand (CL/CR-groups).
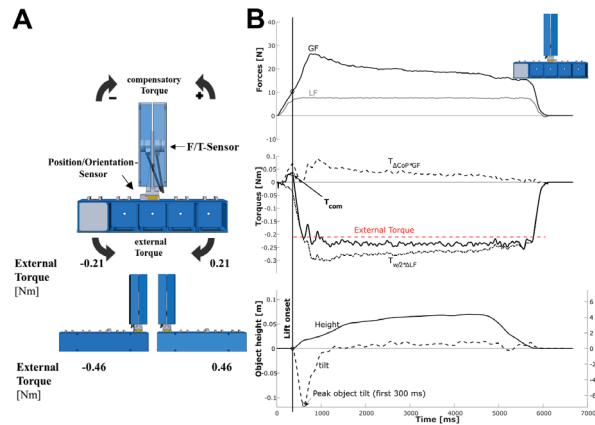
Figure 1: Experimental apparatus and variables. (A) The custom-built grip-device. Upper panel: Variation of the hidden weight position in the 'no cues' condition. Lower panel: variation of the grip handle position (B)

Results: Both stroke groups presented deficits in learning to generate torques by modulating the centers of pressure (CoP) along the grip sides when the hidden weight was placed on the contralesional side but not when placed on the ipsilesional side. In contrast, torque anticipation was similar across groups when visual cues were present and when the CoM was randomly varied.
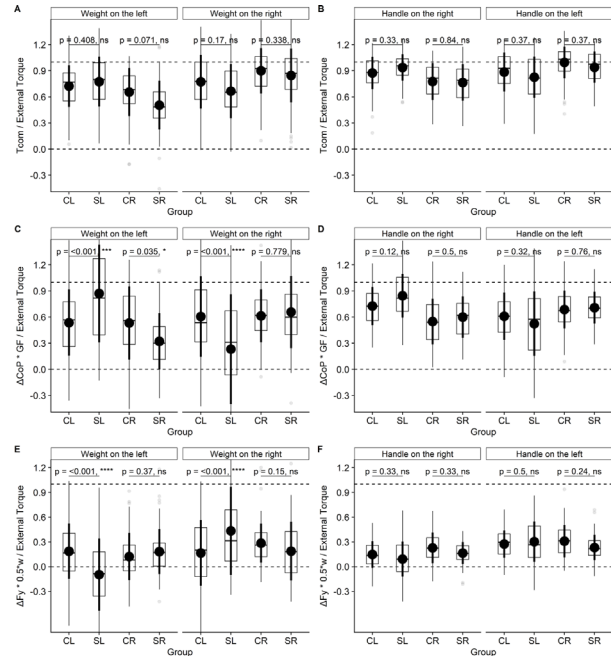
Figure 2: Relative torque ratios for trials 4-8 in the blocked conditions. No cue conditions: panels A, C, D. Visual cues conditions: panels B, D, F.
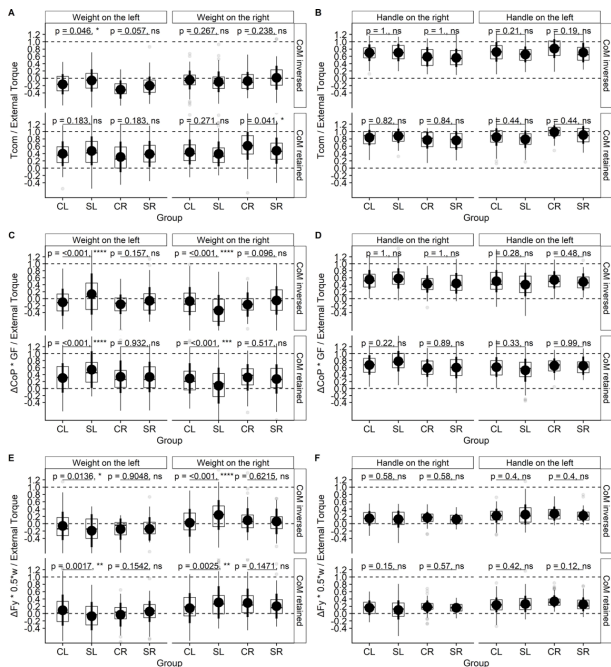
Figure 3: Relative torque ratios for trials 4-8 in the pseudorandom conditions. No cue conditions: panels A, C, D. Visual cues conditions: panels B, D, F.

Conclusion: Our findings provide novel evidence that even in the chronic stage unilateral strokes may impair the sensorimotor control of the anticipatory coordination of finger positions with grip forces selectively for external torques directed towards the contralesional side but spare anticipatory load force partitioning suggesting dissociated neural correlates.

Disclosure: We have no disclosures to declare.

OPR-130

Thrombectomy in Basilar Artery Occlusion

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Background and aims: Recent large multicenter trials investigating thrombectomy (TE) for acute ischemic stroke (AIS) in patients with basilar artery occlusion (BAO) provided conflicting evidence. Our aim was to analyze functional outcome after three months in BAO compared to anterior-circulation large vessel occlusion (ACLVO).

Methods: We analyzed data of all patients enrolled to the Austrian Endostroke Registry. Functional outcome was measured by the modified Rankin Scale. We used propensity score matching to control for imbalances and to compare patients with BAO and ACS. A proportional odds model was applied to estimate the effect of localization (BAO vs ACS). Furthermore, we assessed recanalization rates according to the Thrombolysis in Cerebral Infarction Scale (TICI).

Results: From 2013–2018, 2,288 patients underwent TE for AIS with proximal vessel occlusion, of these 267 with BAO. Follow up data were complete for 2,243 patients; 264 patients with BAO (98.9%). Rates for successful recanalization (TICI2b-3) were high in both BAO (76.9%) and ACLVO (79.5%) and did not differ (p=0.62). We matched 264 patients with BAO and 264 with ACS. In a multivariate proportional odds model we did not detect any difference in functional outcome (OR=1.17, 95%CI 0.85–1.6; p=0.34). In patients with an onset-to-door-time 270 minutes BAO was associated with poor functional outcome (OR=2.55; 95%CI 1.11–5.88; p=0.03).

Conclusion: Functional outcome did not differ after TE in patients with BAO and ACLVO. However, if patients with BAO arrived late, outcome was worse.

Disclosure: Nothing to disclose.

OPR-131

Predicting atrial fibrillation in cryptogenic stroke patients: a score-based approach

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Background and aims: Atrial fibrillation (AF) often remains undiagnosed in patients with cryptogenic stroke (CS), mostly because of limited availability of cardiac long-term rhythm monitoring. Evidence-based pre-selection of CS patients benefiting from such work-up would clearly be of relevance. We therefore sought to develop a clinical risk score to predict AF in this scenario and to evaluate its performance over a 1-year follow-up (FU).

Methods: Our newly proposed risk score comprises variables that have recently been associated with occult AF in CS patients including age, NT-proBNP, electro- and echocardiographic features (supraventricular premature beats, atrial runs, atrial enlargement, left ventricular EF) and brain imaging markers (multi-territory prior cortical infarcts) (range: 0–16 points). To evaluate this, all CS patients admitted to our Stroke Unit from March 2018 to August 2019 had been prospectively followed for AF detection over one year after discharge.

Results: We diagnosed 24 (16%) out of 150 CS patients with AF during FU (detected via ECG-controls, n=18; loop recorder-monitoring, n=6). Our predefined AF Risk Score (cutoff four points, highest Youden's index) had a sensitivity of 92% and a specificity of 68% for the one-year prediction of AF in CS patients. Notably, only two patients with <4 score points were diagnosed with AF later on (negative predictive value: 98%).

Conclusion: We here present a clinical AF risk score for the one-year prediction of AF in CS patients with high sensitivity, reasonable specificity and very high negative predictive value. Generalizability of our score needs to be tested in external cohorts with continuous cardiac rhythm monitoring.

Disclosure: Nothing to disclose.

OPR-132

Off-label alteplase use in anterior spinal artery syndrome – a supportive case report

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Background and aims: Anterior spinal artery syndrome (ASAS) tends to have a severe functional outcome. Although intravenous thrombolysis with alteplase is well recommended in ischemic stroke, only a few cases of systemic thrombolysis in ASAS have been reported so far, with limited evidence for efficacy or safety.

Methods: Clinical case report of a patient admitted to the emergency room (ER) with ASAS.

Results: We present the case of a 56 year-old male, a former smoker, with a history of diabetes, hypertension and dyslipidemia. He was admitted to the ER for atraumatic chest pain after physical effort, followed by acute lower limb weakness, starting 2.5h before arrival. Neurologic examination showed a flaccid areflexic paraparesis, urinary retention and loss of thermo-algic sensitivity below T10, but preserved vibratory and proprioceptive sensitivity. Thoracolumbar spine CT and CT-angiography revealed no evidence of bleeding, trauma, compressive or intra-axial masses, aortic dissection or arteriovenous malformations. Assuming a probable ASAS of microatheromatous etiology and existing no formal contraindications, the patient, after informed consent, was given 0.9mg/kg alteplase, showing partial clinical improvement about 30 minutes later. A subsequent MRI confirmed the typical T2 "snake-eyes sign", extending from T3 to T11. Intermittent catheterization, antiedematous treatment and secondary prevention with acetylsalicylic acid and atorvastatin were started, with slow progressive improvement. He was transferred to a rehabilitation center, with full motor recovery at discharge three months later.
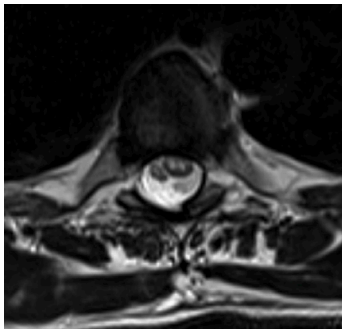
T2 "snake eyes" sign on thoracic MRI

Conclusion: Despite the absence of formal approval, this case supports that off-label systemic thrombolysis could be safe and useful for the treatment of ASAS – warranting further investigation.

Disclosure: Nothing to disclose.

OPR-133

Abstract withdrawn

OPR-195

Liver fibrosis is associated with atrial fibrillation and worse outcome in large vessel occlusion stroke

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Background and aims: We aimed to explore whether clinically inapparent liver fibrosis is related to neurological outcome, mortality and intracranial haemorrhage in ischemic stroke patients after mechanical thrombectomy.

Methods: We included consecutive patients with anterior circulation large vessel occlusion stroke treated at our centre with mechanical thrombectomy between January 2011 and April 2019 and collected clinical data prospectively. We calculated three established non-invasive liver fibrosis scores: Fibrosis-4 index (FIB-4), Forns index and Easy Liver Fibrosis Test (eLIFT). Main outcomes were postinterventional intracranial haemorrhage, unfavourable functional status (modified Rankin scale scores of 3–6) and mortality three months post-stroke.

Results: In the 465 patients (mean age 69 years, 49.5% female) analysed, FIB-4, Forns index and eLIFT indicated advanced liver fibrosis in 22.6%, 37.6% and 58.7% of patients, respectively. All three indices were associated with unfavourable neurological outcome and mortality three months post-stroke after correction for stroke severity, recanalization status and relevant comorbidities (e.g., Odds Ratio 2.06 for unfavourable outcome in patients with positive FIB-4, 95% CI 1.20–3.55, p=0.009, and Odds Ratio 2.18 for mortality, 95% CI 1.25-3.79, p=0.006). However, liver fibrosis was not related to haemorrhagic transformation or symptomatic intracranial haemorrhage. Atrial fibrillation was more frequent in patients with liver fibrosis (60.6% vs. 36.1% in patients with vs. without positive FIB-4, p<0.001).

Conclusion: Clinically inapparent liver fibrosis (based on simple non-invasive tests) represents an independent risk factor for unfavourable outcome including mortality after stroke thrombectomy. Elevated liver fibrosis indices warrant further hepatological work-up and thorough screening for atrial fibrillation in stroke patients.

Disclosure: Nothing to disclose.

Headache and Pain 2

OPR-134

Long-term Safety and Tolerability of Atogepant: Once Daily Dosing Over one Year for the Preventive Treatment of Migraine

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Background and aims: Atogepant is an oral, small molecule, CGRP receptor antagonist in development for the preventive treatment of migraine. We evaluated the safety and tolerability of atogepant over 52 weeks.

Methods: Multicenter, open-label trial (NCT03700320). Adults with migraine were randomized 5:2 to atogepant 60 mg once daily or oral standard-of-care migraine prevention medicine. The primary objective was to assess the safety and tolerability of atogepant. Standard-of-care was included to primarily help contextualize hepatic safety data.

Results: The trial included 744 randomized participants (n=546 atogepant) with 739 in the safety population (n=543 atogepant). Adverse events (AEs) were reported by 67.0% of atogepant-treated participants; 18.0% reported AEs that were considered treatment-related. Most commonly reported AEs (5% of participants) were upper respiratory tract infection (10.3%), constipation (7.2%), nausea (6.3%), and urinary tract infection (5.2%) following atogepant treatment. Serious AEs were reported by 4.4% of atogepant-treated participants; no event was seen in >1 participant and no event was considered treatment-related. Two deaths were reported in atogepant-treated participants (victim of homicide and a group A beta-hemolytic streptococcal sepsis [toxic shock syndrome]); both were considered not related to atogepant. Discontinuation due to AEs was 5.7% following atogepant treatment. Cases of alanine aminotransferase/aspartate aminotransferase levels three times the upper limit of normal were reported for 2.4% of atogepant-treated participants (n=13/531) and 3.2% for standard-of-care (n=6/190). No cases of potential Hy's Law were reported.

Conclusion: Long-term, once daily use of atogepant 60 mg for the preventive treatment of migraine over one year was safe and well-tolerated with no safety concerns identified.

Disclosure: Study was sponsored by AbbVie

OPR-135

Real-world evidence for chronic migraine control in patients receiving treatment with CGRP mAbs and onabotulinumtoxinA

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Background and aims: Combining onabotulinumtoxinA and calcitonin generelated peptide monoclonal antibody therapy (CGRP mAbs) could potentially be more effective than either treatment alone for preventing chronic migraine (CM).

Methods: This retrospective, longitudinal chart review included adults with CM treated with ≥2 consecutive onabotulinumtoxinA injections before ≥1 month of onabotulinumtoxinA plus CGRP mAb (erenumab, fremanezumab, or galcanezumab) combination treatment (primary cohort). Safety/tolerability (adverse events [AEs], discontinuations) and outcome measures (monthly headache days [MHDs], migraine-related disability [MIDAS]) were reviewed. Patients who completed ~12 months of onabotulinumtoxinA treatment after initiating CGRP mAb (completers) were evaluated.

Results: Of 300 charts reviewed, 257 were included in the primary cohort (mean age: 50 years; 82% women) and 103 (40%) met criteria for completers. CGRP mAb included erenumab (primary: 78%; completers: 84%), galcanezumab (16%; 11%) and fremanezumab (6%; 5%). In the primary cohort, AEs were reported in 28% of patients; the most common AE was constipation (9%). Mean MHDs were 21.5 and 22.4 days before onabotulinumtoxinA initiation in the primary and completer cohorts, respectively, and 12.1 days before adding CGRP mAb in both cohorts. After ~6 months, positive changes were noted in the primary and completer cohorts: 82% and 83% had decreased MHDs, and 57% and 55% had improved MIDAS (Figure). All reductions were significant given non-overlapping CIs.
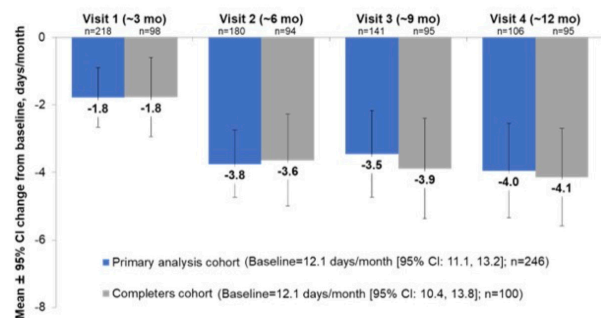
CGRP mAb, calcitonin gene–related peptide monoclonal antibody.

Mean change from baseline in monthly headache days during combination therapy with onabotulinumtoxinA and CGRP mAbs

Conclusion: This real-world study of CM patients demonstrated clinically meaningful benefits with onabotulinumtoxinA alone and additive benefits after adding CGRP mAb with no new safety signals. More real-world studies and controlled trials are needed to further quantify potential benefits of this multimodal treatment paradigm.

Disclosure: This study was supported by Allergan (prior to its acquisition by AbbVie).

OPR-136

Consistent efficacy and safety of erenumab in episodic migraine patients during a 5-year, open-label extension study

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Background and aims: Erenumab demonstrated significant reduction in migraine frequency in short-term studies; however, long-term data are not available. The long-term efficacy and safety of erenumab was evaluated in episodic migraine patients who completed a 5-year open-label treatment phase (OLTP; NCT01952574).

Methods: Following a 12-week placebo-controlled, double-blind treatment period (DBTP), 383 patients continued into the OLTP, receiving erenumab 70mg every four weeks, and increasing to 140mg after a protocol amendment (after ~2 years in OLTP). Overall, 214 patients completed the 5-year OLTP; 138 patients had efficacy data at Week 268 (end of 5-year OLTP) and were included in this analysis.

Results: At Week 268, the mean(SD) change from the DBTP baseline in monthly migraine days (MMD) and monthly acute migraine-specific medication (AMSM) days was 5.3(3.9) and 4.4(3.3), respectively (Table 1). The proportion of patients who achieved ≥50%, ≥75% and 100% reduction in MMD at Week 64/268 was 62%/71%, 41%/47% and 26%/36%, respectively. Clinically meaningful improvements were observed in headache impact test-6TM: 68%/73% of patients achieved ≥5-point reduction from baseline at Weeks 64/268. Exposure-adjusted patient incidence of adverse events (AEs) and serious AEs during OLTP was 91.6 and 2.8 per 100 subject-years, respectively; this was lower than that observed for erenumab 70mg during DBTP. One fatality occurred during the safety follow-up period¬ when no erenumab was administered and was considered unrelated to study drug by the investigator.

Outcomes	Baseline	Week 64	Week 268
Change from the DBTP baseline in MMD	8.5(2.5)	−4.8(3.9)*	−5.3(3.9)**
Change from the DBTP baseline in AMSM	6.2(2.7)	−3.2(3.4)	−4.4(3.3)

Data presented are mean(SD). *Mean of last 4 weeks of 1-year OLTP; ** Mean of last 4 weeks of 5-year OLTP. All patients received erenumab 70mg at Week 64 and 140mg at Week 268.
AMSM, acute migraine-specific medication; DBTP, double-blind treatment phase; MMD, monthly migraine days; OLTP, open-label treatment phase

Study outcomes at the end of 5-year OLTP among completers

Conclusion: Patients receiving erenumab over 5-years demonstrated consistent and sustained response. Safety was comparable to that observed in patients who received erenumab 70mg during the randomised phase of the trial.

Disclosure: Amgen Inc., Thousand Oaks, CA, funded this study. Erenumab is co-developed by Amgen and Novartis. A detailed disclosure from each author will be included in the oral/poster presentation.

OPR-137

Brain structural MRI predicts outcome of surgical treatment in trigeminal neuralgia

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Background and aims: To determine structural magnetic resonance imaging (MRI) alterations occurring in trigeminal neuralgia (TN) patients and to assess the predictive capability of abnormal neuroimaging findings for pain-maintenance and surgical outcomes.

Methods: 30 patients with idiopathic or classic TN, who underwent Gamma Knife radiosurgery and were followed for at least 24 months, were retrospectively analysed. Patients' structural pre-treatment MRI, and their pre- and post-operative clinical features were investigated. 15 age- and sex-matched healthy controls without any pain condition were also enrolled. Cortical thickness and subcortical gray matter (GM) atrophy were assessed in TN patients relative to controls, and among patient subgroups according to treatment outcomes (initial responders/non-responders, recurrence/long-lasting pain relief). MRI predictors of treatment outcomes were also explored.

Results: Cortical thinning of temporal, prefrontal, cingulate and somatosensory areas bilaterally were found in TN patients relative to controls. No significant cortical thickness and GM volume differences were found when TN initial (6 months after treatment) responder and non-responder patients were compared. Patients who experienced TN recurrence after initial pain relief were characterized by thicker parahippocampal and temporal lobe cortex bilaterally and higher volume of right amygdala and hippocampus compared to patients with long-lasting pain relief at last follow-up. Furthermore, baseline cortical thinning of right parahippocampal, left fusiform, left middle temporal cortex values and disease duration were associated with poor outcome after treatment at last follow-up in all TN patients ($R2= 0.57$, $p < 0.001$).

Conclusion: The study provides novel insights into TN brain structural alterations, which might contribute to TN development and its maintenance.

Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

OPR-138

NMA of migraine day reductions with CGRP pathway-targeting mAbs in migraine patients with multiple preventive failures

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Background and aims: Head-to-head randomized, controlled trials(RCT) comparing the efficacy of monoclonal antibodies(mAbs) targeting the calcitonin gene-related peptide(CGRP) pathway for migraine preventive treatment are not available. This network meta-analysis(NMA) assessed the relative efficacy of mAbs targeting the CGRP pathway for reducing average number of monthly migraine days(MMD) in patients with chronic or episodic migraine(CM or EM) with multiple prior treatment failures.

Methods: A systematic literature review(SLR) was conducted to identify placebo-controlled RCT evaluating the effects of fremanezumab quarterly(675mg), fremanezumab monthly(225mg), galcanezumab(120mg), erenumab(140mg), and erenumab(70mg) on MMD in CM or EM patients with 2–4 and ≥3 prior preventive treatment failures. A Bayesian NMA was conducted to assess change from baseline in MMD over weeks 1–12 in patients with 2–4 and ≥3 prior treatment failures.

Results: The SLR identified six RCT for EM and four for CM for patients with ≥2 prior failures. Compared with placebo, median reductions in MMD among EM patients with 2–4 prior treatment failures were significantly greater for fremanezumab quarterly (3.10[95% credible interval(CrI):1.89,4.31]), fremanezumab monthly (3.20 [1.99,4.41]), galcanezumab 120mg (2.61[1.85,3.39]), and erenumab (70mg:0.87[1.34,3.06]; 140mg:1.87[1.27,2.47]). Reductions were numerically but not statistically significantly greater for fremanezumab versus erenumab(Table). There were no significant differences for fremanezumab versus erenumab or galcanezumab in the CM and CM/EM groups with 2–4 prior failures or the EM, CM, and CM/EM groups with ≥3 prior failures (Table).

Table. Comparison of Changes in MMD From Baseline Over Week 1-12 Among Patients With 2-4 and ≥3 Prior Migraine Preventive Treatment Failures

Comparison for MMD, median (95% CrI)	Fremanezumab quarterly	Fremanezumab monthly	Galcanezumab 120 mg	Erenumab 140 mg	Erenumab 70 mg
2-4 prior failures					
EM					
Vs placebo	3.10 (1.89, 4.31)	3.20 (1.99, 4.41)	2.61 (1.85, 3.39)	1.87 (1.27, 2.47)	0.87 (-1.34, 3.06)
Vs erenumab 70 mg	2.22 (-0.28, 4.73)	2.33 (-0.16, 4.84)	1.74 (-0.58, 4.08)	1.00 (-1.17, 3.19)	—
Vs erenumab 140 mg	1.22 (-0.12, 2.57)	1.32 (-0.02, 2.69)	0.73 (-0.24, 1.72)	—	—
Vs galcanezumab 120 mg	0.49 (-0.96, 1.92)	0.60 (-0.85, 2.01)	—	—	—
CM					
Vs placebo	3.09 (1.84, 4.37)	3.70 (2.45, 4.96)	4.07 (2.85, 5.31)	3.90 (3.01, 4.79)	2.50 (1.61, 3.39)
Vs erenumab 70 mg	0.59 (-0.94, 2.14)	1.20 (-0.35, 2.76)	1.57 (0.08, 3.09)	1.40 (0.44, 2.35)	—
Vs erenumab 140 mg	-0.80 (-2.34, 0.73)	-0.20 (-1.74, 1.35)	0.17 (-1.32, 1.68)	—	—
Vs galcanezumab 120 mg	-0.97 (-2.73, 0.78)	-0.37 (-2.12, 1.39)	—	—	—
CM/EM					
Vs placebo	3.10 (2.27, 3.93)	3.50 (2.67, 4.33)	3.10 (2.25, 3.94)	N/A	N/A
Vs galcanezumab 120 mg	-0.00 (-1.18, 1.18)	0.40 (-0.77, 1.59)	—	N/A	N/A
≥3 prior failures					
EM					
Vs placebo	3.98 (1.84, 6.13)	3.98 (1.86, 6.07)	2.90 (1.09, 4.70)	N/A	N/A
Vs galcanezumab 120 mg	1.09 (-1.71, 3.90)	1.09 (-1.70, 3.82)	—	N/A	N/A
CM					
Vs placebo	2.90 (1.33, 4.46)	3.00 (1.41, 4.58)	5.18 (3.27, 7.12)	N/A	N/A
Vs galcanezumab 120 mg	-2.29 (-4.79, 0.22)	-2.18 (-4.71, 0.33)	—	N/A	N/A
CM/EM					
Vs placebo	3.39 (2.05, 4.74)	3.49 (2.15, 4.81)	4.49 (2.57, 6.45)	N/A	N/A
Vs galcanezumab 120 mg	-1.11 (-3.47, 1.24)	-1.00 (-3.36, 1.31)	—	N/A	N/A

MMD, monthly migraine days; EM, episodic migraine; CrI, credible interval; CM, chronic migraine; N/A, not available.

Table. Comparison of Changes in MMD From Baseline Over Week 1–12 Among Patients With 2–4 and 3 Prior Migraine Preventive Treatment Failures

Conclusion: Fremanezumab, galcanezumab, and erenumab showed statistically significant reductions in MMD versus placebo in migraine patients with multiple prior preventive failures. No statistically significant differences were noted for fremanezumab versus erenumab or galcanezumab.

Disclosure: This network meta-analysis (NMA) was funded by Teva Pharmaceuticals.

OPR-139

Pooled analysis of efficacy of fremanezumab for reducing disability and acute medication overuse in migraine patients

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Background and aims: Migraine patients who overuse acute headache medications may experience higher levels of pain and disability. Fremanezumab, a fully-humanized monoclonal antibody (IgG2a) that selectively targets calcitonin gene-related peptide (CGRP), has proven efficacy for migraine prevention in adults. These pooled analyses evaluated fremanezumab in a subgroup of patients who overused migraine-specific acute medication (triptan or ergot use 10 days/month) at baseline (MO subgroup).

Methods: These pooled analyses included data from three clinical trials (HALO episodic migraine [EM], HALO chronic migraine [CM], and FOCUS), in which patients were randomized to 12 weeks of double-blind treatment with quarterly fremanezumab, monthly fremanezumab, or placebo. Assessments included changes from baseline in monthly migraine days (MMDs), days of acute headache medication use, and disability outcomes (6-item Headache Impact Test [HIT-6] and Migraine Disability Assessment [MIDAS]), as well as the proportion of patients who reverted to not overusing acute medication in the MO subgroup.

Results: Of the pooled population of 2,842 patients, 749 were included in the MO subgroup. Quarterly and monthly fremanezumab treatment provided significant reductions in MMDs and monthly days of acute medication use versus placebo (Table). Fremanezumab treatment also resulted in significant reductions in HIT-6 and MIDAS scores versus placebo (Table). A significantly higher proportion of patients reverted to no medication overuse with fremanezumab treatment versus placebo (Table).

Table. Efficacy, Disability, and Medication Use in Patients Overusing Acute Migraine-specific Medications at Baseline

Outcome	Placebo (n = 240)	Quarterly fremanezumab (n = 270)	Monthly fremanezumab (n = 239)
Change from baseline in MMDs during 12 weeks, LSM (SE)	−1.7 (0.37)	−4.8 (0.37)[a]	−5.4 (0.38)[a]
Change from baseline in monthly days with acute medication use during 12 weeks, LSM (SE)	−1.6 (0.36)	−4.9 (0.35)[a]	−5.4 (0.37)[a]
Change from baseline in HIT-6 score during 12 weeks, LSM (SE)[b]	−2.7 (0.55)	−5.1 (0.51)[c]	−6.7 (0.52)[a]
Change from baseline in MIDAS score during 12 weeks, LSM (SE)[d]	−9.1 (4.43)	−23.3 (4.42)[a]	−31.2 (4.65)[a]
Patients reverting to no medication overuse at 12 weeks, n (%)	67 (28)	143 (53)[a]	145 (61)[a]

MMDs, monthly migraine days; HIT-6, 6-item Headache Impact Test; MIDAS, Migraine Disability Assessment.
[a]P <0.0001 versus placebo.
[b]Pooled HALO CM/FOCUS population: placebo, n = 211; quarterly fremanezumab, n = 246; monthly fremanezumab, n = 223.
[c]P = 0.0002 versus placebo.
[d]Pooled HALO EM/FOCUS population: placebo, n = 141; quarterly fremanezumab, n = 151; monthly fremanezumab, n = 137.
[e]P = 0.0040 versus placebo.

Table. Efficacy, Disability, and Medication Use in Patients Overusing Acute Migraine-specific Medications at Baseline

Conclusion: Treatment with fremanezumab was effective and resulted in significant reductions in disability and overuse of acute migraine-specific abortive medications, demonstrating the benefits of fremanezumab in those with overuse of acute migraine-specific medications.

Disclosure: Studies and analyses were funded by Teva Pharmaceuticals.

COVID-19 2

OPR-140

CNS and PNS complications of COVID-19: a prospective tertiary center cohort with 3-month follow-up

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Background and aims: To systematically describe CNS and PNS complications in hospitalized COVID-19 patients.

Methods: We conducted a prospective, observational study of adult patients from a tertiary referral center with confirmed COVID-19. All patients were screened daily for neurological and neuropsychiatric symptoms during admission and discharge. Three-month follow-up data were collected using electronic health records. We classified complications as caused by SARS-CoV-2 neurotropism, immune-mediated or critical illness-related.

Results: From April-September 2020, we enrolled 61 consecutively admitted COVID-19 patients, 35 (57%) of whom required ICU management for respiratory failure. Forty-one CNS/PNS complications were identified in 28 of 61 patients and were more frequent in ICU compared to non-ICU patients. The most common CNS complication was encephalopathy (n=19, 31.1%), which was severe in 13 patients (GCS 12), including eight with akinetic mutism. Length of ICU admission was independently associated with encephalopathy (OR=1.22). Other CNS complications included ischemic stroke, a biopsy-proven acute necrotizing encephalitis, and transverse myelitis. The most common PNS complication was critical illness polyneuromyopathy (13.1%), with prolonged ICU stay as independent predictor (OR=1.14). Treatment-related PNS complications included meralgia paresthetica. Of 41 complications in total, three were para/post-infectious, 34 were secondary to critical illness or other causes, and four remained unresolved. Cerebrospinal fluid was negative for SARS-CoV-2 RNA in all five patients investigated.
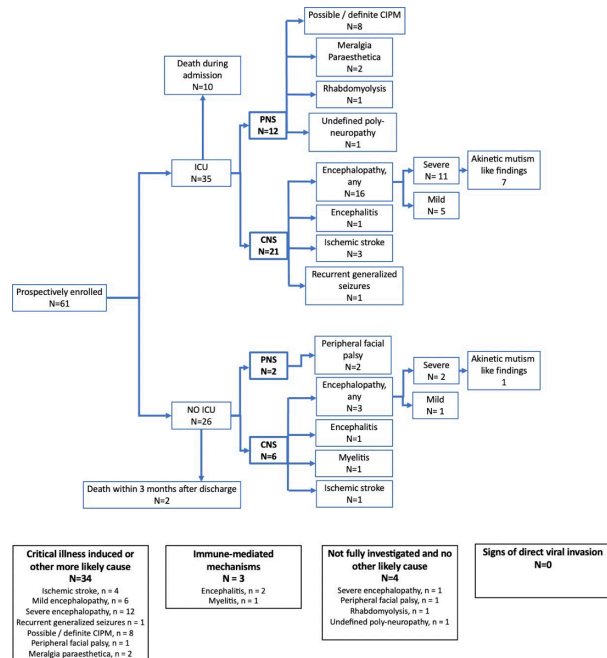
FIGURE 1 – Flow-chart of patient inclusion and observed neurological complications
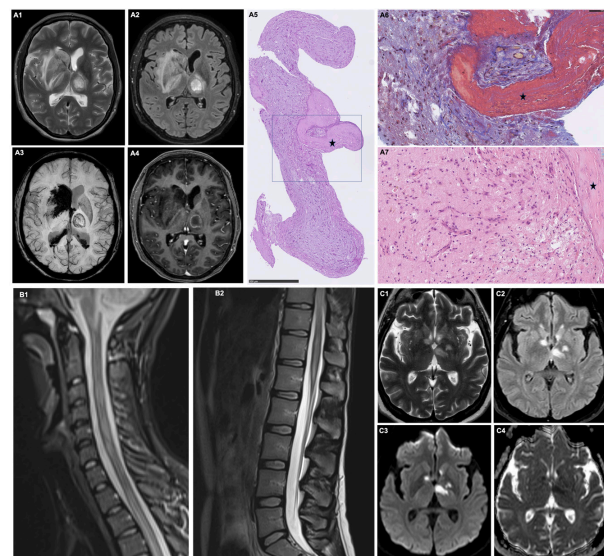
FIGURE 2 – Brain and spinal imaging and histopathology from probable COVID-19 encephalitis and myelitis

Conclusion: CNS/PNS complications were common in hospitalized COVID-19 patients, particularly in the ICU, and often attributable to critical illness. When COVID-19 was the primary cause for neurological disease, no signs of viral neurotropism were detected, but laboratory changes suggested autoimmune-mediated mechanisms.

Disclosure: The authors declare that they have no conflcts of interest.

OPR-141

Neuro-COVID in the northern Portuguese population

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Background and aims: COVID-19 related acute neurological phenotypes have been reported in over 30% of hospitalized patients. However, multicentric studies providing a population-based overview are still lacking.
Methods: We conducted a retrospective multicentric study in five hospitals in Northern Portugal, between March 1st and June 30th 2020. Patient e-records were systematically revised using a standardized form to identify neurological manifestations stratified by type and severity.
Results: From a total of 13,144 persons diagnosed with COVID-19 in the northern region, 2,795 (21.3%) required hospitalization. We reviewed a sample of 1,261 (45.1%) hospitalized patients and found a rate of 362 neurological manifestations per 1000 admitted COVID-19 patients, estimating a total of 1009 hospitalized patients with a neurological manifestation in the Northern Region. Patients with neurologic manifestations were younger (p=0.002), and the most frequent neurological symptoms were headache (13.4%), delirium (10.1%) and impairment of consciousness (9.7%). We observed a rate of 7.8 severe neurological events per every 1000 COVID-19 infected patients, including stroke, seizures, Guillain-Barre syndrome and myelopathy. The fatality among patients with neurological manifestations was 19.8%, and 15.6% had a modified Rankin Scale of 4-5 at hospital discharge.
Conclusion: We characterized the population of hospitalized COVID-19 patients from the northern region of Portugal and found that neurological symptoms are common and associated with a high degree of disability. CNS involvement with criteria for in-hospital admission was observed in a significant proportion of patients. Neurology support is highly relevant in the multidisciplinary care of COVID-19 patients.
Disclosure: This work was partially funded by "Fundação para a Ciência e Tecnologia", Grant nº229 (RESEARCH4 COVID-19). No conflicts of interest to report.

OPR-142

Brain metabolism and persistent olfactory deficits after SARS-CoV-2 infection: an FDG-PET study

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Background and aims: Coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 infection has been associated with a number of neurological complications, including persistent hyposmia. Despite its relative frequency the neural bases of hyposmia post-SARS-Cov2 infection are to date poorly understood.
Methods: 22 patients (12 males and 10 females; mean age 64±10.5 years, range 35–79) underwent whole-body [18] F-FDG-PET including a dedicated brain acquisition following their recovery after SARS-CoV-2 infection. Patients that previously required mechanic ventilation or showed severe respiratory distress syndrome due to SARS-CoV-2 infection were excluded given the potential independent effect of these clinical scenarios on brain metabolism. Among the enrolled patients, presence of isolated persistent hyposmia, as assessed with the smell diskettes olfaction test, was shown in fourteen subjects. A voxelwise analysis was used to identify brain regions of relative hypomebolism in hyposmic patients compared to a group of 61 age- and sex-matched healthy controlsStructural connectivity of these regions was assessed with the BCB toolkit.
Results: Relative hypometabolism was demonstrated in bilateral parahippocampal and fusiform gyri and in left insula in hyposmic patients with respect to controls. Structural connectivity maps showed the involvement of the bilateral longitudinal fasciculi.
Conclusion: Here we provide the first evidence of cortical hypometabolism in patients with isolated persistent hyposmia after SARS-CoV-2 infection without an history of severe respiratory distress. ^{18}F-FDG-PET may play a role in the identification of long-term brain functional sequelae of COVID-19.
Disclosure: Silvia Morbelli and Flavio Nobili have received speaker honoraria from G.E. Healthcare. Matteo Pardini receives research support from Novartis. All other authors declare no conflict of interest.

OPR-143

Primary intracerebral haemorrhage during SARS-CoV-2 outbreak

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R. Altavilla [8], M. Roncoroni [9], S. Beretta [10], L. Lorusso [11],
A. Cavallini [12], A. Prelle [13], D. Guidetti [14], S. La Gioia [15],
P. Santalucia [8], C. Zanferrari [16], G. Grampa [17], E. D'Adda [18],
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Background and aims: Mounting data has been published as to the impact of SARS-CoV-2 on cerebrovascular events, particularly on ischemic strokes. Our study addresses the clinical course of patients with cerebral haemorrhage and simultaneous SARS-CoV-2 infection, paying particular attention to both SARS-CoV-2 positive and negative patients hospitalized during the pandemic.

Methods: The Italian Society of Hospital Neurosciences (SNO) promoted a multicentre, retrospective, observational study (SNO-COVID-19), involving 20 Neurology Units in Northern Italy. Data were collected on patients consecutively admitted to neurological departments, from March 1st to April 30th with cerebrovascular diseases, occurring either at home or during hospitalization for other causes.

Results: 949 patients were enrolled (average age 73.4 years; 52.7% males); 135 patients had haemorrhagic stroke and 127 (13.4%) had a primary ICH. Only 16 patients with ICH (12.6%) had laboratory confirmed SARS-CoV-2 infection, clinically expressed or not. SARS-CoV-2 related pneumonia or respiratory distress, lobar location and previous antiplatelet or anticoagulant treatment were the only factors significantly associated with increased mortality in ICH. SARS-CoV-2 infection, regardless of respiratory involvement, led to a non-significantly increased risk of in-hospital death.

Conclusion: Our study confirms that age, ICH location and previous antiplatelet or anticoagulant treatment are predictors of in-hospital death. Unlike ischemic stroke, ICH in SARS-CoV-2 patients led only to a slight increase in mortality, mainly due to respiratory involvement.

Disclosure: The authors declare that they have no conflict of interest

OPR-144

COVID-19 in patients with dementia : clinical features and predictive factors of mortality in a cohort of 125 patients

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Background and aims: There is limited evidence on the characteristics and outcome of COVID-19 in patients with dementia. We report a cohort study on 125 patients with dementia hospitalized for a confirmed SARS-CoV-2 infection.

Methods: We conducted a prospective study in two gerontologic Covid Units in Paris, France, from March 14th 2020 to May 7th 2020. Patients with dementia hospitalized for confirmed infection were systematically enrolled. A binary logistic regression analysis was performed to identify factors associated with mortality at 21 days.

Results: We included 125 patients. Median age was 86 (IQI 82–90); 59.4% were female. Most common causes of dementia were Alzheimer's disease, mixed dementia and vascular dementia. 67.2% had two comorbidities; 40.2% lived in a long-term care facility. The most common symptoms at COVID-19 onset were confusion and delirium (79%), asthenia (74.4%) and fever (70.5%) before polypnea (49.6%) and desaturation (48.8%). Falls were frequent at the initial phase of the disease (34%). The fatality rate at 21 days was 22.4%. Chronic kidney disease and CRP at admission were independent factors of death. Persisting confusion, mood and behavioral disorders were observed in survivors (19.2%).

Conclusion: In demented patients, SARS-CoV-2 was frequently revealed by confusion and asthenia and was associated with severe outcome. COVID19 testing should be considered in front of any significant change from baseline in patients with dementia.

Disclosure: No conflict of interest

Movement disorders: Clinical

OPR-075

Ferroptosis, a recently identified cell death, as a therapeutic target for Parkinson's disease

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Background and aims: Ferroptosis is a new form of regulated cell death characterized by the iron-dependent accumulation of lipid hydroperoxides to lethal levels, which is a key marker of this pathway. Recently, we demonstrated that ferroptosis is prevalent in pro-oxidant models of Parkinson's disease. Furthermore, several reports have characterized LOXs as key drivers of lipid peroxidation during ferroptosis. We aim to determine in a cell model, neuroprotective effects of targeting lipoxygenases (LOXs), central players in Ferroptosis.
Methods: By qPCR, we examined the expression pattern of LOXs in LUHMES cells, a human neuronal precursor derived cell line, which can be differentiated into mature dopaminergic neurons. To determine whether the inhibition of LOXs confer resistance to ferroptosis, we treated LUHMES cells with lipoxygenases inhibitors or silenced LOXs genes using siRNA. Then we induced ferroptosis with two inducers, RSL3 and Erastin. Cell death was measured after 24 hours of treatment by rezasurin assay and levels of lipid peroxidation were detected by flow cytometry using a lipophilic reactive oxygen species sensor (Bodipy 581/591 C11)
Results: We have observed that selective LOXs inhibitors conferred a high neuroprotection against RSL3 and Erastin-induced ferroptotic cell death. Similar results were obtained by decreasing the expression levels of genes detected par qPCR (15-LOX, 15B-LOX and 12B-LOX). Levels of lipid peroxidation in response of RSL3 or Erastin were equally reduced by pharmacologic or genetic inhibition of LOXs.
Conclusion: The implication of ferroptosis in neurodegeneration of PD offers wide possibilities of neuroprotective strategies and targeting lipoxygenases in particular seems to be a promising one.
Disclosure: The authors have nothing to declare.

OPR-092

Parkinson's disease Mobile Application v2 detects potential disease modifying effect of prasinezumab

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Background and aims: Digital health technologies (DHTTs) enable remote and frequent monitoring of motor symptoms in Parkinson's disease (PD), and may more readily detect effects of disease modifying therapies compared to infrequently administered clinical scales. We report the effects of prasinezumab, an anti-alpha synuclein monoclonal antibody, on motor disease progression measured with the Roche PD Mobile Application v2 (ph2 PASADENA study; NCT03100149).
Methods: 316 individuals recently diagnosed with PD were randomized to placebo, 1500mg and 4500mg dose groups. All received a smartphone/watch, performed daily active motor tests, and carried/wore devices throughout the day. Seventeen pre-specified sensor features were aggregated over fortnights. Linear mixed effect models with random slopes fit each feature's change from baseline. Random mixed effects models modeled nonlinear data. Effects of interest were defined as $p < 0.2$, and multiple comparison correction was applied at 15% false discovery rate.
Results: Features from speeded tapping, hand-turning, U-turning and spontaneous hand gestures showed treatment effects favoring prasinezumab. One feature (spiral drawing accuracy/time) showed an effect favoring placebo, with divergent results for drawing accuracy and time. Tremor, Speech, Sustained Phonation and SDMT features did not differ across groups. Two features survived FDR-correction, both favoring prasinezumab: least affected side speeded tapping, and gesture power in daily life reflecting an impact on patients' spontaneous motor behavior in daily life. Additional subgroup analyses will be presented.
Conclusion: In individuals with PD treated with prasinezumab, daily quantification of motor severity via a DHTT showed a divergence of slopes, which is consistent with an effect of disease progression.
Disclosure: This research has been funded by F. Hoffmann-La Roche AG and Prothena Biosciences Inc.

OPR-093

Assessment of brain concentration of UCB0599, in development for Parkinson's disease (PD), in humans using PET

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Background and aims: Alpha-synuclein misfolding is one of the best genetically and pre-clinically validated early steps in the cascade leading to loss of dopaminergic neurons, the hallmark of PD. UCB0599, an orally administered, brain penetrant, small molecule inhibitor of alpha-synuclein monomer misfolding, is under investigation for the potential to slow the progression of PD. The safety, tolerability, pharmacokinetics and brain biodistribution of UCB0599 were assessed using PET in a phase 1 study.

Methods: Healthy volunteers (aged 25–55 years; n=4) underwent PET/CT twice on Day 1: once after an intravenous micro-dose (maximum of 10ug) of 11C-UCB0599, and once after an intravenous micro-dose of 11C-UCB0599 in addition to a single 360mg oral dose of UCB0599.

Results: There were no severe, serious or drug-related treatment-emergent adverse events. UCB0599 uptake was observed in all white and grey matter regions. Good brain penetration of UCB0599 was observed. The PET outcome measure (11C-UCB0599 volume of distribution) corresponding to total brain:total plasma at equilibrium (range: 0.3 to 0.8) and brain biodistribution appeared to be independent of dose administered. The rate of UCB0599 brain uptake was consistent with rapid free distribution of UCB0599 across the blood-brain-barrier.

Conclusion: Oral UCB0599 was generally well-tolerated and distributed throughout the brain. UCB0599 brain exposure was similar to data obtained in animal models of PD, which were associated with reductions in alpha-synuclein pathology and improved phenotype. Coupled with the data from animal models of PD, these results support the continued development of UCB0599 for the potential to slow the progression of PD.

Disclosure: This study was funded by UCB Pharma.

OPR-104

Phase II PASADENA Part one Week 52 results: Evaluating safety and efficacy of prasinezumab in early Parkinson's disease

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Background and aims: No current treatments slow the progression of Parkinson's disease (PD). The PASADENA study (NCT03100149), a 52-week randomised, double-blind, placebo-controlled study, evaluated the efficacy and safety of intravenous prasinezumab, a monoclonal antibody targeting extracellular alpha-synuclein, in early PD.

Methods: 316 participants were enrolled (diagnosis ≤2 years; Hoehn & Yahr Stages I–II). The primary endpoint was the change in Movement Disorder Society-Unified Parkinson's disease Rating Scale (MDS-UPDRS) Total score from baseline to Week 52. Secondary and exploratory endpoints included: changes in MDS-UPDRS Part III, MDS-UPDRS Part III subscores, other clinical and digital endpoints, and imaging biomarkers.

Results: MDS-UPDRS Total score was -1.30 (-14%; 80% CI: -3.18, 0.58) for pooled doses versus placebo; -2.02 for prasinezumab 1500mg (–20.8%; 80% CI: -4.21, 0.18) and -0.62 for prasinezumab 4500mg (-6.4%; 80% CI: –2.82, 1.58). MDS-UPDRS Part III was -1.44 (-25.0%; 80% CI: -2.83, -0.06) for pooled treatment versus placebo; -1.88 for prasinezumab 1,500mg (-33.8%; 80% CI: -3.49, -0.27) and -1.02 for prasinezumab 4,500mg (-18.3%; 80% CI: -2.64, 0.61). MDS-UPDRS Part III site rating (Figure 1), MDS-UPDRS Part III bradykinesia subscore, digital motor endpoints (Figure 2), and time to worsening of motor symptoms supported this signal. Additional subgroup analyses will also be presented. There were no life-threatening adverse events or immunogenicity concerns.
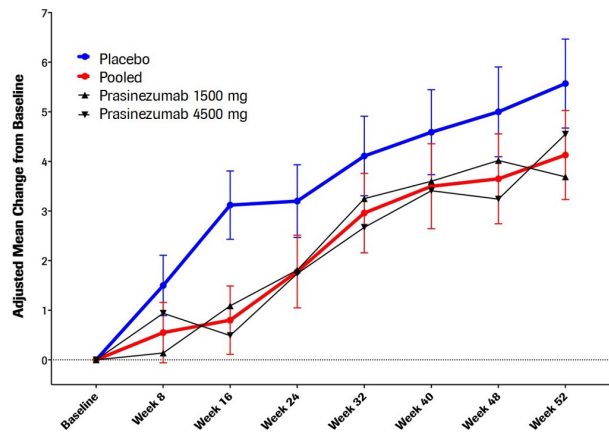
Figure 1. Change in MDS-UPDRS Part III Total Score from baseline at Week 52 (site rating)
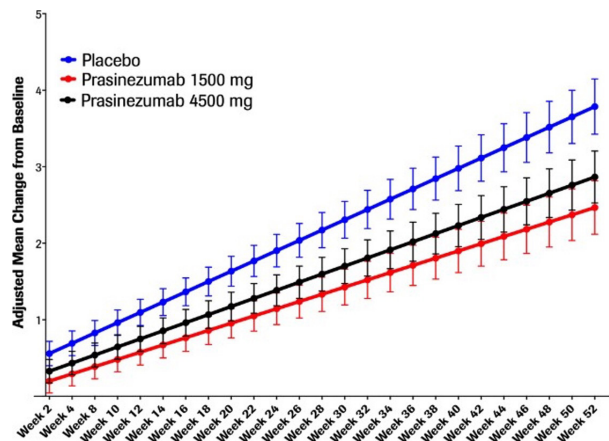

Figure 2. Change in Digital PASADENA Motor Score

Conclusion: Prasinezumab had a favourable safety profile and is the first anti-alpha-synuclein antibody showing efficacy signals on clinical progression of PD motor features, warranting further study.

Disclosure: This study was sponsored by Prothena Biosciences Inc and F. Hoffmann-La Roche Ltd.

OPR-108

Safinamide Improves Non-Motor Symptoms Burden in Parkinson´s Disease: An Open-label Prospective Study

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Background and aims: Some studies observed a benefit of Parkinson´s disease (PD) patients after treatment with safinamide in some non-motor symptoms (NMS). The aim of this study was to analyze the effectiveness of safinamide on NMS burden in PD.

Methods: SAFINONMOTOR (an open-label study of the effectiveness of SAFInamide on NON-MOTOR symptoms in Parkinson´s disease patients) is a prospective open-label single-arm study conducted in five centers from Spain. The primary efficacy outcome was the change from baseline (V1) to the end of the observational period (six months) (V4) in the Non-Motor Symptoms Scale (NMSS) total score.

Results: 50 patients were included between May/2019 and February/2020 (age 68.5±9.12 years; 58% women; 6.4±5.1 years from diagnosis). At six months, 44 patients completed the follow-up (88%). The NMSS total score was reduced by 38.5% (from 97.5±43.7 in V1 to 59.9±35.5 in V4; p<0.0001; table 1 and figure 1). By domains, improvement was observed in sleep/fatigue (-35.8%; p=0.002), mood/apathy (-57.9%; p<0.0001), attention/memory (-23.9%; p=0.026), gastrointestinal symptoms (-33%; p=0.010), urinary symptoms (-28.3%; p=0.003), and pain/miscellaneous (-43%; p<0.0001) (table 1 and figure 2). Quality of life (QoL) also improved with a 29.4% reduction in the PDQ-39SI (from 30.1±17.6 in V1 to 21.2±13.5 in V4; p<0.0001) (table 1 and figure 2). A total of 21 adverse events in 11 patients (22%) were reported, Five of which were severe (not related to safinamide). Dyskinesias and nausea were the most frequent (6%).
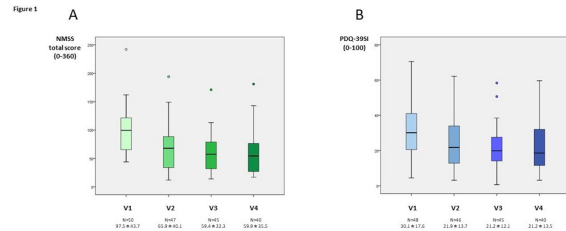

Figure 1.

Figure 2.

Conclusion: Safinamide is well tolerated and improves NMS burden and QoL in PD patients at six months.

Disclosure: Nothing to disclose..

	V1	N	V4	N	Δ V1-V4	p
NMSS total score	97.48 ± 43.70	50	59.91 ± 35.49	44	-38.5%	<0.0001
- Cardiovascular	9.58 ± 2.46	50	6.72 ± 11.94	44	-29.9%	0.268
- Sleep / fatigue	36.08 ± 21.77	50	23.15 ± 18.12	44	-35.8%	0.003
- Mood / apathy	34.42 ± 29.89	50	14.49 ± 19.63	44	-57.9%	<0.0001
- Perceptual symptoms	4.33 ± 8.67	50	2.84 ± 5.88	44	-34.4%	0.630
- Attention / memory	17.50 ± 17.09	50	13.32 ± 18.19	44	-23.9%	0.026
- Gastrointestinal symptoms	19.61 ± 18.01	50	13.13 ± 13.39	44	-33.0%	0.016
- Urinary symptos	42.72 ± 30.41	50	30.62 ± 23.94	44	-28.3%	0.004
- Sexual dysfunction	28.25 ± 35.69	50	25.28 ± 33.58	44	-10.5%	0.784
- Miscellaneous	33.33 ± 20.73	50	18.99 ± 14.03	44	-43.0%	<0.0001
PDQ-39SI	30.07 ± 17.61	49	21.24 ± 13.48	44	-29.4%	<0.0001
- Mobility	34.55 ± 27.79	49	29.09 ± 26.85	44	-15.8%	0.037
- Activities of daily living	26.50 ± 23.94	49	17.80 ± 17.96	44	-32.8%	0.014
- Emotional well-being	44.30 ± 29.34	49	26.33 ± 23.01	44	-40.6%	<0.0001
- Stigmatization	15.82 ± 22.79	49	7.67 ± 13.13	44	-51.5%	0.021
- Social support	7.48 ± 16.51	49	3.59 ± 12.63	44	-52.0%	0.302
- Cognition	27.17 ± 22.00	49	23.72 ± 22.49	44	-12.7%	0.876
- Communication	20.07 ± 26.73	49	12.12 ± 15.19	44	-39.6%	0.203
- Pain and discomfort	44.56 ± 27.35	49	33.33 ± 19.93	44	-25.2%	0.018

Percentage of change in the NMSS total score and the PDQ-39SI and each domain of both scales from V1 (baseline) to V4 (6 months ± 15 days). P values were computed using the Wilcoxon signed-rank test. NMS, Non-motor symptoms; PD, Parkinson´s disease; PDQ-39SI, 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index.

Table 1.

OPR-150

Parkinson's disease Symptoms Before and After Levodopa-Carbidopa Intestinal Gel: a Subanalysis From the COSMOS Study

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Background and aims: Patients with Parkinson's disease (PD) initially present with motor and nonmotor symptoms that worsen with progressive disease. There is limited information regarding the response of individual symptoms to levodopa-carbidopa intestinal gel (LCIG) treatment.

Methods: COSMOS (COmedication Study assessing Mono- and cOmbination therapy with levodopa-carbidopa inteStinal gel; NCT03362879) is a retrospective, cross-sectional, multicountry, postmarketing observational study. Patients with advanced PD were evaluated at a single study visit conducted at least 12 months after LCIG initiation and via retrospective record review. This subanalysis assessed changes in PD symptoms following LCIG introduction (improvement/no change vs worsening).

Results: Of 409 total patients, most reported improvement or no change in individual symptoms following LCIG initiation [Table 1]. In general, patients experiencing improvement or no change in symptoms were younger, had shorter disease duration, had greater improvements in "Off" time following LCIG treatment, and had greater improvements in dyskinesia severity following LCIG treatment compared with patients experiencing symptom worsening [Table 2]. Rates of healthcare resource use generally aligned with progression of motor symptoms. Patients with balance problems, freezing of gait, or gait impairment at study visit had the highest rates of resource use [Table 3]. Adverse events were similar to those reported in other LCIG studies.

Table 1. Change in Symptoms Following LCIG Treatment

Motor Symptoms	Improved, n (%)	Not Changed, n (%)	Worsened, n (%)
Tremor	207 (52.5)	156 (39.6)	31 (7.9)
Dystonia/cramps	166 (43.2)	173 (45.1)	45 (11.7)
Gait impairment	183 (46.2)	129 (32.6)	84 (21.2)
Balance problems	151 (38.5)	136 (34.7)	105 (26.8)
Freezing of gait	202 (52.2)	131 (33.9)	54 (14.0)
Dyskinesia	202 (52.6)	105 (27.3)	77 (20.1)
Nonmotor Symptoms			
Anxiety	144 (38.4)	183 (48.8)	48 (12.8)
Pain	142 (37.7)	179 (47.5)	56 (14.9)
Cognitive impairment	50 (12.9)	210 (54.1)	128 (33.0)
Depression	136 (35.1)	173 (44.6)	79 (20.4)
Apathy	66 (18.0)	216 (59.0)	84 (23.0)
Fatigue	143 (40.6)	133 (37.8)	76 (21.6)
Urinary symptoms	107 (29.4)	144 (39.6)	113 (31.0)
Constipation	163 (44.5)	141 (38.5)	62 (16.9)
Orthostatic hypotension	46 (12.3)	265 (71.0)	62 (16.6)
Symptoms Related to Treatment			
Hypersexuality	23 (6.2)	332 (89.0)	18 (4.8)
Compulsive shopping	13 (3.4)	351 (91.9)	18 (4.7)
Gambling	16 (4.2)	361 (94.0)	7 (1.8)
Binge eating	23 (6.0)	340 (88.5)	21 (5.5)
Punding	25 (6.6)	325 (85.3)	31 (8.1)
DDS	22 (5.7)	348 (90.9)	13 (3.4)

Values represent the proportions of patients reporting improvement, no change, or worsening of symptoms from before LCIG initiation to patient visit.
Improved indicates positive changes on prevalence, severity, or frequency.
Not changed indicates that an existing symptom did not change; or that the symptom had not been present and did not develop.
Worsened indicates negative changes on prevalence, severity, or frequency.
DDS, dopamine dysregulation syndrome; LCIG, levodopa-carbidopa intestinal gel.

Table 2. Clinical Characteristics by Change in PD Motor Symptoms

Characteristic	Tremor		Dystonia		Gait Impairment		Balance Problems		Freezing of Gait		Orthostatic Hypotension	
Age at LCIG initiation, years	66.5 n = 348 (P = .3103)	67.6 n = 29	66.3 n = 326 (P = .2650)	67.6 n = 44	65.9 n = 296 (P = .0089)**	68.6 n = 82	66.0 n = 274 (P = .0515)	68.1 n = 103	66.1 n = 317 (P = .0643)	68.1 n = 53	66.3 n = 303 (P = .0308)*	68.9 n = 59
Time from PD diagnosis to LCIG initiation, years	13.0 n = 349 (P = .3119)	11.9 n = 29	12.8 n = 327 (P = .3223)	13.5 n = 44	12.8 n = 297 (P = .3706)	13.0 n = 82	12.6 n = 275 (P = .2125)	13.2 n = 103	12.7 n = 318 (P = .3026)	13.5 n = 53	12.5 n = 304 (P = .0210)*	14.7 n = 59
Change[a] in "Off" time, hours	–4.1 n = 252 (P = .3105)	–2.9 n = 19	–4.1 n = 241 (P = .2870)	–2.8 n = 27	–4.2 n = 221 (P = .0044)**	–3.1 n = 52	–4.2 n = 207 (P = .2271)	–3.7 n = 65	–4.2 n = 236 (P = .0255)*	–2.8 n = 34	–4.1 n = 224 (P = .5873)	–4.1 n = 44
Change[a] in dyskinesia duration, hours	–1.8 n = 244 (P = .9963)	–2.1 n = 20	–1.8 n = 235 (P = .6905)	–1.7 n = 26	–2.0 n = 214 (P = .0473)*	–0.9 n = 51	–1.7 n = 200 (P = .7210)	–2.1 n = 65	–1.9 n = 232 (P = .2395)	–1.3 n = 31	–1.7 n = 215 (P = .6054)	–2.4 n = 44
Change[a] in dyskinesia duration or "Off" time (during waking hours), hours	–6.0 n = 235 (P = .7797)	–5.5 n = 17	–6.1 n = 227 (P = .2256)	–4.1 n = 22	–6.3 n = 207 (P = .0067)**	–4.1 n = 46	–6.0 n = 194 (P = .9165)	–5.9 n = 59	–6.2 n = 222 (P = .0171)*	–4.0 n = 29	–5.9 n = 207 (P = .3493)	–6.5 n = 43
Change[a] in the severity of dyskinesias[b]	–0.9 n = 326 (P = .0581)	–0.5 n = 30	–0.9 n = 314 (P = .0078)**	–0.3 n = 39	–0.9 n = 281 (P = .0598)	–0.6 n = 79	–0.9 n = 257 (P = .4259)	–0.7 n = 99	–0.9 n = 304 (P = .0153)*	–0.4 n = 47	–0.9 n = 284 (P = .2414)	–0.7 n = 60

Values represent means for patients experiencing improvement or no change in individual motor symptoms (tremor, dystonia, gait impairment, balance problems, freezing of gait, or orthostatic hypotension).
Asterisks indicate statistical significance between patients with symptoms that improved or had no change vs patients with symptoms that worsened; $P < .05$ (*) and $P < .01$ (**).
[a]Change is measured from before LCIG treatment to study visit.
[b]Calculated as the weighted average of the change in the proportion of patients with dyskinesia from before LCIG initiation to patient visit.
LCIG, levodopa-carbidopa intestinal gel; PD, Parkinson's disease.

Table 3. Percentage of Patients that Use Healthcare Resources by Symptom Presence at Patient Visit

Healthcare Resource Use, %	Tremor	Dystonia	Gait Impairment	Balance Problems	Freezing of Gait	Orthostatic Hypotension
Primary occupancy						
Retired due to PD[a]	16	17	35	31	28	13
Sick leave due to PD[b]	0	33	50	33	17	33
Living situation[c]						
Permanent living in a nursing/home institution	25	25	81	63	63	31
Help in ADL	37	33	76	70	51	31
Problems before starting LCIG[c]						
Forgetting to take the pill	36	41	77	72	54	36
Dosage or medication error	34	42	78	71	49	38
Problems swallowing the pill	52	57	83	83	63	28
Help to remember to take the medication[c]	35	40	79	73	54	37
Physician-visit hospitalisation[c]						
Scheduled visits to physician	36	41	68	64	57	29
Extra visits to physician	36	44	63	63	50	31
Emergency room visits	52	48	91	83	61	37
Hospitalisation	43	51	80	80	56	27
Admissions due to PD	43	46	78	76	57	24
Frequency of visits[d]						
General practitioner (increased vs reduced[e])	8 vs 21	9 vs 23	8 vs 23	8 vs 23	7 vs 19	6 vs 27
Nurse (increased vs reduced[e])	16 vs 8	13 vs 8	18 vs 9	17 vs 8	14 vs 7	23 vs 10

[a]Based on the total number of retired patients, regardless of symptoms or reasons for retirement.
[b]Based on the total number of patients on sick leave, regardless of symptoms or reasons for sick leave.
[c]Based on the total number of patients using a given healthcare resource, regardless of symptom.
[d]Based on the total number of patients reporting a given symptom at study visit.
[e]Compared to before LCIG initiation.
ADL, activities of daily living; LCIG, levodopa-carbidopa intestinal gel.

Conclusion: Following more than 12 months of LCIG treatment, most patients experienced improvement or no change in symptoms, despite the natural progression of the disease. Treatment with LCIG may help control symptoms that impact healthcare resource use.

Ageing and Dementia 2

OPR-121

Promising diagnostic accuracy of Plasma GFAP within the AD continuum

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Background and aims: Due to the increasing number of patients suffering from Alzheimer's disease (AD), recent studies have been looking for a possibility to establish fluid biomarkers with conventional blood analysis. A promising biomarker for tracking neurodegeneration could be Glial Fibrillary Acidic Protein (GFAP), an intermediate filament protein of astrocytes. Analysis of GFAP in blood has shown an increase in patients with AD in comparison to healthy controls. The aim of this study was to examine the utility of GFAP as a possible biomarker along the AD continuum.

Methods: We included a total of 185 Patients, 141 Patients with a diagnosis along the clinical spectrum of AD, i.e. Subjective Cognitive Decline (SCD, n=18), Mild Cognitive Impairment (MCI, n=63), AD (n=60), and additionally 44 age-matched healthy controls (HC) with no sign of neurodegenerative disorder or cognitive decline. Concentrations of GFAP in Plasma and CSF were quantified using ultrasensitive single molecule array (SIMOA).

Results: Median Concentration of GFAP in plasma was 79pg/ml in HC, 111 pg/ml in SCD, 167.5pg/ml in MCI and 181.9pg/ml in AD. We observed a good diagnostic discrimination between HC, MCI and AD groups (p<0.001). Interestingly, analysis of GFAP in plasma could further distinguish between groups with SCD and AD (p=0.01).

Conclusion: Analysis of GFAP in plasma has shown a good diagnostic accuracy in differentiating patients with AD from healthy controls. Furthermore, this biomarker could aid in a better distinction of patients in different predementia stages and potentially give more information about disease progression than already established AD biomarkers.

Disclosure: Nothing to disclose.

OPR-122

Plasma Neurofilaments, Semantic Verbal Fluency and Clock Drawing Test may detect Alzheimer's disease Fast Decliners

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Background and aims: Alzheimer's disease (AD) is characterized by a heterogeneous course. Predicting a fast rather than a slow decline over time is crucial to provide a reliable prognosis and to elaborate stricter enrolment criteria in clinical trials. We aimed at identifying progression rate predictors to assess already at baseline the risk to fast progress

Methods: 65 AD subjects were included. At baseline, CSF AD biomarkers, neuropsychological assessment and plasma neurofilaments (NfL) concentrations were available. Magnetic Resonance Imaging (MRI) based adjustment for hippocampal volume and vascular burden was available in a sub-sample of 27 patients. Patients were labelled FAST or SLOW depending on the Mini Mental State Test (MMSE) points lost per year (FAST if more than three points). We adopted Receiver Operating Characteristics (ROC) curves and Linear Regression Models to assess the risk to fast decline

Results: At baseline no differences were found between FAST and SLOW subgroups in demographics, CSF AD biomarkers' concentrations and MMSE scores. FAST decliners had higher plasma NfL concentrations and performed worse at two neuropsychological tests: Semantic Verbal Fluency (SVF) and Clock Drawing Test (CDT). After adjustment for MRI parameters, CDT kept a trend towards significance (p=0.056). The risk to FAST decline over time was 4% if no predictor was abnormal and 79% if all the three predictors were abnormal

Conclusion: An easily applicable algorithm including plasma neurofilament measurement and two neuropsychological tests that are worldwide adopted in clinical practice (SVF and CDT) may allow the clinicians to reliably assess the risk to fast decline already at baseline

Disclosure: Nothing to disclose

OPR-123

Time in the salience network predicts conversion in presymptomatic mutation carriers in familial frontotemporal dementia

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Background and aims: Familial frontotemporal dementia (FTD) is characterised by a long presymptomatic prodrome followed conversion to symptomatic disease. There is a pressing need to understand the underlying pathophysiology caused by FTD mutations, and their relationship to clinical symptoms. Neurotransmitter changes, network topology and clinical phenotypes suggest that connectivity changes in FTD are dynamic.

Methods: For hypothesis generation, 38 participants with sporadic behavioural variant frontotemporal dementia and 30 healthy controls were recruited from Cambridge University. For hypothesis testing, 150 symptomatic FTD mutation carriers, 320 presymptomatic mutation carriers and 309 family members without mutations were included from the longitudinal multinational Genetic FTD Initiative (GENFI). They underwent clinical and neuropsychological testing and resting-state functional MRI. Dynamic connectivity was quantified by hidden Markov models, excluding participants with supra-threshold motion parameters. Key metrics of dynamic connectivity (switching rates, fractional occupancy), focussed on the salience network.

Results: In both cohorts, FTD increased the proportion of time spent with activation of the salience network, and components of the default mode network. In symptomatic participants, salience network occupancy correlated with neuropsychological impairment. In mutation carriers, salience network occupancy were related to age and Expected Years until Onset. In presymptomatic mutation carriers occupancy differed between those who subsequently converted to the symptomatic phase within two years. Baseline salience network occupancy predicted subsequent decline in neuropsychological function.
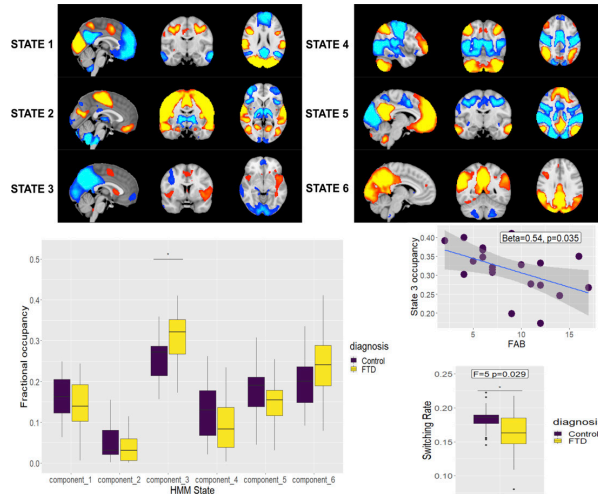
Mean activation maps for the six hidden Markov model states from Cambridge. Participants with frontotemporal dementia had increased time in state 3 (salience; F=7.8, corrected p=0.042), and time in this state correlated with the Frontal Assessment Battery.
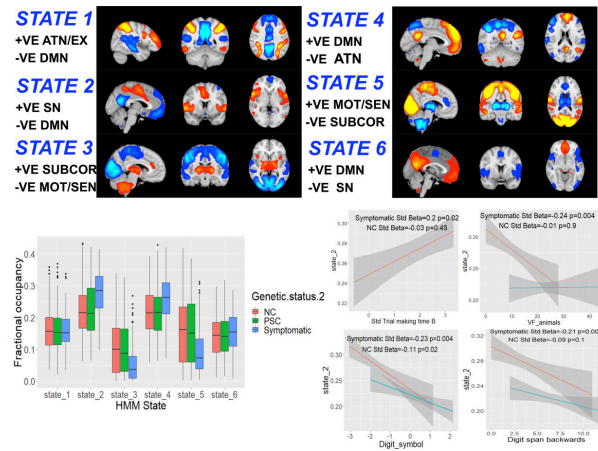
Dynamic connectivity in GENFI. Symptomatic participants had increased time in states predominantly representing salience network, correlating with neuropsychological assessment (symptomatic participants in red, non-carriers in blue).

SYMPTOMATIC
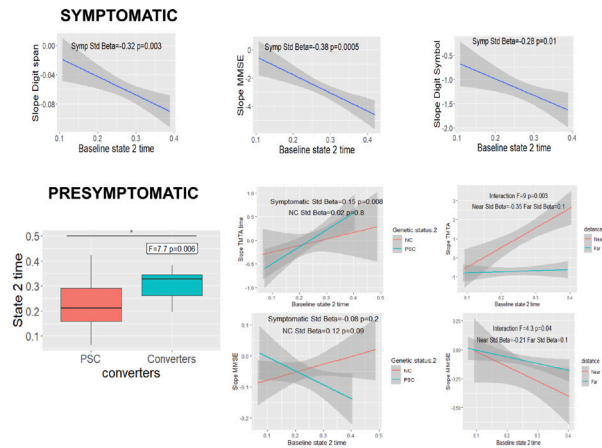
PRESYMPTOMATIC

Longitudinal GENFI analysis. Baseline salience occupancy predicts a) further cognitive decline in symptomatic patients, b) age-related decline in the presymptomatic phase and c) differed between converters and other presymptomatic mutation carriers

Conclusion: Dynamic network abnormalities in frontotemporal dementia predict cognitive decline and conversion to symptomatic disease

Disclosure: All authors have no disclosures relevant to this study

OPR-124

Interleukin 1B in Multiple Sclerosis: analysis of a polymorphism in the gene promoter region

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Background and aims: Increased IL-1B expression in and around multiple sclerosis (MS) lesions has been reported. The rs16944 (-511C>T) polymorphism, known to increase IL-1B expression, has been studied in MS populations, with inconsistent results. Our aim is to assess the role of rs16944 polymorphism in MS susceptibility and clinical outcome in a Portuguese cohort.

Methods: rs16944 polymorphism was genotyped in a cohort of 599 patients with a definitive MS diagnosis and 237 ethnically matched healthy controls. Demographic and clinical data, including the Expanded Disability Severity Score (EDSS), Multiple Sclerosis Severity Scale (MSSS) and Age-Related Multiple Sclerosis Severity (ARMSS), were reviewed. Statistical analyses were performed using SPSS (v26).

Results: No statistically significant differences were observed comparing genotypic frequencies between MS patients (47.1% CC, 42.1% CT, 10.8% TT) and controls (45.6% CC, 46.8% CT, 7.6% TT). We did not observe statistically significant differences according to HLA-DRB1*15, gender, MS course or disease modifying treatment. The presence of the rs16944T allele may predispose to a better clinical outcome measured by EDSS and ARMSS (EDSS: CC=4±2.5; CT+TT=3.5±2.5 p=0.041; ARMSS: CC=4.93±2.92; CT+TT=4.44±2.82, p=0.037).

Conclusion: The rs16944 (-511C>T) polymorphism may have a role on the MS clinical outcome. Further studies of the genetic and epigenetic mechanisms regulating IL-1B pathway are needed to clarify the link between this polymorphism and disease severity.

Disclosure: Nothing to disclose.

OPR-125

Benefit of albumin replacement to treat functional impairment in alzheimer's is robust to common sources of confounding

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Background and aims: The Alzheimer's Management By Albumin Replacement (AMBAR) study examined treatment effects over 14-months on the Alzheimer's disease Cooperative Study – Activities of Daily Living (ADCS-ADL), one of two AMBAR primary endpoints. AMBAR-treated patients with MMSE scores ranging from 18 to 26 had significantly less decline in ADCS-ADLs than placebo patients (Boada et al., 2020). This research presents sensitivity analyses on testing robustness of clinical trial and HEOR modeling assumptions.

Methods: AMBAR study details are reported elsewhere (Boada et al., 2020). In this analysis, three active treatment arms were pooled and compared to the placebo arm. Treatment response, defined as the difference in ADCS-ADL from the baseline to the final visit at month 14, was adjusted for patient level missing data (pattern-mixtures) and multiplicity in three sensitivity analyses.

Results: The analysis sample included 169 individuals receiving active treatment and 64 on placebo. The sample had a mean age of 69 years and was 54% female. A total of 70.5% of the sample completed all study visits. Among the 29.5% missing at least one visit, the majority (n=26, 8.1%), were lost to follow-up. Adjusted p-values obtained from the sensitivity analyses ranged from 0.0439, to 0.0491, to 0.0490), indicating sustained robust significance.

Conclusion: The previously reported functional benefits of AMBAR treatment on ADCS-ADL remained robust after sensitivity analyses adjusting for missing data and multiple comparisons.

Disclosure: This study was funded by Grifols SSNA a maker of Albutein®

OPR-126

Association of blood pressure, its treatment and treatment efficacy with white matter lesions in the 1000BRAINS study

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Background and aims: White matter lesions (WMLs) are a frequent finding in cerebral MRI scans of older people. Since vascular risk factors, especially hypertension, are associated with small vessel disease, offering a potential for preventive strategies, we analysed the association of blood pressure (BP), its treatment and treatment efficacy with WML volume in the population-based 1000BRAINs study.

Methods: In 560 participants of the 1000BRAINS study (65.2±7.5 years, 51.4% males), we analysed the association of systolic blood pressure (SBP), diastolic blood pressure (DBP) and antihypertensive medications with WML volume in univariable and multivariable linear regression models adjusting for confounding variables. Further, we analysed treatment efficacy using a classification of six BP treatment groups defined by antihypertensive medication and level of BP: 1) untreated BP <120/<80mmHg, 2) untreated SBP 120–139mmHg or DBP 80-89mmHg, 3) untreated BP 140/90mmHg, 4) treated BP <120/<80mm Hg, 5) treated SBP 120-139mmHg or DBP 80-89mmHg, 6) treated BP 140/90mmHg.

Results: In multivariable regression models adjusting for age, sex, education, depression, alcohol consumption and smoking, continuous SBP (B=0.63 per 10mmHg, 95%CI=0.32–0.94), DBP (0.64, 0.37–0.91) and antihypertensive treatment (1.23, 0.14–2.23) were significantly associated with WML volume (in cm3). Regarding treatment efficacy, only participants with hypertension despite treatment (treated BP 140/90mmHg) had significantly increased WML volume (4.24, 2.36–6.13) compared with normotension without treatment (untreated BP <120/<80mmHg).

Conclusion: Our results suggest, that WMLs represent a marker of advanced hypertension pathology, calling for early markers of brain damage such as structural and functional connectivity.

Disclosure: Nothing to disclose.

OPR-194

Genotype-phenotype data of PSEN1 p. CYS263PHE carriers in Belgian-Flanders Alzheimer's disease patients

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Background and aims: We identified 13 unrelated index patients carrying the presenilin 1 (PSEN1) missense mutation, p.Cys263Phe in an Alzheimer's disease (AD) patient's cohort of Flanders Belgian. In DR1633 family three affected relatives were identified (n=17). We aimed to delineate a clinicopathological phenotype compared to genotype–phenotype data of AD patients carrying other causal mutations i.e. PSEN1 (n=25), PSEN2 (n=1), and APP (n=5).

Methods: Reviewing medical records of mutation carriers to obtain clinicopathological data for defining genotype-phenotype data.

Results: Mean onset age of Cys263Phe carriers was 63.6±5.9 years (range 53–74), with a disease duration of 9.0±4.0 years (range 4–13). A positive familial history was present in 92.9% of the carriers and autosomal dominant co-segregation of AD in family DR1633. Amnestic presentation was present in all carriers, however five (38.5%) patients also showed significant frontal symptoms. OS1004 Neuroimaging (n=12) displayed diffuse (sub) cortical atrophy, with evident hippocampal atrophy in three carriers. We observed severe signs of small vessel disease in five patients. Cerebrospinal fluid AD biomarkers were characteristic for AD in all.

Neuropathology in two patients demonstrated severe levels of AD hallmarks plus severe signs of cerebral amyloid angiopathy (CAA). Carriers of p.Cys263Phe had a later age at onset (63.6 years) than other PSEN1 carriers (50.8 years) or other causal gene mutation carriers (51.1 years).

Conclusion: PSEN1 p.Cys263Phe carriers present with early-onset AD. Severe levels of AD neuropathology were seen with high levels of CAA. Disease onset of p.Cys263Phe carriers was later than other causal gene mutation carriers.
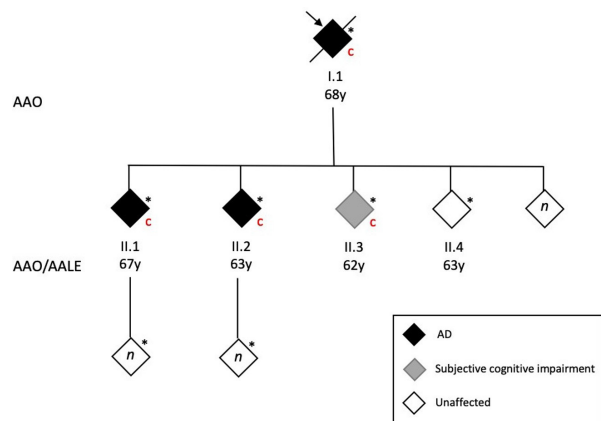
Figure 1. Pedigree DR1633 To protect the privacy of the family members, the gender of each person was masked, the order of sibs was scrambled and the number (n) of tested at-risk individuals shown in white diamonds was not specified. Filled symbols are clinically affected patients with their age at onset (AAO) or age at last examination (AALE) in years (y) below the symbol. An asterisk identifies the family members of whom genomic DNA was available and a 'c' identifies the *PSEN1* p.Cys263Phe mutation carriers. The arrow identifies the proband of the family. Only the clinically affected patients known to carry the mutation and of whom clinical records were available, were described in this paper. Other family members pictured as clinically affected were not described because the clinically affected state was only based on oral information obtained from relatives or because their mutation status was not known.

Pedigree DR1633

Disclosure: Nothing to disclose

Monday, June 21 2021
Epilepsy: Anti-seizure medications, surgery, and outcomes

OPR-060

Temporal Lobe Resection Reorganizes Language Networks in Patients with Epilepsy

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Background and aims: Anterior temporal lobe resection (ATLR) can control seizures in patients with intractable temporal lobe epilepsy (TLE) but may impair language function. We used functional magnetic resonance imaging (fMRI) to study changes of the functional language connectome in left-hemisphere dominant patients after left or right ATLR.

Methods: We studied 44 patients with unilateral medial TLE due to hippocampal sclerosis (24 left) and 18 healthy controls on a three Tesla MRI scanner. All subjects performed language fMRI (verbal fluency) and neuropsychological testing (verbal fluency, naming) preoperatively, and again four months after ATLR. Connectome analysis was based on 50 cortical language-related and four hippocampal regions of interest (ROIs). Network-based statistics was used to analyse network changes between pre- and postoperative data for left and right TLE individually.

Results: For both left and right TLE, a significantly reduced connectivity structure (p<0.0001) was observed after ATLR. Left TLE showed primarily impaired connectivity for the left and right inferior frontal cortex (IFC) and both temporal lobes, while right TLE showed alterations particularly for the right IFC. Left TLE showed increased fronto-temporal connectivity within left and right hemisphere, and within the right IFC. Right TLE showed a widespread increase in connectivity especially for the right IFC to ipsi- and contra-lateral regions.

Conclusion: Widespread disruptions of the language connectome primarily in left TLE emphasized the critical role of the left hippocampus during language tasks, and post-operative reorganization provided evidence of multiple systems supporting language function.

Disclosure: Nothing to disclose.

OPR-152

Deep brain stimulation of the ANT for drug resistant epilepsy in a real-world setting: MORE registry 2-year results

J.T. Peltola [1], A. Colon [2], J. Pimentel [3], V. Coenen [4], A. Gil-Nagel [5], A. Gonçalves Ferreira [6], K. Lehtimäki [7], P. Ryvlin [8], R. Taylor [9], F. Gielen [10], T. Brionne [11], A. Abouihia [12], P. Boon [13]
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Background and aims: The efficacy of deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) in drug resistant epilepsy (DRE) patients was demonstrated in the double-blind Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) randomized controlled trial. The Medtronic Registry for Epilepsy (MORE) aims to understand the safety and longer-term effectiveness of ANT-DBS therapy in routine clinical practice.

Methods: MORE is an observational registry collecting prospective and retrospective clinical data. Participants were at least 18 years old, with focal DRE recruited across 25 sites from 13 countries. They were followed for at least two years in terms of seizure frequency (SF), health-related quality of life (Quality of Life in Epilepsy Inventory 31 (QOLIE-31), depression, and safety outcomes. Outcomes in the complete case population at two years are reported.

Results: Of the 191 patients recruited, 170 (mean age of 35.6 years, 43% female) were analysed. At entry, 38% of patients reported cognitive impairment. Over two years the median monthly SF decreased progressively by 33,1% (p-value<0.0001) and QOLIE-31 improved by a median 2-point. No change in depression severity was seen. Factors influencing SF reduction included seizure type, absence of cognitive impairment and site implant volume. The most reported adverse events were new or worsening seizures (16% of patients), memory impairment (15%) and depression (13%).

Conclusion: The MORE registry supports the benefit and safety of ANT-DBS therapy in a real-world setting in the 2-years following implantation. Patients without cognitive impairment may benefit more from this type of neuromodulation therapy.

Disclosure: This study was sponsored by Medtronic plc

OPR-153

Safety of adjunctive cenobamate in adults with uncontrolled focal seizures: time to onset, duration, and severity of AEs

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Background and aims: Cenobamate is a new antiseizure medication (ASM) approved in the US for uncontrolled partial-onset (focal) seizures in adults. Two international, double-blind, placebo-controlled trials with open-label extensions (OLEs; C013/C017) and a large international open-label safety study (C021) demonstrated efficacy and safety. Here we characterize the most common adverse events (AEs) in these studies.

Methods: Adults with uncontrolled focal seizures and taking 1-3 concomitant ASMs were enrolled (C013/C017/C021). Concomitant ASM changes were not allowed during the double-blind period (DB) but were allowed during OLEs (C013/C017) and for most C021 patients. C021 cenobamate titration started lower and up-titrated slower than C013/C017. Time of 1st onset (pooled C013/C017 DB and OLEs; C021), duration of all AE occurrences (pooled C013/C017 DB), and severity (pooled C013/C017 DB; C021 first 18 weeks) of somnolence, dizziness, and fatigue were examined.

Results: First onset of the most common AEs emerged throughout the DB (Figure 1) and OLE (Figure 2), mostly during titration. In C021 the peak occurred when dosing reached 50 mg/day (Figure 2). Median duration in days (DB, all occurrences) was: somnolence 32 cenobamate versus 22 placebo, dizziness 11 cenobamate versus eight placebo, and fatigue 34 cenobamate versus 20.5 placebo. AEs in the DB were primarily mild or moderate, with few severe AEs (Figure 3). In C021, more patients reported mild AEs and fewer reported moderate and severe AEs.

Conclusion: Onset of the most common AEs occurred primarily during titration; AEs were generally self-limited in duration and were mainly mild or moderate in severity. Slower titration reduced the severity of AEs.

Figure 1. Time of first onset of somnolence, dizziness, and fatigue during the double-blind period (pooled C013 and C017).
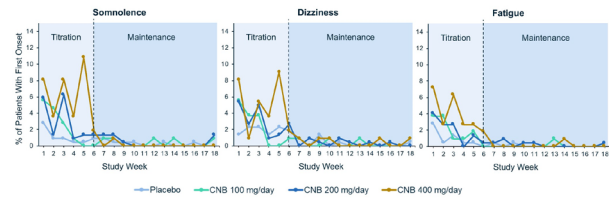
C013 titration: starting dose 50 mg/day, increased 50 mg/week every 2 weeks to 200 mg/day target. Amended C017 titration: starting dose 50 mg/day, increased 50 mg/week until target of 100 or 200 mg/day reached; once 200 mg/day reached, dose was increased by 100 mg/day per week to target dose 400 mg/day. Prior to amendment, 46/437 patients (10.5%) received a starting dose of 100 mg/day, increased 100 mg/week to target. CNB, cenobamate.

Figure 1.

Figure 2. Time of first onset of somnolence, dizziness, and fatigue during the OLE (pooled C013 and C017) and the open-label safety study (C021).
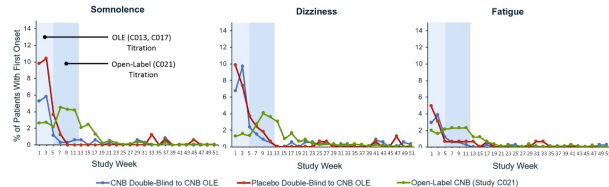
C013 OLE titration: initial 100 mg/day dose increased by 50 mg/week every 2 weeks to 200 mg/day; further increases up to 400 mg/day allowed. C017 OLE titration: 2-week conversion to the target dose of 300 mg/day. C021 titration: initial 12.5 mg/day (2 weeks) increased to 25 mg/day (2 weeks), 50 mg/day (2 weeks), then increased by 50 mg/day every 2 weeks to 200 mg/day. Further biweekly increases by 50 mg/day allowed up to 400 mg/day. CNB, cenobamate; OLE, open-label extension.

Figure 2.

Figure 3. Among patients experiencing AEs, the percentage reporting mild, moderate, and severe.
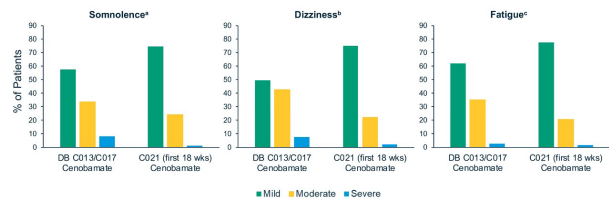
[a]Total patients reporting somnolence in DB was 109/442 (24.7%) and in C021 was 356/1340 (26.6%). [b]Total patients reporting dizziness in DB was 103/442 (23.3%) and in C021 was 275/1340 (20.5%). [c]Total patients reporting fatigue in DB was 71/442 (16.1%) and in C021 was 210/1340 (15.7%). AEs, adverse events; DB, double-blind period.

Figure 3.

OPR-186

Vanishing of multidien cycles with seizure freedom in focal epilepsy

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Background and aims: In refractory focal epilepsy, cycles of epileptic brain activity organize seizures over multi-day (multidien) timescales, but whether variation in these cycles influences clinical outcome is unknown.

Methods: We identified patients from the RNS System clinical trials (implanted with an intracranial brain stimulator for detecting and treating seizures) who self-reported seizure freedom for at least 12 months. Wherever continuous chronic recordings of EEG features (cEEG) were available, we characterized multidien cycles of interictal epileptiform activity (IEA) using a wavelet transform and compared power spectra before and after clinical seizure freedom. We tested significant peak periodicity against surrogate time series (random permutation of 100 calendar days and their corresponding 24-hour IEA).

Results: 25 out of 256 participants (9.8%) had cEEG available for at least 24 continuous months, the last 12 months without reported seizures. In 15 of them (60%) abrupt seizure freedom coincided with an identifiable treatment change (Fig. 1 a, c, g, e, i), while the rest had a progressive decrease in seizure frequency culminating in seizure freedom. While still having seizures 20 of these 25 participants (80%) had multidien cycles of IEA. Upon becoming seizure free, the magnitude of these cycles strongly decreased in 13 out of 20 subjects (65%) (Fig 1 b, d ,f, h, j).
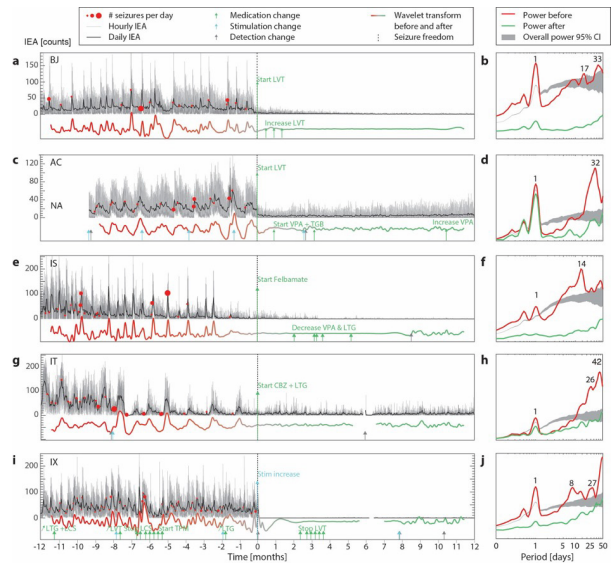
IEA counts (left) and power spectra (right) for five individuals who reported seizure freedom for at least 12 months following therapy adaptation. During seizure freedom multidien cycles of IEA are strongly reduced (green) compared to the period before (red)

Conclusion: In this cohort, clinical seizure freedom was consistently associated with a decrease in magnitude of multidien IEA cycles, often vanishing completely. Although causal relationships cannot be established, this suggests that multidien IEA cycles may represent novel biomarkers for seizure recurrence over long periods (months to years).

Disclosure: MOB is an employee of the Wyss Center and has a patent pending for Neural Interface System. VRR has been consultant for NeuroPace, Inc. (NP), but declares no funding for this study. TKT/TS are NP employees and declare equity stock options.

Multiple Sclerosis: Therapy: outcome measures

OPR-155

Structural and functional connectivity of the amygdala explain social cognition performances in multiple sclerosis

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Background and aims: Social cognition (SC) can be impaired in multiple sclerosis (MS) with theory of mind (ToM) as the main domain affected in MS. Amygdala has been shown to be a key structure in modulating social behaviors.

Methods: We prospectively recruited 20 RRMS patients and 15 healthy controls. SC was assessed with the Faux Pas test and a false belief task to evaluate ToM. All participants underwent extensive neuropsychological assessment in addition to the MRI protocol evaluating amygdala-based structural connectivity, using diffusion weighted imaging, and functional connectivity (FC), using both resting-state fMRI and a task-based paradigm consisting of the Reading the Mind in the Eyes Test.

Results: SC and classical cognitive performances of patients did not differ from those of controls. Amygdala was not altered in patients in terms of volume, fractional anisotropy and mean diffusivity (MD). Resting-state FC between the left amygdala and the left frontal pole and paracingulate gyrus was decreased in patients compared to controls ($p < 0.001$) and was associated to the ratio of right answers during the mental task ($r=0.42$; $p<0.05$). As for the mental paradigm, patients showed increased FC between amygdala and temporal and infratentorial regions ($p<0.05$; Figure1), associated to a significant increase in MD of the related tracts ($r=0.74$; $p<0.001$).

Differences between groups (multiple sclerosis > controls) in regional brain responses for the mental task. Color bar represents t-statistics. The z coordinates are in the MNI (Montreal Neurological Institute) space.

Conclusion: The current study supported the importance of amygdala-dependent pathways in the regulation of social behaviors in MS patients. Our population demonstrated preserved SC despite the presence of structural damage. We showed that specific functional reorganization at this stage could represent a beneficial response to structural injury.

Disclosure: Authors have nothing to disclose in relation to the current work.

OPR-156

Symptom severity in neuromyelitis optica spectrum disorder: psychometric properties of the SymptoMScreen questionnaire

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Background and aims: The assessment of self-reported outcomes in neuromyelitis optica spectrum disorder (NMOSD) is limited by the lack of disease-specific measures. The SymptoMScreen (SMSS) is a validated, patient-reported questionnaire for measuring symptom severity in key neurologic domains affected by MS, but has not been thoroughly evaluated in NMOSD. The aim of this study was to assess the dimensional structure and item distributions of the SMSS in a sample of patients with NMOSD.

Methods: A non-interventional, cross-sectional study in adult subjects with NMOSD (Wingerchuk 2015 criteria) was conducted at 13 neuro-immunology clinics across Spain. A non-parametric item response theory procedure, Mokken analysis, was performed to assess the underlying dimensional structure and scalability of items and overall questionnaire. All analyses were performed with JASP (v 0.14.1) and R (v 4.0.3) using the mokken library.

Results: A total of 70 patients were studied (mean age= 47.4 years±14.9, 81.7% female, mean time since diagnosis= 6.1 years±3.9). Symptom severity was low (median SMSS score=19.0 [interquartile range 10.0, 32.0]). The SMSS showed excellent internal reliability (Cronbach's alpha 0.90 [95% CI 0.86, 0.93]) and behaved as a unidimensional scale with all items displaying scalability coefficients (Hi) >0.30. The overall SMSS scalability was 0.45 conforming to a medium scale according to Mokken's criteria. Fatigue (Hi=0.53) and pain (Hi=0.52) were the domains with the highest impact.

Conclusion: The SMSS shows appropriate psychometric characteristics and may constitute a valuable and easy-to-implement addition to measure symptom severity in patients with NMOSD.

OPR-157

A Functional Composite Endpoint to Characterize Disease Progression in Patients with Active or Non-active SPMS

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Background and aims: Composite endpoints (CEPs) capture disease progression more comprehensively as they account for functions not, or not optimally, captured by Expanded Disability Status Scale (EDSS) alone. A previous analysis, combining SDMT and EDSS, demonstrated high sensitivity in determining treatment effects. Here, 9-Hole Peg Test (9HPT) and Timed 25-Foot Walk Test (T25FWT) are included with SDMT and EDSS in the construction of CEPs. By exploring novel CEPs more relevant to secondary progressive multiple sclerosis (SPMS), we may be able to better characterize progressive disease including differences in active and non-active SPMS.

Methods: In this post hoc analysis, two definitions for time to 6-month confirmed disease progression (6mCDP) were applied for all SPMS patients participating in the EXPAND Core study and in subgroups with active and non-active disease: CEP1 based on EDSS (1-point/0.5-point worsening from baseline of 5/>5, respectively), or 4-points worsening on SDMT, or 20% increase in 9HPT; and CEP2 that in addition to CEP1 included the component of 20% increase in T25FWT (only for patients with baseline EDSS 5.5, since T25FWT was unstable in patients with higher baseline EDSS in the EXPAND study).

Results: Risk reductions of 6m-CDP in the overall, active and non-active SPMS patients assessed by EDSS alone, CEP1 and CEP2 are presented in the table.

Table: 6m-CDP risk reductions based on EDSS alone,ds CEP1 and CEP2

Parameters	6m-CDP risk reduction (%)	HR ratio (95% CI)	P-value
EDSS Overall population (siponimod [n=1099], placebo [n=546])	26%	0.74 (0.60; 0.92)	p=0.006
• Active group (siponimod [n=516], placebo [n=263])	37%	0.64 (0.47; 0.87)	p=0.004
• Non-active group (siponimod [n=557], placebo [n=270])	13%	0.87 (0.64; 1.19)	p=0.376
CEP1: EDSS/SDMT/ 9-HPT Overall population (siponimod [n=1099], placebo [n=546])	27%	0.73 (0.62; 0.86)	p<0.001
• Active group (siponimod [n=516], placebo [n=263])	30%	0.70 (0.55; 0.88)	p=0.003
• Non-active group (siponimod [n=557], placebo [n=270])	21%	0.80 (0.63; 1.01)	p=0.061
CEP2: EDSS/SDMT/ 9-HPT/T25FWT Overall population (siponimod [n=1099], placebo [n=546])	25%	0.75 (0.64; 0.88)	p<0.001
• Active group (siponimod [n=516], placebo [n=263])	29%	0.71 (0.57; 0.89)	p=0.003
• Non-active group (siponimod [n=557], placebo [n=270])	19%	0.81 (0.64; 1.02)	p=0.070

Cox proportional hazards model was used for detection of treatment effects on EDSS alone, CEP1 and CEP2.
6m-CDP, 6-month confirmed disease progression; 9-HPT, 9-Hole Peg Test; CEP, composite endpoints; EDSS, Expanded Disability Status Scale; HR, hazard ratio; SDMT, Symbol Digital Modalities Test; T25FWT, Timed 25-Foot Walk Test

Conclusion: Adding SDMT and 9HPT to the EDSS assessment (CEP1) allows detection of treatment effects on a broader spectrum of symptoms in SPMS compared with EDSS alone, including in patients with non-active disease. Addition of T25FWT in CEP2 did not increase precision of HR ratio estimates.

Disclosure: The study was supported by Novartis Pharma AG, Switzerland. The detailed author disclosures will be presented in the subsequent presentation.

OPR-158

Association Between Brain Volume and Clinical/Patient-Reported Outcome Measures for Patients With Multiple Sclerosis

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Background and aims: Brain volume loss is an important attribute to multiple sclerosis (MS) patients. We estimated the association between brain volume and clinical/patient-reported outcomes in MS.

Methods: Data from the Comprehensive Longitudinal Investigation of MS at Brigham and Women's Hospital (CLIMB) were included in this retrospective analysis. Eligible patients had two MRI scans 24 months apart with corresponding clinical visits with Expanded Disability Status Scale (EDSS) scores. Whole brain volume was determined from MRI at baseline and month 24. Data also included the following outcome measures for a subset of patients: mental component summary (MCS) and physical component summary scores from the Medical Outcomes Short-Form Health Survey, Modified Fatigue Impact Scale, Center for Epidemiologic Studies-Depression Scale (CES-D), and Symbol Digit Modalities Test. The association between baseline brain volume and 24-month change in brain volume with each outcome measure at baseline, months 24 and 60 was estimated using linear regression adjusting for age, sex, and disease duration.

Results: Baseline whole brain volume was associated with baseline MCS, CES-D, and EDSS (p<0.05 each comparison) and with month 60 CES-D and EDSS (p<0.05 each comparison); 24-month change was associated with month 60 CES-D (p=0.04). No significant associations were observed between 24-month change in brain volume and change in outcome measures.

Conclusion: Whole brain volume was associated with concurrent and month 60 EDSS and CES-D and was a stronger predictor of clinical/patient-reported outcomes. While 24-month change in brain volume was associated with CES-D, longer follow-up may be required to identify association with other outcome measures.

Disclosure: BH, BIG, TC, and HW: Employment – Brigham and Women's Hospital ES and KH: Employment – Analysis Group DS, TP, KG: Employment – Bristol Myers Squibb

Multiple Sclerosis: Neuromyelitis Optica Spectrum Disorder (NMOSD)

OPR-159

MR T2-relaxation time as an indirect measure of brain water content and disease activity in NMOSD

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Background and aims: In neuromyelitis optica spectrum disorders (NMOSD), autoantibodies target astrocytes' aquaporin-4 (AQP4) water channel (the main regulator of CNS water homeostasis), possibly leading to increased blood-brain barrier permeability. In this work, we aim to provide an indirect estimation of brain water content in NMOSD by measuring T2-relaxation time (T2rt) and to assess whether it differs in patients having a short-term relapse.

Methods: In this multicenter MR study, T2rt was calculated from brain dual echo turbo spin echo images assuming a mono exponential decay. T2rt maps of normal appearing white matter (NAWM), gray matter (GM) and basal ganglia were obtained from 77 AQP4-positive NMOSD and 84 HC. Short-term relapses were defined as occurring within one month before or after MRI scan. Differences between NMOSD and HC were assessed with age-, sex- and site-adjusted linear models. ROC analyses were run to identify discriminators between stable and short-term relapsing patients.

Results: Compared to HC, T2rt was increased in the GM (103 vs 97ms), NAWM (88 vs 84ms) and putamen (75 vs 72 ms) of NMOSD patients (p<0.001 for all). Short-term relapses occurred in 20/77 (26%) of patients. T2rt cut-offs of 87 ms (NAWM and thalamus) and 88ms (caudatum) were able to discriminate between short-term relapsing and stable patients with good accuracy (AUC=0.70, 0.76 and 0.79 respectively, p=0.027).

Conclusion: NMOSD patients had increased T2rt values, suggesting a subclinical water accumulation in this disorder. The burden of T2rt alterations might be useful for identifying patients with incipient or recent relapses.

Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

OPR-160

Long term safety outcomes with inebilizumab treatment in neuromyelitis optica spectrum disorder: the N-MOmentum trial

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Background and aims: N-MOmentum was a 28-week randomized trial comparing inebilizumab and placebo for neuromyelitis optica spectrum disorder (NMOSD). Treatment safety profile was comparable between groups. Participants could enter the open-label period (OLP; minimum two years), assessing long-term efficacy and safety of inebilizumab.

Methods: OLP participants received intravenous inebilizumab 300 mg every 28 weeks. A limited interim analysis was performed (full end-of-study OLP analysis due Q4 2020). Safety endpoints include treatment-emergent adverse events (AEs), severe and opportunistic infections, infusion-related reactions (IRRs), anti-drug-antibodies, immunoglobulin levels, leucocyte counts, and B-cell counts.

Results: Interim analyses showed 51/56 (91.1%) of those randomized to placebo (RP) and 165/174 (94.8%) randomized to inebilizumab (RI) entered the OLP. Mean (SD) OLP inebilizumab exposure in RP and RI groups was 2.4 (1.1) and 2.3 (1.1) years, respectively. AE incidence rates per 100 person-years were 304.5 (RP) and 251.4 (RI); most commonly urinary tract infection (UTI: 14.9; 7.2), nasopharyngitis (7.1; 6.9) and upper respiratory tract infection (4.7; 5.7), respectively. The most common serious AEs were UTI (4.7; 0.5) and pneumonia (0.8; 0.7), respectively. IRRs occurred in six (11.8%) RP- and 9 (5.5%) RI-participants. No correlations were found between infection rates and low concentrations of IgG or IgM (p>0.05). Two OLP participants died: one from complications of a severe NMOSD attack and one from a CNS event of unclear etiology. The full safety profile of longer-term inebilizumab treatment will be presented.

Conclusion: Interim analyses of the OLP indicate no additional safety concerns arising with multiple doses of inebilizumab in participants with NMOSD.

Disclosure: N-MOmentum was funded by Viela Bio. JLB, BGW, HJK, SJP, KF, GC, RM, OA, HPH, AJG report personal fees from Viela Bio and others. JD, DS, DC, WR, JNR, EK are employees of Viela Bio. BACC, DW, FP, report personal fees from other sources.

OPR-161

Long term efficacy outcomes with inebilizumab treatment in neuromyelitis optica spectrum disorder: the N-MOmentum trial

B. Cree [1], J. Bennett [2], B. Weinshenker [2], D. Wingerchuk [3], F. Paul [4], H. Kim [5], S. Pittock [2], K. Fujihara [6], G. Cutter [2], R. Marignier [7], O. Aktas [8], H. Hartung [8], A. Green [1], J. Drappa [2], D. She [2], D. Cimbora [2], W. Rees [2], J. Ratchford [2], E. Katz [9]

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Background and aims: The N-MOmentum study was a 28-week randomized trial comparing inebilizumab and placebo for neuromyelitis optica spectrum disorder (NMOSD). The trial met the primary endpoint of reduction in attack risk and showed benefit in the secondary endpoint of disability worsening. After the randomized controlled period (RCP), participants could opt-in to the open-label period (OLP; minimum two years) where the long-term efficacy and safety of inebilizumab was assessed.

Methods: OLP participants received inebilizumab 300 mg every 28 weeks. A limited interim analysis was performed (full end-of-study OLP analysis due Q4 2020). Efficacy endpoints included analyses of attack rates, disability-related outcomes and cumulative MRI lesion activity. Safety data is covered in a companion abstract.

Results: Interim analyses showed that 216/230 participants initially randomized and dosed opted to enter the OLP, 51/56 (91.1%) of those originally randomized to placebo (RP) and 165/174 (94.8%) of those originally randomized to inebilizumab (RI). During the RCP, 87.7% receiving inebilizumab and 60.7% receiving placebo remained attack-free. In the OLP, 87.7% in the RI group and 83.4% in the RP group remained attack-free for up to four years. At OLP baseline, mean (SD) EDSS scores were lower in the RI than the RP group; 3.82 (1.76) versus 4.16 (1.71). By OLP week 78, EDSS scores were lower than baseline in both groups; RI: 0.24 (0.87); RP: 0.12 (0.73). The full OLP efficacy profile of inebilizumab treatment will be presented.

Conclusion: Interim analyses indicate that benefits of inebilizumab seen in the RCP of N-MOmentum are maintained in the OLP.

OPR-162

Immunoglobulin kinetics and infection risk after long-term inebilizumab treatment for NMOSD

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Background and aims: Long-term use of B-cell depleting monoclonal antibodies is associated with reduced immunoglobulin (Ig) levels, increasing infection risk. The association between Ig levels and infection was assessed in the 28-week randomized controlled phase (RCP) and optional open-label period (OLP; minimum two years) of the N-MOmentum trial of inebilizumab for neuromyelitis optica spectrum disorder.

Methods: Ig levels were centrally recorded. Adverse events, including infections, were monitored. Opportunistic infections were predefined based on medical review.

Results: Ig levels were analyzed for 174/230 participants receiving inebilizumab for 4.75 years. There was a 35% mean decrease in total Ig with inebilizumab. Mean percent change from baseline was -62% for IgM, -50% for IgA and -30% for IgG. During the RCP, the rate of infection per 100 person-years was 140.2 (placebo) and 138.1 (inebilizumab). Infection rates per 100 person-years were lower in the OLP than the RCP: year 2: 69.9, year 3: 61.5, and year 4: 62.3 (follow-up: 614.6 person-years). The most common infections were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis and influenza. The proportion of participants with an infection was similar for those with IgG levels below and above lower limit of normal (78.9% vs. 72.9%). Eight participants had IgG level <300 mg/dL at least once. The proportion of participants with infection did not differ between those with IgG<300 mg/dL and IgG 700 mg/dL (75.0% vs. 72.9%).

Conclusion: Despite declining Ig levels, infection rate did not increase with long-term inebilizumab treatment or differ between participants with normal and low IgG.

OPR-163

Satralizumab in adults with AQP4-IgG seropositive NMOSD: Efficacy and safety results from the phase 3 SAkura studies

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Background and aims: Satralizumab reduced the risk of protocol-defined relapse (PDR) in two randomized, phase 3 clinical trials in neuromyelitis optica spectrum disorder (NMOSD): SAkuraSky (satralizumab in combination with baseline immunosuppressants; NCT02028884), and SAkuraStar (satralizumab monotherapy; NCT02073279). We assessed the efficacy and safety of satralizumab in adults with AQP4-IgG-seropositive (AQP4-IgG+) NMOSD.

Methods: Patients received satralizumab 120mg or placebo at Weeks 0, 2, 4, and Q4W thereafter. Using data from the double-blind period, between-group comparisons were made for time to first PDR, and the rates of adverse events (AEs), serious AEs, infections, and serious infections. Laboratory values were also compared. To assess longer-term safety, data from the overall satralizumab treatment (OST) periods were evaluated (all patients receiving one dose of satralizumab in the double-blind and/or open-label extension periods; cut-off: 7 June 2019).

Results: 116 AQP4-IgG+ adults were included. Satralizumab significantly reduced PDR risk vs placebo in SAkuraSky (78% reduction) and SAkuraStar (74% reduction), with higher proportions of relapse-free patients at Week 96 (Figure). Rates of AEs and serious AEs were similar between treatment groups in both studies; infection and serious infection rates were not higher in the satralizumab groups vs placebo, and did not increase with additional satralizumab exposure in the OST period (Table). Decreases in neutrophil and platelet counts and elevations in liver enzymes were more frequently observed with satralizumab vs placebo; these were not associated with serious infections or bleeding events.

Figure – Time to first protocol-defined relapse in SAkuraSky and

Events per 100 PY (95% CI)	SAkuraSky (combination therapy)			SAkuraStar (monotherapy)		
	Double-blind period		OST period	Double-blind period		OST period
	Placebo (n=26; 33.0 PY)	Satralizumab (n=26; 52.7 PY)	Satralizumab (n=44; 137.4 PY)	Placebo (n=23; 26.8 PY)	Satralizumab (n=41; 80.4 PY)	Satralizumab (n=62; 150.6 PY)
AEs	657.5 (572.9–751.0)	458.9 (402.9–520.5)	417.9 (384.4–453.5)	519.7 (436.9–613.6)	440.5 (395.8–488.9)	379.8 (349.3–412.2)
Serious AEs	30.3 (14.5–55.7)	17.1 (7.8–32.4)	16.0 (10.0–24.3)	11.2 (2.3–32.8)	17.4 (9.5–29.2)	12.6 (7.6–19.7)
Infections	184.8 (141.4–237.4)	115.7 (88.5–148.6)	129.6 (111.3–150.1)	157.0 (113.2–212.3)	93.3 (73.4–117.0)	77.0 (63.6–92.4)
Serious infections	9.1 (1.9–26.6)	3.8 (0.5–13.7)	4.4 (1.6–9.5)	3.7 (0.1–20.8)	5.0 (1.4–12.7)	3.3 (1.1–7.8)

AE, adverse event; CI, confidence interval; OST, overall satralizumab treatment; PY, patient-years

Table – Adverse event rates in the double-blind and OST periods of the SAkura studies

Conclusion: In AQP4-IgG+ adults with NMOSD, satralizumab significantly reduced relapse risk vs placebo, was well tolerated and showed a favourable safety profile.

Disclosure: Funded by F. Hoffmann-La Roche. Writing and editorial assistance was provided by David Mayes, MChem, of ApotheCom, London, UK; ClinicalTrials.gov, NCT02028884/NCT02073279.
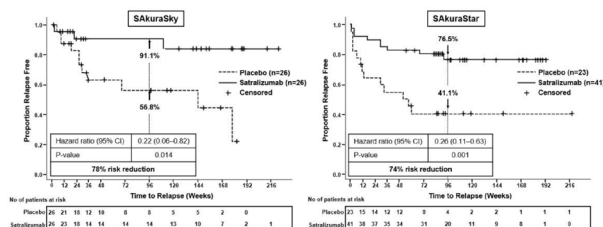
OPR-164

Satralizumab in patients with neuromyelitis optica spectrum disorder (NMOSD) and concomitant autoimmune disease

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Background and aims: NMOSD is frequently associated with one or more concomitant autoimmune diseases (CAIDs). The SAkura studies (SAkuraSky [NCT02028884], SAkuraStar [NCT02073279]) enrolled diverse NMOSD populations reflective of real-world practice, including patients with CAIDs. In SAkuraSky (satralizumab in combination with baseline immunosuppressants) and SAkuraStar (satralizumab monotherapy), satralizumab reduced patients' risk of protocol-defined relapse (PDR) versus placebo and had a favourable safety profile. We evaluated the efficacy and safety of satralizumab in NMOSD patients with CAIDs from the SAkura studies.

Methods: This analysis used pooled data from patients with a medical history of CAIDs in the intention-to-treat population of the SAkura studies. The incidence of PDRs in each treatment arm was reported. Safety was evaluated throughout the double-blind period using adverse event (AE) rates per 100 patient-years.

Results: 31 patients with CAIDs were enrolled (SAkuraSky, n=15; SAkuraStar, n=16); of these, 15 received satralizumab and 16 received placebo. The most commonly reported systemic and organ-specific CAIDs are shown in the Figure. Consistent with the primary efficacy analysis, fewer patients experienced a PDR with satralizumab versus placebo (3 [20%] vs 7 [44%]). The rates of AEs, infections, and serious infections were comparable between satralizumab and placebo (Table). There was a numerically higher rate of serious AEs in the satralizumab group vs placebo, driven mainly by multiple events in one patient in SAkuraStar that were assessed to be unrelated to study treatment.
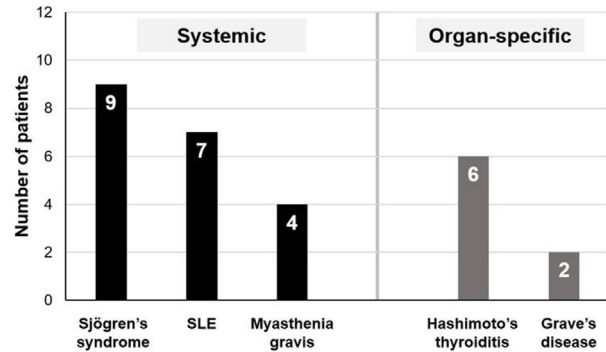
SLE, systemic lupus erythematosus.

Figure – Most common systemic and organ-specific CAIDs in the SAkura studies

	Placebo (N=16) (PY=21.11)			Satralizumab (N=15) (PY=29.66)		
	No. of AEs	Patients n (%)	Events per 100 PY (95% CI)	No. of AEs	Patients n (%)	Events per 100 PY (95% CI)
Adverse events	168	16 (100)	795.9 (680.1–925.7)	210	15 (100)	708.0 (615.5–810.5)
Serious AEs	7	5 (31)	33.2 (13.3–68.3)	13	7 (47)	43.8 (23.3–75.0)
Infections	49	10 (63)	232.1 (171.7–306.9)	52	12 (80)	175.3 (130.9–229.9)
UTI	5	3 (19)	23.7 (7.7–55.3)	13	4 (27)	43.8 (23.3–75.0)
URTI	10	3 (19)	47.4 (22.7–87.1)	5	3 (20)	16.9 (5.5–39.3)
Serious infections	1	1 (6)	4.7 (0.1–26.4)	3	3 (20)	10.1 (2.1–29.6)

AE, adverse event; PY, patient-years; URTI, upper respiratory tract infection; UTI, urinary tract infection.

Table – Adverse events in the SAkura CAIDs population

Conclusion: Satralizumab was well tolerated in NMOSD patients with CAIDs, with comparable safety and efficacy to the overall SAkura study populations.

Disclosure: Funded by F. Hoffmann-La Roche. Writing and editorial assistance was provided by Patricia Lobo (BSc) of ApotheCom, London, UK; ClinicalTrials.gov, NCT02028884/NCT02073279.

Neuroimmunology 2

OPR-165

Detection of Neuronal Surface antibodies by commercial vs in-house cell based assay: experience of a referral centre.

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Background and aims: Commercial diagnostic kits have improved the accessibility of neuronal surface antibodies (NSab) detection in suspected cases of autoimmune encephalitis. We evaluated the sensitivity of a commercial kit based on antigen-transfected-cells (cell-based assay: CBA) for the detection of NSab in samples with positive reactivity on rat-brain-immunohistochemistry (tissue-based assay: TBA).
Methods: Between 10/2016 and 10/2020, 6213 serum/CSF samples were screened using TBA. Samples showing positive reactivity were tested with commercial and in-house CBAs for NMDAR, AMPAR, LGI1, Caspr2, GABAbR and DPPX antigens, and CBAs for less common antigens (only detectable by in-house CBA).
Results: TBA showed positive reactivity in 404/6213 (6.5%) samples. Of these, 241 (60%) were negative and 163 (40%) positive by commercial CBA, confirming the presence of NSab (68 NMDAR+, 52 LGI1+, 16 AMPAR+, 11 GABAbR+, 15 Caspr2+ and one DPPX+). Of the 241 negative samples, 21 (8.7%) were positive by in-house CBA (1 NMDAR+, 11 LGI1+, two AMPAR+ and seven GABAbR+), giving false-negative results on the kit. Other 21/241 (8.7%) samples were positive for antibodies not included in the kit (13 IgLON5+, 3 SEZ6L2+, 2 mGluR1+, 1 mGluR2+, 1 mGluR5+ and 1 GABAaR+).
Conclusion: In our study the commercial CBA was not able to detect 42 (20.5%) of the 205 samples with NSab. Half of these cases were detected by in-house CBAs but not with the commercial CBA that included similar antigen specificities. In patients with high suspicion of autoimmune encephalitis and negative results on the kit we recommend to study NSab using TBA and in-house CBAs.
Disclosure: No financial disclosures

OPR-166

Pediatric neuromyelitis optica spectrum disorders in Portugal

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Background and aims: Neuromyelitis optica spectrum disorders (NMOSD) are more frequent in adulthood, with few cases reported in pediatric age. Other manifestations are known in addition to optic neuritis (ON) and transverse myelitis (TM), broadening its clinical spectrum.
Methods: Analysis and description of patients with NMOSD in pediatric age, identified in a national multicentric NMOSD Portuguese registry.
Results: From 180 NMOSD Portuguese patients identified in the national database, 20 (11,1%) were diagnosed in pediatric age, 8M: 12F. The average age of onset was 11.3 years. The initial clinical manifestation was a TM in 10 patients, four of these had ON concomitantly and two patients had a brainstem syndrome (BSS). Nine patients (45%) had pleocytosis in the CSF, with a mean cell count of 36/uL. Six exhibited anti-AQP4 antibodies, 13 anti-MOG antibodies, and one was seronegative. Four anti-AQP4+ patients had more than one relapse (three patients-2 and 1–3). Seven anti-MOG+ patients have been monophasic to date, five patients had two relapses and one had 3. The seronegative patient had three relapses. Cerebral and spinal MRI showed: ON-10, TM-9, longitudinally extensive TM (LETM)-2, brainstem lesions-2 and medullary-spinal involvement-1. In the acute phase, all were treated with IV methylprednisolone, nine with IVIg and four with plasma exchange. One died, being also diagnosed with systemic lupus erythematosus systemic and autoimmune hepatitis. Ten patients (5 anti-AQP4+/5 anti-MOG+) are on immunosuppressive therapy.
Conclusion: NMOSD may present in pediatric age. It is essential to establish the diagnosis and promptly start therapy, in order to improve the prognosis.
Disclosure: Pediatric NMOSD Portugal

OPR-167

Autoimmune Encephalitis Related to Cancer Treatment with Immune Checkpoint Inhibitors: Systematic Review

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Background and aims: Immune checkpoint inhibitors (ICPI) have revolutionized the treatment of oncological patients, but autoimmune neurological adverse events are increasingly recognized. We conducted a systematic review to determine the clinical and laboratory features of ICPI-associated autoimmune encephalitis (ICPI-AIE), to determine if this is a singular clinical entity such as limbic encephalitis or a heterogeneous condition involving extra-limbic areas and if neuronal surface or intracellular AIE antibodies are present.

Methods: We searched PubMed, The Cochrane Library and Embase for ICPI-AIE cases from the first description in 2015 until 01/2020 using standard bibliographic measures including PRISMA guidelines and pre-registration with PROSPERO (CRD42019139838).

Results: 39 studies met inclusion criteria, resulting in 54 ICPI-AIE patients (mean age 58.6 years; 43% females). Common cancers included melanoma (30%) and non-small cell lung cancer (30%). Brain metastases were found in 16 patients (30%). Most frequent ICPI was nivolumab (61%). Onset of ICPI-AIE occurred after a median of 3.5 treatment cycles, but early and late presentations were common. Non-limbic AIE was twice as frequent as limbic AIE ($p<0.05$). The most common laboratory abnormalities included bitemporal FLAIR lesions on MRI, continuous slow waves and diffuse slowing on EEG, and monocytic pleocytosis on cerebrospinal fluid analysis. Intraneuronal antibodies were more frequent than neuronal surface antibodies, and a significant predictor for lack of improvement after 1st line immunotherapy ($p<0.05$).
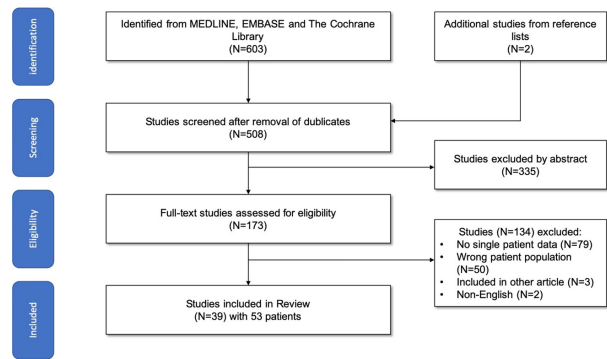
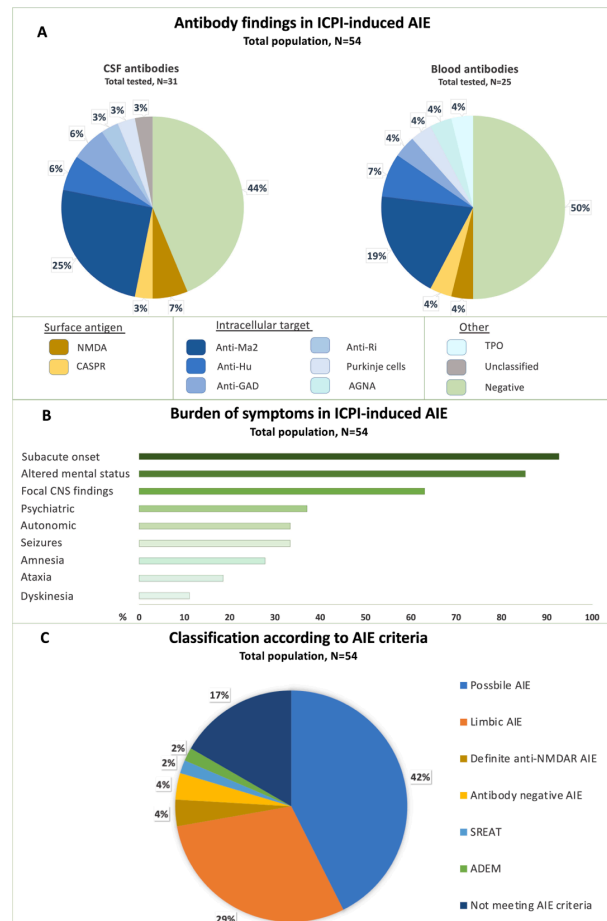FIGURE 1 – Flow-chart of literature search

FIGURE 2 – Symptoms, antibody findings and AIE classification in ICPI-induced AIE
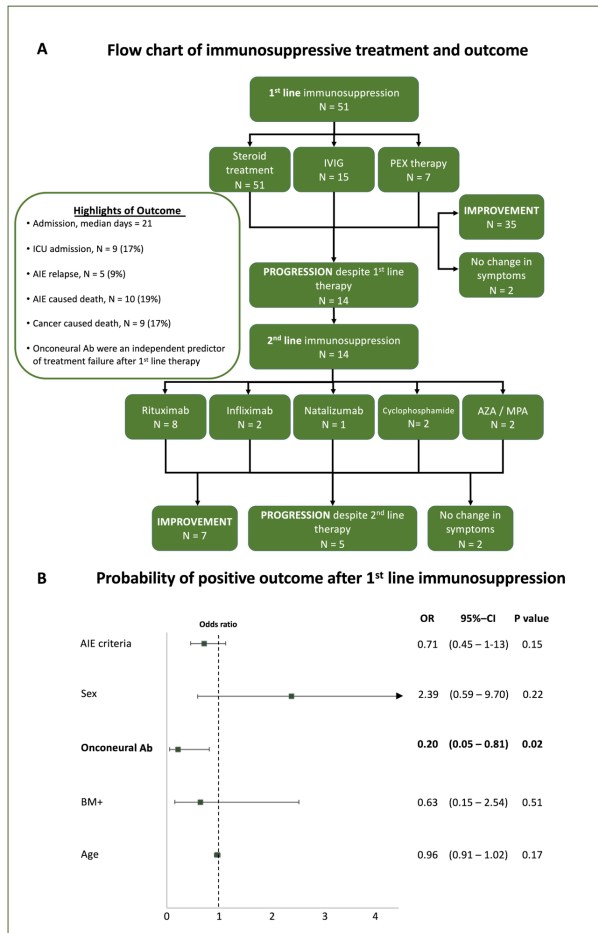
FIGURE 3 – Treatment outcome in ICPI-induced AIE

Conclusion: ICPI-AIE consists of a heterogenous group of conditions. Neurologists will likely encounter ICPI-AIE more often in the future, but important unresolved questions include the exact pathophysiological mechanisms, the epidemiology and the best treatment approaches for ICPI-AIE.

Disclosure: The authors declare that they have no conflicts of interest.

OPR-168

Involvement of the Visual Pathway in Antibody-mediated Central Nervous System Autoimmunity

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Background and aims: In autoimmune demyelinating disorders of the central nervous system (CNS), the visual system is a prominent target and retinal degeneration might serve as a generalizable biomarker of neuronal loss. However, data comparing different autoimmune demyelinating CNS disorders in patients and murine models are inconclusive. Here, we compare manifestations associated with antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG), aquaporin 4 (AQP4-IgG) or unspecific isotype antibodies (Iso-IgG) in murine experimental models of CNS demyelination.

Methods: We induced active MOG35-55 experimental autoimmune encephalomyelitis (EAE) and administered AQP4-, MOG- or Iso-IgG. Visual outcome was assessed longitudinally via optomotor reflex and optical coherence tomography (OCT). Histological correlates of disease manifestations in spinal cord, optic nerve and retina were quantified using LFB/PAS staining, immunohistochemistry and -fluorescence.

Results: Disease severity was highest after application of MOG-IgG compared to AQP4-IgG or Iso-IgG. Both, MOG-IgG and AQP4-IgG administration increased disease incidence compared to Iso-IgG. Visual acuity declined in both antibody-exacerbated models over time. Histological correlates of demyelination and immune cell infiltration in spinal cord and optic nerve were found in all groups. Retinal ganglion cell numbers were decreased in chronic MOG-IgG-exacerbated EAE compared to acute phase. OCT and histological evaluation of retina and optic nerve are ongoing.

Conclusion: Previous findings that administration of MOG-IgG worsens the disease course of EAE were confirmed and corroborated by histopathological findings in the spinal cord. Although administration of AQP4-IgG did not aggravate disease symptoms compared to Iso-IgG, incidence was increased suggesting different pathophysiological mechanisms. Differences regarding the manifestations in the visual system are currently further investigated.

Disclosure: This project is supported by a research grant from the Multiple Sclerosis Society Switzerland (to AS). Besides the project funding, the authors do not declare conflicts of interest with regards to this project.

OPR-169

High incidence of NMDAR encephalitis among Austronesians: a population-based study in Sabah, Malaysia

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Background and aims: There are observations that NMDAR encephalitis may be more common among non-Caucasians. While there were several studies on the incidence of NMDAR encephalitis in children, data was scarce in adults or in full population. To our best knowledge, no study has yet been reported from South-East Asia.

Methods: A population-based study was conducted to estimate the incidence of NMDAR encephalitis in the state of Sabah, Malaysia, where the population consists predominantly of Austronesians (84%), with a Chinese minority. Registries of NMDAR encephalitis at adult and paediatric neurology referral centres, and laboratory database were searched, and medical records were reviewed for case ascertainment.

Results: From January 2015-December 2019, there was a total of 31 incident cases (29 Austronesians and two Chinese). The female-to-male ratio was 2.1:1, and 18 patients (58%) had onset 19 years. The annual incidence rate was 2.29/million (Austronesians: 2.56/million, Chinese: 1.31/million). Among paediatric population, the incidence was 3.63/million among Austronesians, and 2.59/million among Chinese.

Conclusion: Our study demonstrated higher incidence of NMDAR encephalitis among Austronesians than the predominantly Caucasian populations in Europe and USA, both in paediatric and adult populations. Racial and genetic factors, and probably environmental factors, may contribute to risks of developing NMDAR encephalitis.

Disclosure: Nothing to disclose.

OPR-170

Acute parkinsonism and small vessel cerebral vasculitis secondary to anti PD-1 therapy

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Background and aims: We describe a case of acute and reversible parkinsonism with gait apraxia related to therapy with nivolumab.

Methods: 70-year-old man, diagnosed of renal cell carcinoma with pulmonary metastases in treatment with nivolumab, who presented gait impairment, right hemiparesis and bilateral bradykinesia. Magnetic resonance imaging (MRI) revealed bilateral T2 hyperintensities, some showing restricted diffusion and others having enhancement of gadolinium, suggestive of vasculitis (Image 1). Cerebrospinal fluid analysis was negative for cytology, viral, and paraneoplastic antibody assay, with characteristics suggestive of encephalitis. Angiography showed no abnormalities suggestive of large or medium vessel vasculitis. An immune-mediated etiology was assumed due to the use of nivolumab, and megadose of methylprednisolone was started followed by tapering, with gradual improvement of motor function, parkinsonism, and gait apraxia. A second brain MRI showed resolution of lesions that previously showed gadolinium enhancement, followed by a third MRI three months later with marked resolution of the hyperintense areas (Image 2).
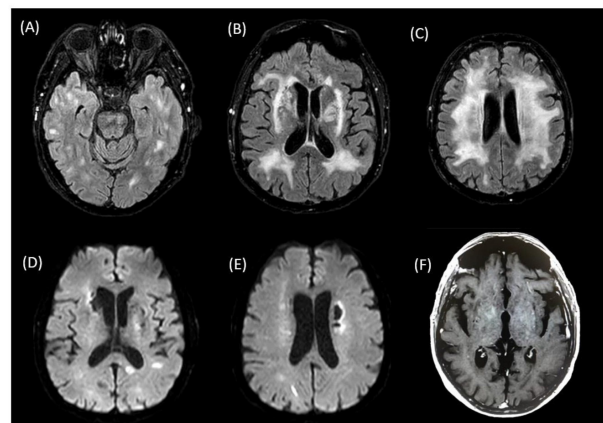
Brain MRI that showed bilateral confluent fronto-parieto-temporal hyperintensities (A,B,C), with restricted diffusion at the left margin of corpus callosum and parietal lobes (D,E), and contrast enhancement of the basal ganglia and both temporal areas (F)
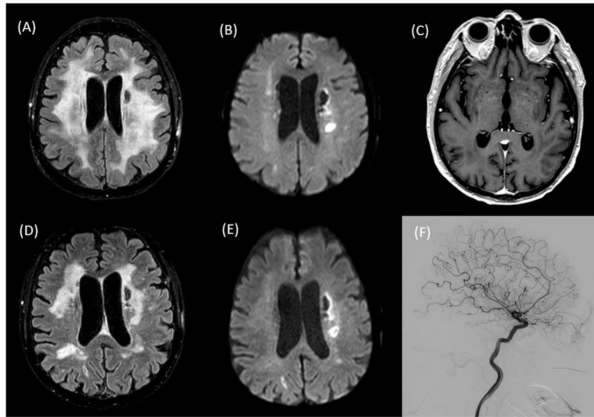
Second brain MRI (A,B,C) showed persistence of the confluent subcortical hyperintensities and resolution of gadolinium enhanced lesions. Third MRI (D,E) showed marked resolution of the hypersignal areas. Artheriography (F) with no signs of vasculitis

Results: Nivolumab is an immune checkpoint inhibitors (ICI) that target programmed death receptor-1 (PD-1), used in the management of some advanced cancers. Neurological autoimmunity is estimated to occur in 4.2% of patients receiving ICI monotherapy. To our knowledge, this is the first case described of autoimmune and reversible parkinsonism due to vasculitis of small cerebral vessels secondary to anti PD-1 treatment.

Conclusion: We describe a not previously reported antibody/syndrome association related to anti PD-1 therapies, which broadens the clinical spectrum of autoimmune neurologic disorders related to ICI therapies.

Disclosure: No disclosures

Motor Neurone Disease 2

OPR-171

Investigating cytoskeletal integrity in the sensory nerve fibers in healthy individuals

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Background and aims: Neurons with long neurites seem to be especially vulnerable in motor neurone diseases, such as amyotrophic lateral sclerosis (ALS). Neurofilament light chain (NfL), a component of the neuronal cytoskeleton, is an established biomarker for ALS (Bacioglu et al. 2016). In this study we analyse the axonal diameter and the expression levels of microtubules, neurofilaments, and actin in skin biopsies of healthy individuals.

Methods: Skin biopsies of 27 men (mean age 54.2±18.9 a, from 24 a to 79 a) were immunostained for non-phosphorylated neurofilament heavy chain (npNfH), betaIII-tubulin, and actin (phalloidin). Confocal images of the dermis were analysed for the mean grey values and diameter. This study was approved by the local ethics committee. Participants gave informed written consent.

Results: Cytoskeletal components (npNfH, betaIII-tubulin, actin) drastically increased with age. NpNfH increased 2.7-fold, whereas betaIII-tubulin levels increased 3.2-fold from 24- to 75-year-old individuals. Actin showed a change of 3.8-fold from the youngest to the 62-year-old controls (peak, maximum values). Sensory axon caliber increased 2.2-fold from the 29- (1.35µm) to the 78/79-year old (2.97µm) controls. Statistical analysi (Mann-Whitney U test) showed highly significant results between each staining/caliber and age (p<0.001).

Conclusion: Our results suggest an age-driven 'ossification' of the axonal cytoskeleton in peripheral sensory axons, which might influence cytoskeletal functionality. These findings are in accordance with the increased susceptibility of aged individuals to motor neurone diseases. The results reported here will be validated in a second independent cohort (27 men, age 26 to 74).

Disclosure: The authors have no relevant conflicts of interest to disclose.

OPR-172

PULSE: a French multi-centric, multi-modal cohort to predict the disease progression of ALS and to define endophenotypes

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Background and aims: Amyotrophic Lateral Sclerosis (ALS), devastating disease for which no treatment can effectively slow its progression, is a complex heterogenous and multifactorial disorder influenced both by genetic and environmental factors. The development of successful neuroprotective drugs requires patients' stratification according the prognosis (for statistical power) and the drug targeted mechanism (drug efficacy) with the monitoring of biomarkers (endophenotypes).

Methods: 16 French expert ALS centers have implemented a web-based solution to prospectively collect multimodal data every three months from diagnosis up to 36 months with an objective of 1000 patients. Data include clinic, ALSFRS, muscular testing, cognitive assessment, electrophysiology (EMG, MUNIX, triple stimulation), respiratory assessment, polysomnography, biological samples and 3T MRI.

Results: PULSE cohort includes 430 ALS patients and 70 healthy controls. All data are collected into an eCRF. A central biobank ensures quality and conformity of all biological samples (DNA, plasma, serum, CSF, biopsies). A. central brain- and spinal cord-imaging bank ensure the quality of all MRIs sequences. Statistical approaches with joint latent class analyses, linear mix model analysis and machine learning will be used.

Conclusion: PULSE is the largest prospective multi-centric French cohort of ALS patients followed from the diagnosis. It will allow 1) to define the prognosis factors of the survival, 2) to define prognosis factors of the rate of ALSFRS decline, 3) to determine endophenotypes according to prognosis factors and physiopathological biomarkers in order to develop relevant clinical trials. PULSE is funded by the French Charity association ARSLA

Disclosure: No conflict of interest

OPR-173

Chinese-German comparison of mutational and clinical features of ALS patients with SOD1 mutations

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Background and aims: The antisense oligonucleotides therapy for ALS patients carrying SOD1 mutations is coming in soon. The genetic-phenotypic analysis of ALS patients of different ethnics will facilitate to assess potential treatment effects.

Methods: Demographic and clinical features were collected from two longitudinal cohorts in both countries. Chinese and German patients carrying SOD1 mutations were compared with regard to mutational distribution, age of onset, site of onset, BMI at diagnosis, diagnostic delay, progression rate, and survival.

Results: A total of 66 Chinese and 84 German patients with 69 distinct SOD1 mutations were identified (Figure1). The most common mutation in both populations was p. His47Arg. It was found in eight Chinese and two German patients and consistently showed a benign course of disease in both countries. Across all mutations, Chinese patients showed a younger age of onset (43.9 vs 49.9 years, p=0.002), a higher proportion of young-onset cases (62.5% vs 30.7%, p<0.001) and a lower BMI at diagnosis (22.8 vs 26.0, p<0.001) compared to German patients (Table1). Although riluzole intake was less frequent in Chinese patients (28.3% vs 81.3%, p<0.001), no difference in survival was observed. Female patients had a longer survival compared to male patients (Figure2).

Table 1   Clinical characteristics of *SOD1* mutation populations

	Total (data available)	China	Germany	P value**	Male	Female	P value**
Nominal variables, n (%)							
Numbers of subjects	150	66	84		80	44	
Sex, male	80 (55.6%) (144)	35 (53.8%)	45 (57.0%)	0.70			-
Familial ALS	114 (78.6%) (145)	47 (71.2%)	67 (84.8%)	0.05	66 (83.5%)	46 (71.9%)	0.09
Juvenile ALS (< 25 years)	3 (2.2%) (139)	2 (3.1%)	1 (1.3%)		2 (2.6%)	1 (1.6%)	-
Young-onset ALS (25-45 years)	65 (47.5%) (139)	40 (62.5%)	25 (30.7%)	<0.001	30 (39.5%)	33 (52.4%)	0.10
Site of onset, spinal	116 (94.3%) (123)	57 (91.9%)	59 (96.7%)	0.25	66 (94.3%)	50 (94.3%)	0.99
Pure LMN	16 (20.0%) (80)	9 (17.3%)	7 (25.0%)	0.41	8 (20.0%)	8 (20.0%)	1.00
riluzole	54 (53.5%) (101)	15 (28.3%)	39 (81.3%)	<0.001	32 (60.4%)	22 (45.8%)	0.14
Continuous variables, mean (95%CI)							
Age of onset (years)	47.2 (45.2-49.1) (139)	43.9 (41.6-46.2)	49.9 (47.0-52.8)	0.002	48.7 (46.0-51.4)	45.3 (42.6-48.1)	0.08
BMI at diagnosis	24.1 (23.2-24.9) (91)	22.8 (21.9-23.7)	26.0 (24.7-27.4)	<0.001	24.4 (23.3-25.4)	23.8 (22.4-25.2)	0.49
Continuous variables, median (IQR)							
Diagnostic delay (months)	12.0 (6.0-31.0) (107)	14.5 (6.0-36.5)	11.0 (6.0-32.0)	0.59	11.0 (5.0-24.0)	13.0 (5.0-47.0)	0.61
ALS-FRSR at diagnosis	41.0 (35.0-45.0) (116)	42.0 (35.5-46.0)	40.0 (31.0-44.0)	0.04	41.0 (35.0-45.0)	40.0 (34.0-44.0)	0.55
Early progression rate (onset to first visit)	0.42 (0.14-0.90) (116)	0.33 (0.15-0.90)	0.46 (0.15-0.93)	0.79	0.49 (0.20-0.92)	0.31 (0.13-1.00)	0.45
Late progression rate (first to last visit)	0.26 (0.09-0.79) (69)	0.28 (0.08-0.80)	0.17 (0.11-0.77)	0.89	0.30 (0.11-0.90)	0.20 (0.09-0.58)	0.32
Survival (months)	141.0 (21.0-364.0) (148)	NA	198.0 (22.0-364.0)	0.90	60.0 (17.0-350.0)	240.0 (44.0-419.0)	0.005
Follow-up period*	24.0 (7.3-40.0) (88)	30.0 (10.0-42.0)	19.0 (7.0-31.0)	0.26	13.0 (7.0-31.0)	30.0 (9.0-45.0)	0.12

** χ² test for nominal variables ; t test for nominally distributed continuous variables; Mann-Whitney U test for non-nominally distributed continuous variables; log-rank test for overall survival. Bold p-values are significant. LMN: lower motor neuron

Table 1.Clinical characteristics of SOD1 mutation populations
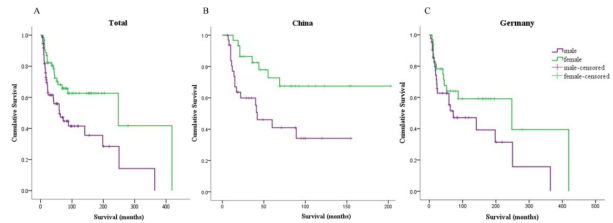
Figure 2. Sex and Survival. Kaplan Meier curves show survival for male (purple) and female (green) patients overall (A: p=0.005), in China (B: p=0.009), and Germany (C: p=0.15).

Conclusion: Our data demonstrate the distinct mutational and clinical spectrums of SOD1-mutant patients in Asian and European populations. Clinical phenotypes seem to be influenced by mutation-specific and ethnicity-specific factors simultaneously, indicating that there is no monocausal relationship between the genetic mutations and clinical phenotypes. Further large-scale transethnical studies are needed to clarify determinants and modifiers of SOD1 phenotypes.

Disclosure: All authors have nothing to disclose.
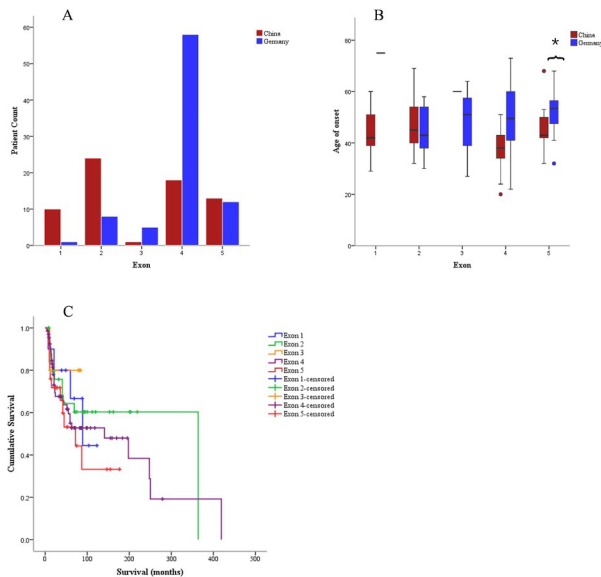
Figure 1. Demographic and clinical features of patients carrying SOD1 mutations by exons.

OPR-174

A systematic review of extra-motor symptom evaluation in clinical trials for amyotrophic lateral sclerosis.

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Background and aims: Amyotrophic lateral sclerosis (ALS) is increasingly recognised as a multi-system disorder. Extra-motor symptoms such as cognitive impairment, behavioural change, neuropsychiatric symptoms, sleep disturbances, fatigue, sialorrhea, and pain are common in, and impactful upon, people with ALS. We aimed to systematically review historical clinical trials in ALS to identify if extra-motor features of ALS were explored as outcome measures and if so describe the tools used.

Methods: We reviewed clinical trials of investigative medicinal products in ALS, since the licensing of riluzole. Trial registry databases were searched for Phase II, III or IV trials registered, completed or published between 01/01/1994 and 16/09/2020. No language restrictions applied. We evaluated the use of assessment tools to investigate extra-motor symptom as outcome measures.

Results: 237 clinical trials were included in this review for use of outcome measures. These trials evaluated cognitive impairment (16 trials, 6.8%), behavioural change (38, 16%), neuropsychiatric symptoms (75, 32%), sleep disturbances (12, 5%), fatigue (18), 8%, saliva (182, 77%) and pain (55, 23%). 29 trials (12%) did not include any assessment of extra-motor symptoms. 51 versions or combinations of assessment tools were utilised in these trials.

Conclusion: Extra-motor symptoms have been under-evaluated in trials for people with ALS. Where evaluated, this has been primarily using assessment tools which are not specific to ALS or the extra-motor symptom, which may affect the validity of conclusions drawn regarding the impact of candidate drugs.

Disclosure: Nothing to disclose.

OPR-175

SUNFISH Part 2: 24-month efficacy and safety of risdiplam in patients with Type 2 or non-ambulant Type 3 SMA

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Background and aims: Spinal muscular atrophy (SMA) is a severe, progressive, neuromuscular disease caused by reduced levels of the survival of motor neuron (SMN) protein due to deletions/mutations of the SMN1 gene. A second gene, SMN2, produces only low levels of functional SMN protein. Risdiplam (EVRYSDI™), a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier, received FDA approval for the treatment of patients with SMA, aged two months and older.

Methods: SUNFISH (NCT02908685) is a multicentre, 2-part, randomised (2:1, risdiplam:placebo),

placebocontrolled, double-blind study in patients with Type 2 or 3 SMA (inclusion criteria: 2–25 years at enrolment). Part 1 (n=51) assesses safety, tolerability, and pharmacokinetics/pharmacodynamics of different risdiplam doses. Part 2 (n=180) assesses efficacy and safety of the Part 1-selected risdiplam dose versus placebo in Type 2 and non-ambulant Type 3 SMA. Individuals were treated with risdiplam or placebo for 12 months; all individuals then received risdiplam until Month 24. At Month 24, patients were offered the opportunity to enter the open-label extension.

Results: The primary endpoint of SUNFISH Part 2 was met. A statistically greater change from baseline in the total score of the 32-item Motor Function Measure (MFM32) was observed at Month 12 in patients treated with risdiplam (N=120) compared with those who received placebo (N=60). No treatment-related safety findings leading to withdrawal were reported. Here, we present 24-month SUNFISH Part 2 data.

Conclusion: SUNFISH Part 2 is ongoing and will provide further data on the long-term efficacy and safety of risdiplam in a broad population of children, teenagers and adults.

Disclosure: This study was sponsored by F. Hoffmann-La Roche Ltd, Basel, Switzerland. Writing and editorial assistance was provided by MediTech Media UK, in accordance with GPP3 guidelines, and funded by F. Hoffmann-La Roche Ltd.

Neurogenetics 2

OPR-176

Epigenetic and Radiomics study of progestin-associated meningiomas

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Background and aims: The role of progestins in meningioma development has been described since 1980. Recent reports highlight an increased incidence of meningioma in patients treated with cyproterone acetate (CPA). Molecular analyses underlined the involvement of other tumorigenesis pathway than the NF2 mutations, the main known meningioma driver. However, the epigenetic and radiomics profile of progestin-associated meningioma (PAMs) remain unknown.

Methods: We retrospectively identified 44 patients diagnosed with a meningioma after a minimum of one year of progestin treatment from our hospital database. We established a control cohort of 20 sporadic meningioma. We extracted 150 radiomics features/MRI/ patient (Sophia Radiomics software). Statistics analyses and machine learning algorithms were performed using Rv3.6.2. We obtained global DNA methylation profiles (DFKZ classification, https://www.molecularneuropathology.org/mnp) in a subgroup of 11 operated PAMs using EPIC850K (Illumina) array.

Results: We analyzed 76 meningioma (65% of skull base, 35% of convexity) from 44 patients. Median age at diagnosis was 54 years, and mean progestin treatment duration was 18.2 years. 50% of PAMs (38/76) regressed after cessation of progestin treatment with a median regression rate of 20%/year while 33% of PAM (25/76) stabilized and 17% (13/76) pursued growth. Decrease of small diameter ($p=10^{-6}$) and texture homogeneity ($p=10^{-5}$) were the main changes in radiomics features. Methyloma study highlighted a relatively homogenous epigenetic profile corresponding to MCben2, a benign meningioma subtype.

Conclusion: Our study is the first radiomics and epigenetic analysis of PAMs. It enriches the knowledge on molecular landscape of PAMs, highlighting their molecular homogeneity and it provides extensive radiomics characterization.

Disclosure: This research was undertaken with the assistance of resources and services from the Sophia Genetics Data Science department.

OPR-177

Single nucleotide polymorphisms as possible phenotype modifiers in charcot-marie-tooth 1a disease: a cohort study

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Background and aims: There is a great variability of phenotype expression in Charcot-Marie-Tooth type 1A (CMT1A) even within the same family. To date, no univocal explanations are available. Single nucleotide polymorphisms (SNPs) could play a role in modulating phenotype in CMT1A patients but no definite evidence is available.

Methods: 23 CMT1A patients were enrolled. SNPs rs4280262 in LITAF, rs6875902 , rs3763022 and rs2304034 in SH3TC2, rs10910527, rs4649265, rs7536385 and rs1547740 in SIPA1L2, H63D and C282Y in HFE were analyzed. Each patient was assessed by several validated scales in order to quantify sensory and motor involvement.

Results: The presence of LITAF rs4280262, SH3TC2 rs3763022, SIPA1L2 rs10910527, SIPA1L2 rs4649265 and SIPA1L2 rs7536385 was associated with a more severe phenotype. SH3TC2 rs2304034, SH3TC2 rs6875902 and SIPA1L2 rs1547740 did not appear to have an effect.. HFE H63D was associated with a lower strength in foot dorsiflexion (p=0.022). Patients were classified according to the number of polymorphisms. Correlation analysis showed a positive relationship between the number of SNPs and the burden of disability in the upper (p=0.012) and lower limbs (p=0.019) and the severity of sensory involvement (p=0.025) and an inverse correlation with the meters walked at 6MWT (p=0.011).

Conclusion: SNPs could play a role in modulating CMT1A phenotype. We observed a possible role also for the H63D polymorphism in HFE which was not previously described. Our results showed a possible summation effect of SNPs in influencing the phenotypical expression of the disease. Certainly, larger case studies are needed in order to confirm these observations.

Disclosure: Nothing to disclose.

OPR-178

Genetic study of Italian families affected by small fibre neuropathy identified variants in predisposing pain phenotype

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Background and aims: Peripheral Neuropathy (PN) affects 2.4% of people and almost 50% of general population is known to have pain-related symptoms. Genetic studies in painful PN (PPN) revealed that Voltage Gated Sodium Channels (VGSCs) genes are involved in pain amplification. Here we aimed to broaden the genetic aspect of PPN by using whole exome sequencing (WES).

Methods: Six families with PPN were selected having at least one affected member, positive neurological examination and pain questionnaire result with numerical rating score ≥4. Variants were filtered with manually curated gene panel, allele frequency (AF) and computational predictors. Segregation causative/protective models were applied according to pedigree and sharing models were applied after grouping probands of each family.

Results: According to segregation causative and protective model, we found 129 and 112 variants respectively (AF≤10%) across families. Among genes shared between two families with causative approach, variants were observed in SCN9A, SV2C and DST, whereas protective variants in TRPM2 and LRP1. In shared model, we identified 21 variants and 53 genes shared across ≥3 probands. Among shared genes with predicted high-impact variants in probands were observed in SCN9A, SCN7A, P2RY4, P2RX7, TRPV4 and TRPM1.

Conclusion: WES approach appears powerful in mutation detection and in revealing new genotype-phenotype association. In addition to VGSCs, other gene families including Transient Receptor Potential and Purinergic Receptor seem to play a role in pain modulation. The same approach will be replicated on new families already sequenced before proceeding with ad hoc functional experiments to deepen the role of genes in painful phenotype.

Disclosure: FE:Novartis,Sanofi Genzyme,Almirall,Merck-Serono. FMB:Teva Pharma Industries, Sanofi Genzyme, Merck-Serono, Biogen Idec, Roche, Medday, Excemed. MF:Bayer,Biogen Idec, Merck-Serono, Novartis, Roche, Sanofi Genzyme, Takeda, Teva Pharma

OPR-179

Genotype-phenotype correlations in VCP disease: Results of an International Multicentric Study (The VCP study group)

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Background and aims: Valosin-containing protein (VCP) disease, an adult autosomal dominant disorder caused by mutations in the VCP gene leading to disabling weakness, Paget's disease of bone (PBD) and Fronto temporal dementia, is frequently misdiagnosed with other muscle or motor neuron entities.

Aim: to describe the clinical and genetic features of a large cohort of VCP mutated patients and investigate genotype – phenotype correlations.

Methods: We collected clinical and genetic data from patients with confirmed mutations in the VCP gene from 25 centres in 12 countries.

Results: 128 patients included (70% males, mean age 55.54 years old; SD 9.6). Age at symptom onset 45.42 y.o (SD 10) Diagnostic delay 7.74 years (SD 6). 98% had an heterozygous mutation. c.464G>A and c.463C>T were the most frequent variants. At beginning, 30% had proximal symmetric lower limbs (LL) weakness and 10% LL and/or upper limb (UL) asymmetric weakness. At enrolment, 89% had proximal LL weakness, 56% axial weakness, 44% respiratory symptoms, 22% PBD and 20% cognitive impairment. Dysautonomia (26%) and upper motor neuron symptoms (9%, UMN) appeared within the first two years. 58% required walking assistance at 9,14 (SD 5) y. from onset. The c.463C>T variant had an earlier onset (37.4y.o, SD 7.5) and greater UL and axial weakness. Sixteen patients died (main reason respiratory insufficiency) at a mean of 12 (SD 7) y. from onset.

Conclusion: VCP disease resembled a LGMD, however, the early presence of dysautonomia, UMN and the rapid loss of ambulation should raise awareness of VCP. The c.463C>T variant had a more severe phenotype.
Disclosure: Nothing to disclose.

OPR-199

Evidence of shared biological pathway between Parkinson's disease and psychiatric disorders.

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Background and aims: Epidemiological studies have suggested several possible associations between Parkinson's disease (PD) and psychiatric traits. By studying shared genetic architecture and biology, we can dissect common pathways and suggest new targets for drug development.
Methods: We selected genome-wide association studies (GWASs) summary statistics from recently published PD GWAS and 12 traits from Psychiatric Genomics Consortium. We have applied linkage-disequilibrium score regression (LDSC) to study the genetic correlation between the traits. Next, to identify significant associations between complex traits and gene expression in different tissues, we performed a transcriptome-wide association study (TWAS) using the FUSION software. Correlation between each pair of disorders was calculated using the RHOGE package. We performed a cross-tissue analysis of gene expression using the UTMOST package and identified genes significantly associated with both PD and psychiatric traits. At the next step, we performed gene pathway analysis to identify common pathways across traits.
Results: We found a genetic correlation between PD and attention deficit hyperactivity disorder(ADHD). Analysis of gene expression identified a significant negative correlation between PD and ADHD only in the cortex but not in the other tissues. Interestingly, we found a negative correlation between alcohol consumption and PD in the hypothalamus, hippocampus and a positive correlation between cannabis dependence and PD in the cerebellar hemisphere. In the cross-tissue analysis, we found several genes significant for PD and several psychiatric traits (ADHD, anorexia, alcohol consumption, bipolar disorder and schizophrenia).
Conclusion: In our study, we have found common genes and pathways for PD and psychiatric traits, which could explain epidemiological associations.
Disclosure: Nothing to disclose

Sleep Disorders

OPR-180

Sleep patterns of Parkinson's disease patients and their relation to neural activation during motor learning

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Background and aims: Sleep disorders (SD) are tightly correlated with Parkinson's disease (PD) and considered a major contributor to its pathogenesis. The motor decline associated with the disease can manifest as difficulty in the generation of a motor plan and the development of procedural learning. A possible explanation is that disease specific sleep-abnormality, saboteurs motor-learning consolidation, and prevent an efficient stabilized learning. This study is designed to elucidate the role of SD in the pathophysiology of PD, characterize sleep patterns, and examine their relationship to neuronal activity underlying motor-learning among PD patients and healthy older adults.

Methods: By employing a self-designed motor learning task and high-density EEG recording, this study examines the behavioral and neural correlates of motor-learning among PD patients and healthy controls. By combining polysomnography sleep recording, this study will further characterize the relationship between quantitative sleep patterns and cortical activity during motor-learning.

Results: Preliminary data confirm task validity and provides group behavioral results. Response-locked EEG activity during task performance supports the hypothesis for extended activation patterns among PD subjects and provides neuronal correlations of motor-learning.

Conclusion: this study focuses on the triple bond of PD, sleep, and motor learning with the goal of providing insights into the underlying pathophysiology of neurodegeneration. Initial group differences already emerge in both behavioral and neuronal correlates of motor learning. In the future, more data collection will enable the extraction of sleep patterns characterization, sleep-dependent motor-learning and EEG patterns, and establish group differences among PD patients and age-matched control.

Disclosure: I have nothing to disclose

Grand Average and Topography of Movement Related Potentials During Task Performance
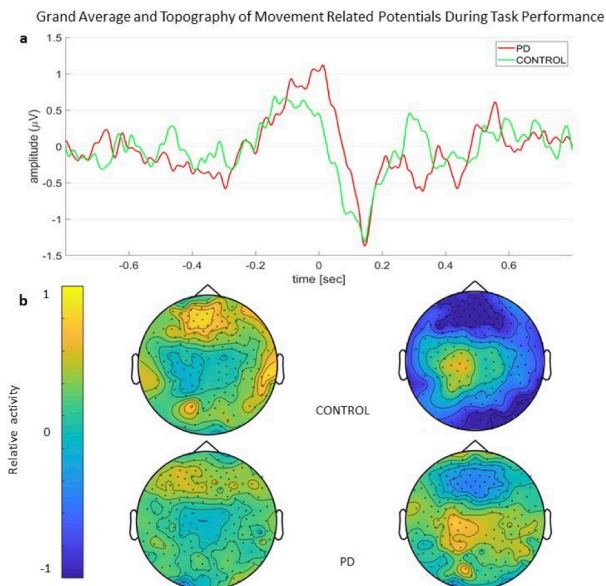
a. grand averaged response-locked activation during motor task performance. Signals are averaged between five control subjects (green line), and 9 PD subjects (red line). b. control (top plots) vs. PD (bottom)

OPR-181

Inter-rater sleep stage scoring reliability between two sleep centres and an automated artificial-intelligence algorithm

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Background and aims: To integrate automatic sleep stage scoring algorithms based on artificial intelligence (AI) in clinical practice, their generalizability to different cohorts needs to be evaluated. In this study we evaluate inter-scorer reliability (IRR) for sleep stage scoring between two sleep centres and the previously validated AI-based Stanford-STAGES algorithm (Stephansen et al., 2018).

Methods: Full night polysomnographies of 1066 subjects (53.47% men, median age 54 years) from the population-based Study of Health in Pomerania (Germany) were included. Sleep stages were manually independently scored by experts at the Hospital Charité, Center of Sleep Medicine, Berlin (Germany) and at the Department of Neurology, Medical University of Innsbruck (Austria). Sleep stages were also automatically scored with the Stanford-STAGES algorithm. For each subject, IRR was evaluated with Cohen's kappa () by comparing 1) Innsbruck to Berlin scorings (INN-vs-BER); 2) Innsbruck to automatic scorings (INN-vs-AUTO); 3) Berlin to automatic scoring (BER-vs-AUTO); and 4) both manual to automatic scorings (MAN-vs-AUTO). Mean and standard deviation of values were calculated across participants.

Results: Overall average sleep stage scoring agreement was substantial for INN-vs-BER (=0.66±0.13), INN-vs-AUTO (=0.68±0.14) and MAN-vs-AUTO (=0.61±0.14), and moderate for BER-vs-AUTO (=0.55±0.15).

Conclusion: The agreement between manual scorers was in line with previously published findings. The overall substantial agreement between manual and automatic scorings suggests that the Stanford-STAGES algorithm is generalizable to new cohorts. Despite future independent studies are needed, we demonstrate that integration of AI methods for automated sleep stage scoring in clinical practice is a goal that could be achieved in the near future.

Disclosure: Nothing to disclose

OPR-182

REM sleep without atonia and nocturnal body position in prediagnostic Parkinson's disease

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Background and aims: Sleep disturbances and polysomnographic (PSG) alterations are features of Parkinson's disease (PD), that can already occur before PD diagnosis. The most investigated prodromal PD sleep disorder is REM sleep behavior disorder (RBD). The relation between other PSG variables and PD and its prediagnostic stages, however, is less clear.

Methods: We performed a retrospective cross-sectional case-control study in 63 PD subjects (33 subjects that underwent a PSG before PD diagnosis [13 with and 20 without RBD] and 30 subjects that underwent a PSG after PD diagnosis) and 30 control subjects. PSGs were analyzed for sleep stages, different REM sleep without atonia (RSWA) variables, body position, arousals, periodic limb movements, REM density and apnea-hypopnea index.

Results: Our results show higher amounts of all RSWA subscores in subjects with PD and prediagnostic PD (with and without RBD) (table 1). Total RSWA, tonic RSWA and chin RSWA severity were significant predictors for the prediagnostic PD group without RBD (table 2). Our study also shows a higher supine body position percentage in all (prediagnostic) PD groups, which is the highest in PD and positively correlates with time since diagnosis.

Sleep time in supine body position (%)	17.73 (26.79)	46.17 (67.30)	42.40 (49.57)	78.57 (45.04)	<0.001
Sleep time in nonsupine body position (%)	83.10 (26.91)	49.07 (67.2)	57.71 (49.57)	23.99 (58.14)	<0.001
RSWA total (%)	0.64 (3.48)	3.21 (17.31)	33.73 (41.08)	7.85 (26.52)	<0.001
RSWA tonic (%)	0.00 (0.00)	2.25 (6.97)	28.57 (42.92)	3.01 (16.96)	<0.001
RSWA phasic total (%)	0.00 (3.39)	0.24 (12.32)	16.12 (33.98)	12.41 (17.07)	<0.001
- Chin	0.00 (0.00)	0.00 (3.71)	11.76 (20.49)	1.22 (9.62)	<0.001
- leg	0.00 (3.38)	0.00 (1.04)	6.45 (21.24)	5.73 (9.80)	<0.001
RSWA chin (%)	0.00 (0.00)	3.22 (8.51)	31.72 (33.15)	4.43 (17.08)	<0.001

Table 1: Results of all RSWA subscores and body position. Medians (interquartile range) are given. PSG=polysomnography, PD= Parkinson's disease, RBD= REM sleep behavior disorder. REM=Rapid-Eye-Movement. RSWA=REM sleep without atonia, AHI=Apnea/hypopnea index. N= number. PLMS= periodic limb movements of sleep. Kruskal Wallis tests were used, P values are corrected for multiple comparison and significant p values (p<0.003) are shown in bold.

Table 1: Polysomnographic characteristics of the study population.

Predictor	Prediagnostic PD RBD −		Prediagnostic RBD +		PD	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
RSWA total	1.26 (1.06-1.50)	**0.010**	1.37 (1.15-1.64)	**0.001**	1.31 (1.10-1.56)	**0.003**
RSWA tonic	1.80 (1.14-2.82).	**0.011**	2.00 (1.27-3.14)	**0.003**	1.85 (1.18-2.90)	**0.008**
RSWA phasic total	1.19 (1.02-1.40)	0.032	1.32 (1.13-1.55)	**0.001**	1.28 (1.10-1.50)	**0.002**
- RSWA phasic leg	1.01 (0.80-1.27)	0.927	1.32 (1.10-1.59)	**0.004**	1.30 (1.08-1.56)	**0.005**
- RSWA phasic chin	2.16 (1.02-4.59)	0.045	2.45 (1.15-5.21)	0.020	2.21 (1.04-4.68)	0.039
RSWA chin total	1.66 (1.12-2.46)	**0.012**	1.83 (1.23-2.72)	**0.003**	1.70 (1.14-2.51)	**0.009**
Supine body position	30.7 (2.16-437.472)	**0.012**	40.97 (2.63-701.31)	**0.008**	570.113 (36.57-8888.23)	**<0.001**
Interaction supine body position and total RSWA	0.816 (0.49-1.36)	0.433	0.892 (0.533-1.50)	0.670	0.84 (0.50-1.39)	0.491
Interaction supine body position and chin RSWA	1.02 (0.28-3.69)	0.976	1.35 (0.37-4.92)	0.652	1.14 (0.315-4.14)	0.840

Table 2. The multinominal logistic regression analyses results are shown for each group with the control group as reference category. Odds ratios (95% confidence interval) and P values are given. PD=Parkinson's disease, RBD=REM sleep behavior disorder, RSWA is REM sleep without atonia. P values are corrected for multiple comparison and significant p values (p<0.017) are shown in bold.

Table 2: The multinominal logistic regression analyses results

Conclusion: These findings suggest that higher total, tonic and chin RSWA subscores, as well as nocturnal supine body position, are already present in prediagnostic PD, independently of iRBD status. Furthermore, they highlight the relevance of monitoring complications of supine body position (such as OSAS) in PD. Prospective longitudinal studies are necessary to investigate their potential role as biomarkers for prediagnostic PD patient selection and monitoring in neuroprotective trials.
Disclosure: Nothing to disclose.

OPR-183

Thyroid gland disorders increase the risk for restless legs syndrome in multiple sclerosis

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Background and aims: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system with various neuropsychiatric symptoms. It is known, that patients with MS are at higher risk for restless legs syndrome (RLS) what leads to increased morbidity and decreased quality of life. MS is an autoimmune disorder and patient often suffer from autoimmune thyroiditis. The purpose of our work was to find the correlation between thyroid gland disorders and RLS among patients with MS.

Methods: We collected data from 200 patients with MS from the Centre for Multiple Sclerosis at the Second Department of Neurology, University Hospital and Comenius University Bratislava. All patients were examined by trained clinician with International Restless Legs Syndrome Questionnaire and International Restless Legs Syndrome Severity Scale. We obtained additional data about age, gender, MS duration, and presence of thyroid disorder.

Results: There were significantly more patients with thyroid disorder among RLS subjects (19.2 versus 3.4%, p<0.001), the risk for RLS was 6.81-times higher in patients with thyreopathy (95% CI 2.21–21.02).
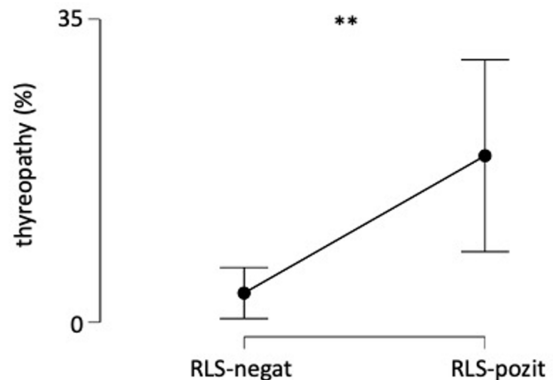
Prevalence of thyroid gland disease in RLS-negative and RLS-positive patients

Conclusion: We confirmed that MS patients with thyroid gland disorder are at higher risk for RLS. When unrecognised, it can lead to sleep disturbances, excessive daytime sleepiness and fatigue. All this increase risk of anxiety and depression, as well as the risk of cardio- and cerebrovascular disorders. That's why patients with MS must be actively screened for restless legs syndrome, especially when they suffer from any thyroid gland comorbidity.
Disclosure: Nothing to disclose.

Tuesday, June 22 2021
Epilepsy: Stroke and acute presentations

OPR-061

Epilepsies associated with anti-neuronal antibody positivity: the experience of a Portuguese tertiary centre

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Background and aims: With the advent of anti-neuronal antibody testing, autoimmunity has been increasingly recognized as the possible cause of epilepsies of previously unknown aetiology, regarded as more refractory to conventional antiepileptic medications and responsive to immunotherapy.

Methods: Using the Immunology Department database from our hospital, we identified all patients with positivity in anti-neuronal autoantibody testing profiles in serum and/or CSF requested for autoimmune encephalopathy/epilepsy/dementia from 2016 to 2020, and identified those that fulfilled diagnostic criteria for epilepsy (ILAE 2014). Their clinical information was then retrospectively reviewed.

Results: Among 207 patients with positive anti-neuronal antibodies, 33(16%) fulfilled diagnostic criteria for epilepsy: 20(61%) male, median age=54-years-old at time of anti-neuronal positivity. 22 (67%) had intracelullar and 11(33%) had cell-surface antibodies. Antibodies identified included anti-GAD65(n=8;24%), anti-NMDAR (n=7;21%), anti-Ma2 (n=6;18%), anti-CASPR2 (n=4;12%), anti-zic4 (n=2;6%), anti-LGI1 (n=1;3%), anti-Yo (n=1;3%), anti-amphiphysin (n=1;3%), anti-recoverin(n=1;3%) and anti-SOX1(n=1;3%). Five (15%) had associated malignancy. Focal seizures with altered awareness were the most common seizure type (n=23;70%), most with either motor onset (n=13;57%) or behaviour arrest onset (n=10;43%). One third presented as refractory epilepsies. EEG was abnormal in 27 (82%) patients, 21 (64%) with paroxistic activity. Inflammatory CSF was present in 18 (55%) and nine (27%) had findings suggesting encephalitis in MRI. 22 patients (67%) were treated with immunotherapy; median time interval between first seizure and treatment was one month; preferred treatment was intravenous methylprednisolone(n=16;48%). 24 (73%) patients were seizure free at last medical visit (follow-up of 1–420 months), with only five (15%), all intracellular antibody-associated, needing more than one antiepileptic drug, and only six (18%) needing chronic immunotherapy.

Conclusion: Epilepsies associated with anti-neuronal antibody positivity may present with a mostly favourable clinical outcome.

Disclosure: Nothing to disclose.

OPR-062

Incidence of Post-Stroke Epilepsy in Denmark

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Background and aims: Stroke is a major cause of epilepsy, and more than half of epilepsies occurring after 60 years of age are caused by stroke. In this study, we investigate the incidence of post-stroke epilepsy in Denmark.

Methods: This is a nationwide register-based cohort study of all individuals who were residents in Denmark and over 18 years of age between April 1 2004 and December 31 2016. We identified all first episodes with stroke through the Danish Stroke Registry. Each stroke patient was matched with five persons without stroke on age, sex and calendar time. We excluded persons with epilepsy prior to inclusion (index date). Patients and matched persons were followed until December 31 2016, death, emigration or diagnosis of epilepsy. We calculated the incidence rate of epilepsy by severity and type of stroke (acute ischemic (AIS), or Intracerebral Hemorrhage (ICH)).

Results: The incidence rate (IR) of epilepsy was 11.4 per 10,000 person years in persons without stroke and in persons with stroke, the incidence rate of epilepsy was 123.6 per 10,000 person years (Incidence rate ratio (IRR): 10.85; 95% CI: 10.54–11.16). Compared to persons without stroke, the highest incidence of epilepsy was found among persons with very severe stroke; very severe ICH (IRR 58.27; 95% CI: 48.55–69.93) and very severe AIS (IRR 45.33; 95% CI: 40.46-–50.80). See tables

	Persons in group	Risk time (yrs)	Cases of epilepsy (n)	Incidencerate (pr 10,000 yrs)	Incidencerateratio	95% CI Low	High
Control	519054	2512085	2862	11,39	1		
Any stroke	103811	389803	4817	123,58	10,85	10,54	11,16
Control	39340	183793	226	12,30	1		
- Very severe	7868	10085	583	578,08	47,01	42,97	51,43
Control	40314	192276	245	12,74	1		
- Severe	8063	20106	713	354,61	27,83	25,65	30,19
Control	73465	351932	406	11,54	1		
- Moderate	14693	49381	860	174,15	15,10	14,05	16,22
Control	273100	1391775	1544	11,09	1		
- Mild	54620	250358	1912	76,37	6,88	6,57	7,21
Control	40380	269154	319	11,85	1		
- Unknown	8076	36865	527	142,95	12,06	11,01	13,22
Control	52455	123154	122	9,91	1		
- TCI	10491	23007	222	96,49	9,74	8,40	11,29

Incidence of epilepsy after stroke

	Persons in group	Risk time (yrs)	Cases of epilepsy (n)	Incidencerate (pr 10,000 yrs)	Incidencerateratio	95% CI Low	High
Control	368499	1806354	2098	11,61	1		
Ischemic stroke	73700	288758	3352	116,08	9,99	9,65	10,35
Control	23840	105265	131	12,44	1		
- Very severe	4768	6966	393	564,17	45,33	40,46	50,80
Control	29794	137899	176	12,76	1		
- Severe	5959	14777	544	368,14	28,84	26,23	31,72
Control	58715	271564	314	11,56	1		
- Moderate	11743	38862	640	164,68	14,24	13,10	15,49
Control	230490	1124434	1255	11,16	1		
- Mild	46098	204009	1449	71,03	6,36	6,03	6,71
Control	25660	167192	222	13,28	1		
- Unknown	5132	24144	326	135,02	10,17	9,04	11,44

Incidence of epilepsy after acute ischemic stroke

	Persons in group	Risk time (yrs)	Cases of epilepsy (n)	Incidencerate (pr 10,000 yrs)	Incidencerateratio	95% CI Low	High
Control	51630	262374	282	10,75	1		
Any ICH	10326	28061	861	306,83	28,55	26,52	30,73
Control	12925	63453	70	11,03	1		
- Very severe	2585	2505	161	642,79	58,27	48,55	69,93
Control	7835	37951	48	12,65	1		
- Severe	1567	3785	141	372,49	29,45	23,97	36,18
Control	8745	42640	47	11,02	1		
- Moderate	1749	5505	155	281,58	25,55	20,93	31,17
Control	15650	77564	82	10,57	1		
- Mild	3130	12391	284	229,21	21,68	18,84	24,94
Control	6475	40767	35	8,59	1		
- Unknown	1295	3875	120	309,64	36,07	28,51	45,62

Incidence of epilepsy after intercerebral hemorrhage

Conclusion: Risk of epilepsy after stroke is overall more than 11 times increased compared to persons without epilepsy. Severity of stroke was strongly associated with risk of epilepsy.

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OPR-063

CT perfusion to diagnose Non Convulsive Status Epilepticus in the Emergency Room

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Background and aims: Failure in recognizing Nonconvulsive status epilepticus (SE) can have important negative consequences leading to diagnostic delay increasing the probability of an unfavorable prognosis. Cerebral perfusion-computed tomography (CTP) is an helpful tool for decision-making in the emergency situation. In this work we illustrate our center's experience and we evaluate the pattern of CTP in relation to Salzburg Consensus Criteria (SCC) for NCSE.

Methods: We included all NCSE studied in the ER with a CTP then confirmed by EEG and/or clinical features-evolution. All the 1st acquired EEGs for each patients were classified in accordance to SCC. CTP were evaluated either by visual inspection or by quantitative evaluation of through regions of interest (ROIs) placement and asymmetry indexes calculation.

Results: We included 21 focal NCSE. An hyper-perfusion pattern was found in 17 patients: 12 with a Definite NCSE (D-NCSE) [fig 1], two with a Possible NCSE (P-NCSE) and three with a post-ictal pattern (N-NCSE). two patients had a normo-perfusion pattern and a D-NCSE and two had an hypo-perfusion pattern and a D-NCSE. All the 10 patients (100%) presenting with continuous EEG ictal patterns showed an hyper-perfusion CTP. Eight patients presented discrete seizures: four (50%) had hyper-perfusion, two (25%) a normal perfusion study, while two (25%) had an hypo-perfusion one.
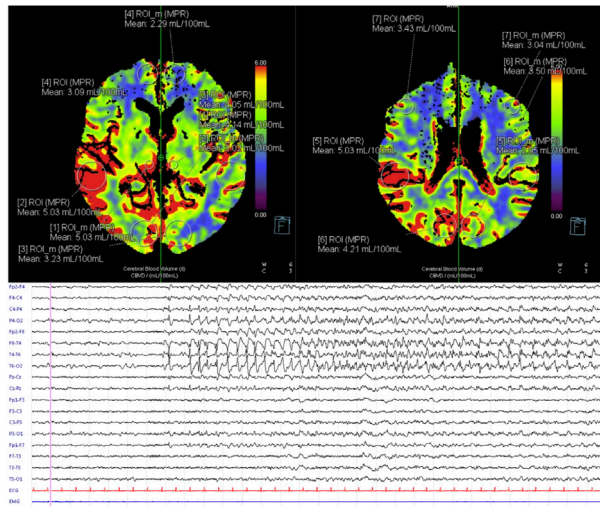
CTP showing rCBV increase in right temporo-parietal areas; EEG showing spike and wave activities at 2Hz with a temporal evolution to a delta activity at 3Hz located in the right temporo-parietal region (SCC: pattern 2c)

Conclusion: In the presence of a clinical suspicion of an epileptic event, finding hyper-perfusion CTP pattern is highly correlated to the presence of a NCSE with continuous ictal activity. CTP can speed up the diagnosis of NCSE in the emergency situation.

Disclosure: I have no disclosure to declare

OPR-184

Seizures following reperfusion treatment for stroke: multicentre, propensity score matched study

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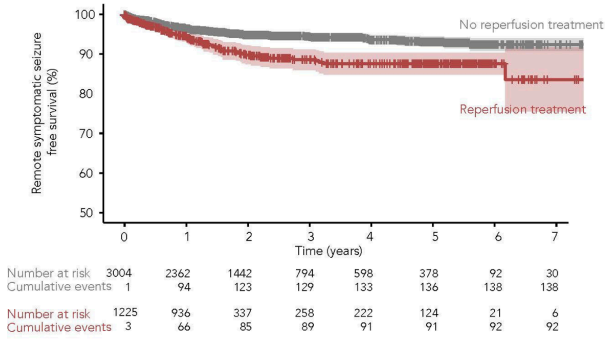
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Background and aims: Reperfusion treatments are the standards of care for acute ischemic stroke. There are concerns that they increase the risk of post-stroke seizures. Here we compared the frequency of seizures after acute ischemic stroke with or without reperfusion treatments.

Methods: This multicenter study included adults from eight European referral centers with ischemic stroke and without a past history of seizures. We compared the risk of post-stroke epilepsy or acute symptomatic seizures between participants with or without reperfusion treatment using intravenous or intraarterial thrombolysis and/or mechanical thrombectomy. We used propensity score matching to reduce confounding due to treatment selection.

Results: The cohort included 4229 participants of whom 1225 (29%) had reperfusion treatment, 196 (5%) experienced acute symptomatic seizures, and 232 (6%) had post-stroke epilepsy. Median follow up time was 1.6 years (interquartile range 1.0–3.3). After matching (n=936 in each group), there was no association between reperfusion treatment and time to post-stroke epilepsy (hazard ratio [HR] 1.05, 95% confidence interval [CI] 0.75–1.48, p=0.74) or risk of acute symptomatic seizures (odds ratio [OR] 1.04, 95% CI 0.70–1.55, p=0.84). In a matched secondary analysis (n=824 in each group), there was no association between receiving intravenous thrombolysis and time to post-stroke epilepsy (HR 1.15, 95% CI 0.80–1.65, p=0.43) and risk of acute symptomatic seizures (OR 1.08, 95% CI 0.72–1.62, p=0.68).

A   Time to remote symptomatic seizure (unmatched)

Time (years)	0	1	2	3	4	5	6	7
Number at risk	3004	2362	1442	794	598	378	92	30
Cumulative events	1	94	123	129	133	136	138	138
Number at risk	1225	936	337	258	222	124	21	6
Cumulative events	3	66	85	89	91	91	92	92

B   Time to remote symptomatic seizure (matched)

Time (years)	0	1	2	3	4	5	6	7
Number at risk	936	690	308	231	186	115	21	5
Cumulative events	0	45	56	59	61	63	65	65
Number at risk	936	728	286	212	101	101	21	6
Cumulative events	3	47	65	69	71	71	72	72
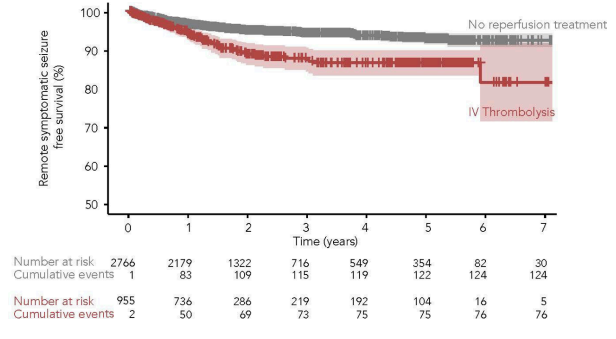
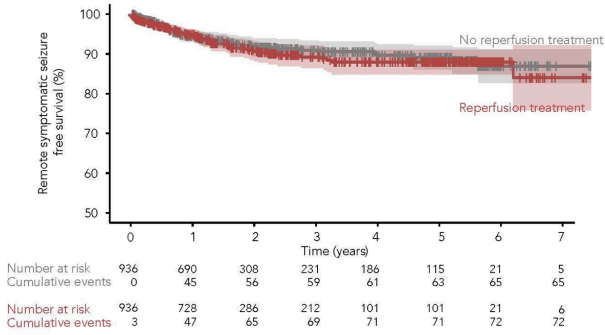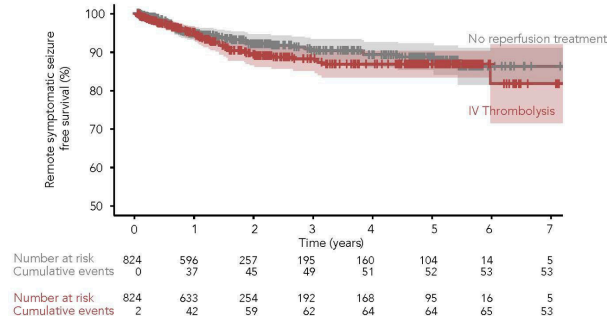Kaplan-Meier estimates of time to post-stroke epilepsy after acute ischemic stroke (A) before and (B) after matching for the propensity to receive or not reperfusion treatment. Time at baseline was index stroke. Shaded bands represent 95% CI

Forest plot showing odd ratios and 95% confidence intervals (horizontal lines) for the risk of acute symptomatic seizures after acute ischemic stroke.

A   Time to remote symptomatic seizure (unmatched)

Time (years)	0	1	2	3	4	5	6	7
Number at risk	2766	2179	1322	716	549	354	82	30
Cumulative events	1	83	109	115	119	122	124	124
Number at risk	955	736	286	219	192	104	16	5
Cumulative events	2	50	69	73	75	75	76	76

B   Time to remote symptomatic seizure (matched)

Time (years)	0	1	2	3	4	5	6	7
Number at risk	824	596	257	195	160	104	14	5
Cumulative events	0	37	45	49	51	52	53	53
Number at risk	824	633	254	192	168	95	16	5
Cumulative events	2	42	59	62	64	64	65	53

Kaplan-Meier estimates of time to post-stroke epilepsy after acute ischemic stroke (A) before and (B) after matching for the propensity to receive or not IV thrombolysis. Time at baseline was index stroke. Shaded bands represent 95% confidence interval.

Conclusion: We did not find an association of reperfusion treatment after ischemic stroke with the risk of acute symptomatic seizures or post-stroke epilepsy.
Disclosure: Nothing to disclose.

OPR-196

Autistic traits and language impairment in children of women with epilepsy are not mediated by unmetabolized folic acid

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Background and aims: Pregnant women with epilepsy using folic acid (FA) supplements may accumulate unmetabolized folic acid (UMFA) in plasma. We examined the effect of UMFA concentrations in pregnancy on autistic traits and language impairment risk in children of women with epilepsy.

Methods: We included 227 children of 203 women with epilepsy on antiseizure medication (ASM) enrolled in the Norwegian Mother, Father and Child Cohort Study (MoBa). Plasma folate and UMFA concentrations were measured in gestational weeks 17–19. Data on ASM use, FA supplement, and autistic traits and language impairment at age 1.5–8 years were collected from parent-reported questionnaires.

Results: In 208 of 227 children, the mothers reported use of FA supplements between gestational weeks -4 to 20. FA dose data were available for 76 children, in 58 of these, high-dose FA intake (1 mg or more) was reported. High maternal folate concentrations correlated with high UMFA concentrations (n=227, Spearman's rho=0.66, p-value<0.001), but not with FA dose (n=76, Spearman's rho=0.21, p-value=0.06). The UMFA concentrations did not differ between children with and without autistic traits and language impairment at any age. Linear regression analyses adjusted for covariates, showed no association between the UMFA concentrations and autistic traits and language scores.
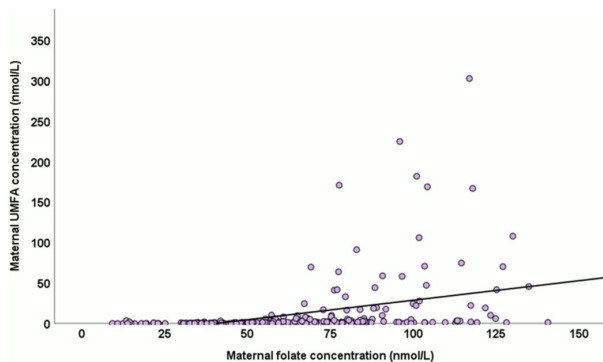

Figure 1; Scatter plot of unmetabolized folic acid (UMFA) concentration and folate concentration measured in maternal plasma in gestational weeks 17–19

		n	Detected UMFA n (%)	Maternal UMFA (nmol/L) mean, median (range)	p-value[c]
Child autistic traits at different ages[a]					
3 years	YES	9	8 (89)	18.8, 3.45 (74.7)	0.272
	NO	110	90 (82)	16.6, 1.32 (303.0)	
8 years	YES	1	1 (100)	91.1, 91.1 (0.00)	0.072
	NO	82	64 (78)	12.8, 1.31 (169.0)	
Child language impairment at different ages[b]					
1.5 years	YES	26	21 (81)	9.1, 1.2 (58.8)	0.733
	NO	124	100 (81)	15.7, 1.3 (303)	
3 years	YES	12	8 (67)	3.7, 1.2 (17.1)	0.255
	NO	110	92 (84)	17.8, 1.5 (303)	
5 years	YES	24	18 (75)	8.0, 1.6 (44.2)	0.732
	NO	58	51 (88)	15.5, 1.7 (182.0)	
8 years	YES	26	19 (73)	10.7, 1.7 (91.1)	0.973
	NO	58	47 (81)	14.9, 1.2 (169.0)	

ASM, antiseizure medication. UMFA, unmetabolized folic acid. [a]Autistic traits at 3 and 8 years according to the Social Communication Questionnaire (SCQ). [b]Language delay at 1.5 years according to the Ages and Stages Questionnaire (ASQ), at 3 years according to the ASQ and one question on expressive language delay, at 5 years according to the ASQ, Twenty Statements about Langue-related Difficulties (Language 20) and the Speech and Language Assessment Scale (SLAS), and at 8 years according to the Language 20 [c]The Mann-Whitney U test for continuous variables was used due to violation of the assumption of normal distribution

Table 1: The pregnancy unmetabolized folic acid (UMFA) concentration in children of women with epilepsy with autistic traits or language impairment at ages 1.5–8 years, respectively, compared to children without autistic traits or language impairment.

		Score interpretation	B	SE B	β[a]	p-value	95% CI
Autistic traits							
3 years	(SCQ)	Lower is normal	-0.013	0.009	-0.135	0.159	-0.031-0.005
8 years	(SCQ)	Lower is normal	0.005	0.011	0.056	0.638	-0.016-0.026
Language impairment							
1.5 years	(ASQ)	Higher is normal	0.013	0.019	0.060	0.489	-0.024-0.050
3 years	(EL)	Higher is normal	0.001	0.002	0.045	0.642	-0.003-0.004
3 years	(ASQ)	Higher is normal	0.007	0.013	0.050	0.606	-0.020-0.034
5 years	(ASQ)	Higher is normal	0.004	0.018	0.026	0.835	-0.032-0.040
5 years	(SLAS)	Higher is normal	0.000	0.002	-0.013	0.915	-0.004-0.004
5 years	(Lang 20)	Lower is normal	-0.014	0.028	-0.063	0.602	-0.070-0.041
8 years	(Lang 20)	Lower is normal	-0.006	0.016	-0.046	0.698	-0.038-0.026

UMFA, unmetabolized folic acid. B, unstandardized beta. β, standardized beta. SE, standard error. SCQ, the Social Communication Questionnaire. ASQ, the Ages and Stages Questionnaire. SLAS, the Speech and Language Assessment Scale. EL, one question on expressive language delay. Lang20, Twenty Statements about Language-related Difficulties. N may vary slightly in the adjusted model due to missing data.
[a]Variables in the adjusted model: maternal age, any AED concentrations (standardized), topiramate use yes/no, SES (single mother or low education or low household income), symptoms of anxiety and/or depression during pregnancy. If the variables SES, maternal depression, smoking and maternal age did not change the β with more than a change in the third decimal, they were not included in the final model

Table 2: The association between maternal plasma UMFA concentration and the autistic trait scores and language scores at ages 1.5–8 years, respectively, adjusted for relevant covariates.

Conclusion: We found no association between UMFA concentrations during pregnancy and risk of autistic traits or language impairment in children of women with epilepsy on ASM. Our study does not support any harmful effect of UMFA on brain development in foetal life, supporting that high-dose FA is safe for ASM-treated women with epilepsy in pregnancy.

Disclosure: There are no relevant disclosures regarding this study.

OPR-197

Progressive DNA methylation reprogramming of neuroinflammatory processes in epilepsy

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[4] *Institute of Biomedical Sciences Abel Salazar of University of Porto, Unit for Multidisciplinary Research in Biomedicine UMIB,, Porto, Portugal,*

Background and aims: Neuroinflammation is an established epileptogenesis hallmark. Exacerbated pro-inflammation has been widely described in epileptic brain, being, in fact, associated with seizure causative effects. Mesial Temporal Lobe Epilepsy (MTLE) patients often suffer from Hippocampal Sclerosis (HS), a pattern of histopathological damage characterized by severe neuronal cell loss and enhanced gliosis. Epigenetic regulatory mechanisms have been proposed to contribute for epiletogenesis onset and progression through the establishment of altered transcriptomic patterns. DNA methylation, a modulator of chromatin structure and accessibility linked to gene expression repression, is considered a prominent player in the unveiling of the ethiopathogenic mechanisms of epilepsy.

Methods: Hippocampal DNA methylation profiling was performed with Infinium HumanMethylationEPIC BeachChips in eight MTLE-HS patients subjected to resective surgery. DNA methylation values were correlated with epilepsy duration (years) using Spearman's correlation ($rho > 0.5$; $p < 0.01$).

Results: We observed 2,601 and 3,104 CpGs whose methylation in the hippocampus correlated inversely and positively with epilepsy duration, respectively. Gene ontology analysis of both clusters showed enrichment of multiple inflammatory terms, with emphasis for MHC and peptide antigen binding. Binding-motif enrichment demonstrated overrepresentation of transcription factors involved in inflammation. We highlighted interferon regulatory factor 1 (IRF1), a known proponent of the disease-associated microglia phenotype.

Conclusion: Epileptogenesis is not static, with increased seizure frequency and severity being regularly observed. DNA methylation is here described has a potential modulator of pro-inflammatory neurodegeneration coupled with epilepsy progression. Special attention must be given to the role of microglia in this landscape.

Multiple Sclerosis: Observational and real-life studies

OPR-188

Cardiovascular risk factors affect brain volume in young multiple sclerosis patients

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Background and aims: We aimed to investigate impact of cardiovascular risk factors (CV-RF) on brain atrophy in multiple sclerosis (MS) patients aged 50, given results for older patients may be confounded by small vessel disease.

Methods: Study included 124 (79 relapsing-remitting, 45 progressive) MS patients (age 36±8, range 18–50), and 95 healthy controls (HC) (age 35±8, range 18–50). Subjects underwent brain 3T MRI with sequences for assessing lesions and atrophy. Traditional CV-RF (smoking5pack-years, presence of hypertension, dyslipidemia, diabetes/prediabetes) were assessed, including more stringent cut-offs (smoking10pack-years, treatment for above conditions). Linear models adjusted for age, sex, disease duration, phenotype and treatment were used to determine the impact of CV-RF on MRI variables.

Results: Nineteen HC and 48 MS patients had one traditional CV-RF, four HC and 15 MS patients had >1. Ten HC and 30 MS patients had one stringent CV-RF, three and eight had >1. In MS patients, the presence of two traditional CV-RF was associated with reduced normalized grey matter volume (NGMV) (p=0.01), white matter volume (NWMV) (p=0.03) and brain volume (NBV) (p=0.003), and not with T2-lesion volume (T2-LV) (p=0.27). In MS patients, the presence of one stringent CV-RF was associated with reduced NGMV (p=0.006), NWMV (p=0.003) and NBV (p<0.001), and higher T2-LV (p=0.03). In HC, no differences were observed according to either traditional or stringent CV-RF presence.

Conclusion: The presence of CV-RF is associated with brain atrophy in MS patients, even under age 50. CV-RF seem to have synergistic effects, determining brain atrophy even for levels of exposure when present in combination.

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

OPR-189

Safety analysis of offspring breastfed by mothers on glatiramer acetate therapy for relapsing multiple sclerosis

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Background and aims: Prescribing labels for most relapsing multiple sclerosis (RMS) disease-modifying therapies (DMTs), including glatiramer acetate (GA), advise against use during breastfeeding. Limited clinical safety data exist for offspring who are breastfed by mothers receiving GA.

Methods: This non-interventional, retrospective analysis used data from the national German MS and Pregnancy Registry (January 2011–January 2020). Eligible participants had a RMS diagnosis, pregnancy resulting in live birth, and received either Copaxone® (GA; 20 or 40 mg/mL) or no DMT while breastfeeding.

Results: Overall, 60 offspring from the GA cohort (59 pregnancies; 58 women) and 60 from the control (60 pregnancies; 60 women) were included. Maternal demographics and RMS prognostic factors were descriptively comparable in both (Table 1). "Cumulative" GA-exposure was higher in the GA cohort vs control, because 86.7% of the offspring's mothers received GA during pregnancy (vs 25%). Safety outcomes ≤18 months postpartum (Table 2) showed offspring hospitalisation frequency and incidence were similar between cohorts. Frequency of annualised hospitalisation events were slightly lower in offspring in the GA cohort (0.20 [confidence interval {CI}=0.09–0.31]) vs the control (0.25 [CI=0.12–0.38]). Frequency and incidence of antibiotic use were similar between cohorts. Growth parameters (body weight, body length and head circumference) were also comparable. Paediatrician check-ups at 12 months identified 3 (2.5%; N=120 [CI=0.52–7.13]) offspring with developmental delays; were in the control cohort (n=60; 5% [CI=1.04–13.92]).

Table 1: Demographic and baseline characteristic data for breastfeeding women with RMS analysed in the COBRA study

	GA-exposed cohort* (n=58)	Unexposed cohort (n=60)
Patient demographics		
Mean (SD) age at the time of conception, years	33.1 (3.3)	32.9 (3.6)
Mean (SD) BMI at the beginning of pregnancy	25.1 (5.6)	24.5 (5.7)[†]
Median (range) follow-up duration, months	13.3 (1.1–42.6)	24.7 (0.3–49.1)
Disease activity		
Mean (SD) disease duration at conception, years	4.6 (4.0)	6.8 (5.1)
Median (range) number of relapses in the 2 years preceding conception	1.0 (0.0–5.0)	1.0 (0.0–6.0)
Median (range) number of relapses during pregnancy	0.0 (0.0–2.0)	0.0 (0.0–2.0)
Median (range) number of steroid pulses during pregnancy	0.0 (0.0–2.0)	0.0 (0.0–1.0)
Pregnancy/breastfeeding		
Median (range) gestational week of pregnancies at entry into the German Multiple Sclerosis and Pregnancy Registry	11.3 (1.0–39.3)	7.8 (3.6–38.3)
Number (%) of infants born preterm[‡]	3.0 (5.0)	3.0 (5.0)
Number (%) of infants who were exclusively breastfed[‡]	47.0 (78.3)	49.0 (81.7)
Median (range) duration of breastfeeding, months	7.9 (0.2–22.4)	8.1 (0.2–28.2)
GA exposure		
Number (%) of infants exposed to GA during pregnancy[‡]	52.0 (86.7)	15.0 (25.0)
Median (range) duration of GA exposure during pregnancy, days	66.0 (21.0–291.0)	29.0 (6.0–41.0)
Median (range) duration of GA-exposed breastfeeding, months	7.0 (0.2–19.1)	NA

BMI, body mass index; GA, glatiramer acetate; NA, not applicable; SD, standard deviation
*One woman gave birth to twins (n=58 women; n=59 pregnancies; n=60 infants)
[†]n=58
[‡]Based on the number of infants (n=60)

Table 2: Safety outcomes for all enroled infants for the period of 12-months postpartum

	GA-exposed (n=60)	Unexposed (n=60)
Hospitalisation (frequency)		
Number of events	12	15
Annualised number of events (95% CI)	0.20 (0.09–0.31)	0.25 (0.12–0.38)
Hospitalisation (incidence)		
Number of infants with an event	11	12
Proportion of population with an event (95% CI)	18.33 (9.52–30.44)	20.00 (10.78–32.33)
Antibiotic treatments (frequency)		
Number of events	13	10
Annualised number of events (95% CI)	0.22 (0.10–0.33)	0.17 (0.06–0.27)
Antibiotic treatments (incidence)		
Number of infants with an event	9	9
Proportion of population with an event (95% CI)	15.00 (7.10–26.57)	15.00 (7.10–26.57)
Diagnosed developmental delays at 12 months postpartum		
Number of infants with an event	0	3
Proportion of population with an event (95% CI)	0.00 (0.00–5.96)	5.00 (1.04–13.92)

Body measurements at 10–12 months postpartum	GA-exposed (n=50)	Unexposed (n=51)
Mean body weight, grams	9636.20	9549.22
Mean body length, cm	75.27	76.30
Mean head circumference, cm	46.07	46.21

CI, confidence interval; GA, glatiramer acetate
GA-exposed=infants breastfed by mothers exposed to GA during lactation; unexposed=infants breastfed by mothers not exposed to any disease-modifying therapy during lactation; overall=both infant cohorts combined

Conclusion: No evidence was found that maternal GA exposure during breastfeeding adversely affected the offspring's body measurements, incidences of developmental delay, and frequency and incidences of hospitalisations or antibiotic treatment use.

Disclosure: A.I.C. has received speaker honoraria from Bayer Healthcare and travel grants from Sanofi Genzyme, Teva and Novartis.

OPR-190

Comparison of the 2017 and 2010 revisions of the McDonald criteria CIS patients: a multicentre MAGNIMS study

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Background and aims: In 2017, a revision of the 2010 McDonald criteria for multiple sclerosis (MS) diagnosis in clinically isolated syndrome (CIS) was proposed. We compared the performance of 2017 and 2010 McDonald criteria in predicting MS development and anticipating MS diagnosis.

Methods: Brain and spinal cord MRI and cerebrospinal fluid (CSF) examination obtained at CIS onset and a follow-up brain MRI acquired 15 months from CIS onset were assessed in 785 CIS patients from nine European centres. Performances of the 2017 and 2010 McDonald criteria for dissemination in space (DIS), time (DIT) and DIS+DIT, also including oligoclonal bands (OCBs) assessment, in predicting a second clinical attack (clinically-definite [CD] MS), and median time to MS diagnosis were evaluated.

Results: At follow-up (median=69.1 months), 406/785 CIS patients (52%) developed CDMS. At month-36, the 2017 DIS criteria had higher sensitivity (0.86 vs 0.78), lower specificity (0.32 vs 0.38), and similar area under the curve (AUC, 0.59 vs 0.58). The 2017 DIS+DIT criteria had higher sensitivity (0.74 vs 0.66), lower specificity (0.54 vs 0.60), and similar AUC (0.64 vs 0.63). OCB assessment increased sensitivity (0.83), decreased specificity (0.39), preserving AUC (0.61). MS diagnosis was earlier with the 2017 vs the 2010 or CDMS criteria, especially with OCB assessment (2017 revision with/without OCBs=3.2/11.4 months; 2010 revision=13.0 months; CDMS=58.5 months).

Conclusion: The 2017 vs 2010 McDonald criteria showed higher sensitivity, lower specificity, and similar accuracy in predicting CDMS. They simplify the clinical use of MRI criteria, allowing an earlier MS diagnosis without reducing accuracy.

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Observational study on real-life experience with alemtuzumab in naïve patients with aggressive Multiple Sclerosis

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Background and aims: Alemtuzumab(ALEM) is an anti-CD52 monoclonal antibody for the treatment of active Multiple Sclerosis(MS) which showed high efficacy also in the subgroup of highly-active patients. We aimed to evaluate efficacy/safety profile of ALEM-treatment in a population of aggressive MS naïve-patients

Methods: We conducted a multicenter prospective observational study in a cohort of aggressive naïve-patients treated with ALEM. Clinical and neuroradiological parameters were collected from clinical records in 27 Italian MS Centers from October 2015 to September 2020

Results: 133 naïve patients were included. Basal characteristics are shown in Table1. Efficacy data were analyzed after the end of the complete therapeutic cycle (two ALEM-courses) because presence of disease activity between the two courses is not indicative of a therapeutic failure. Follow-up data at 24 and 36 months were available for 99/133 and 61/133 subjects, respectively. NEDA-3 at 24 and 36 months was reached by 89,2% and 69,4% of patients, respectively. At 24 and 36 months mean ARR were 0,06 and 0,1; median EDSS were 2,0 and 1,5, respectively. At the same time-points, mean increase in T2 lesions was 0,2 and 0,48 respectively. 5,3% of patients needed a third cycle of therapy. Overall 74,4% of patients reported adverse events (Table2)

Table 1. Basal Characteristics	
Number of patients included	133
Age at treatment, mean ± SD	31.4 ± 8.9
Sex: Females - Males, n(%)	F: 80 (60.2) – M: 53 (39.8)
Time to treatment from disease onset (months), median (IQR)	8 (4 – 27)
Follow-up in months, mean ± SD	34.2 (12.1)
Baseline EDSS, median (IQ range)	3.0 (2.0 – 3.5)
ARR previous year, mean ± SD	1.8 ± 0.9
Number of Brain T2-hyperintense lesions at MRI baseline, mean ± SD	29.8 ± 20.8
Number of brain Gd+ lesions at MRI baseline, mean ± SD	3.4 ± 5.1
Number of spinal cord T2/STIR-hyperintense lesions at MRI baseline, mean ± SD	5.0 ± 3.0
Number of spinal cord Gd+ lesions at MRI baseline, mean ± SD	0.9 ± 1.5

Table 1

Table 2. Adverse events	
Any AEs	99 (74.4%)
Infusion-associated reactions (IARs)	94 (70.1%)
Autoimmune AEs	23 (17.3%)
Thyroid dysfunction	21 (15.8%)
Immune thrombocytopenia (ITP)	1 (0.8%)
Other autoimmune AEs	2 (1.5%)
Infectious AEs	13 (9.8%)
Urinary tract infections (UTI)	4 (3.0%)
Pneumonia	4 (3.0%)
VZV reactivation	2 (1.5%)
CMV reactivation	1 (0.8%)
Listeriosis	2 (1.5%)
Other infectious AEs	1 (0.8%)

Table 2

Conclusion: These results highlight that aggressive naïve-patients are an ideal candidate for immune system resetting, likely due to young age, short disease duration and low disability. Furthermore, absence of previous immuno-modulating/immunosuppressant drugs altering the immune system play a key role in determining effectiveness of this powerful drug. Longer FU is needed to confirm our data

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OPR-192

Comparable efficacy of natalizumab EID and SID on neuroperformance measures in RRMS: real-world evidence from MS PATHS

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Background and aims: Natalizumab extended interval dosing (EID) is associated with lower progressive multifocal leukoencephalopathy risk than standard interval dosing (SID) in anti–JC virus antibody positive multiple sclerosis patients. However, EID efficacy has yet to be demonstrated in a randomised controlled trial, and real-world efficacy data would be valuable.

Methods: This study compared Multiple Sclerosis Performance Test (MSPT) functional changes occurring during treatment with natalizumab EID versus SID in MS PATHS, a network of healthcare institutions providing access to real-world clinical data. An MSPT segment was defined as the time between two MSPT assessments six months apart. MSPT segments with average infusion cycles >35 days and 35 days were defined as EID and SID, respectively. Patients could contribute multiple segments to both groups. Missing covariate data were multiply imputed. Covariates at segment start (Table) were balanced between groups by inverse probability weighting (IPW) based on a logistic propensity score model. Differences in annualized change in MSPT scores were compared between EID/SID arms with weighted linear regression.

Table. Covariates at start of EID and SID MSPT segments in MSPATHS

Baseline Characteristic	EID (n=152)[a]	SID (n=1079)[a]
Natalizumab treatment duration, mean (SD), y	4.74 (3.39)	3.88 (2.98)
Age, mean (SD), y	43.36 (11.24)	43.18 (10.27)
Sex, n (%)		
Female	110 (72.4)	828 (76.7)
Male	48 (31.6)	251 (23.3)
Race, n (%)		
Black/African American	19 (12.5)	152 (14.1)
White	120 (78.9)	872 (80.8)
Other	13 (8.6)	55 (5.1)
Education, mean (SD), y	14.61 (2.33)	15.08 (2.51)
MS duration, mean (SD), y	11.88 (7.40)	10.48 (7.49)
PDDS, mean (SD)	2.09 (1.98)	1.76 (1.95)
Relapses prior to segment, mean (SD)	0.39 (0.70)	0.43 (0.81)
PST z score, mean (SD)	−0.62 (1.32)	−0.35 (1.25)
MDT z score, mean (SD)	−1.14 (1.69)	−0.59 (1.77)
WST z score, mean (SD)	−1.84 (3.02)	−1.44 (4.13)

[a]n=number of MSPT segments. The EID and SID arms had 88 and 387 unique patients, respectively.
MDT, manual dexterity test; MS, multiple sclerosis; MSPT, Multiple Sclerosis Performance Test; PDDS, Patient Determined Disease Steps; PST, processing speed test; SD, standard deviation; WST, walking speed test.

Table. Covariates at start of EID and SID MSPT segments in MSPATHS

Results: Data from 152 EID and 1,079 SID segments were analysed. After IPW, all baseline factors exhibited a standard mean difference 0.05. Annualised change in MSPT scores of processing speed, manual dexterity, and ambulation did not differ significantly between EID and SID. On average, MSPT scores were maintained or improved while on natalizumab (Figure).
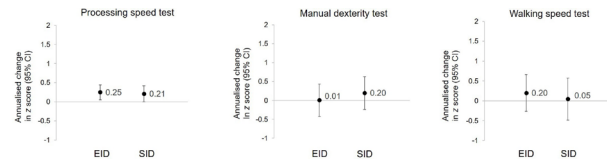

Figure. Annualised change in z score for each neuroperformance measure in the EID and SID arms

Conclusion: Functional outcomes between patients treated with natalizumab EID versus SID were comparable. Cognitive processing speed, manual dexterity, and walking speed were maintained or improved over time for both treatment groups.

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OPR-193

Exit-strategy in Natalizumab responders RRMS patients: an Italian comparison among Ocrelizumab, Rituximab and Cladribine

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Background and aims: The long exposure to Natalizumab (NTZ) treatment and anti-JC virus (JCV) seropositivity expose patients to a higher risk to develop progressive multifocal leukoencephalopathy (PML),

Methods: A multicentre, retrospective, real-world study on consecutive RRMS patients from eleven tertiary Italian MS centres, who switched from NTZ to OCR, RTX and CLA from January 1st, 2018 to December 31st, 2019. The primary study outcome was the annualized relapse rate (ARR) after 18 months on the investigated drugs. Treatment effects were estimated by the inverse probability weighting (IPW) generalized linear regression model for ARR. Additional endpoints included 24 and 48 weeks confirmed disability progression (CDP) as measured by Expanded Disability Status Scale and Magnetic Resonance Imaging activity after 12 months. Adverse events (AEs) were also collected.

Results: Patients fulfilling the required criteria were 120. Out of them, 64 switched to OCR, 36 to RTX and 20 to CLA. Patients from the three groups did not shown differences for baseline characteristics, also after post-hoc analysis. The generalized linear regression model adjusted for IPW revealed that patients on OCR had a lower risk for ARR than patients on CLA (ExpB OCR 0.485, CI 95% 0.264–0.893, p=0.020). No differences were found in other pairwise comparisons (OCR vs RTX and RTX vs CLA). AEs rates were similar among the three groups.

Conclusion: Conclusions: OCR revealed to better control early disease activity compared to CLA. All the DMTs investigated were safe. Further data are needed.

Disclosure: Nothing to disclose.

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