Poster Session I

Diagnosis and differential diagnosis

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An international multicentre validation experiment for MOG antibodies

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Background: Antibodies to myelin-oligodendrocyte-glycoprotein (MOG-ab) are associated with a broad spectrum of human CNS demyelinating diseases including AQP4-ab-seronegative neuromyelitis optica spectrum disorders and related clinical presentations such as isolated optic neuritis and myelitis, acute disseminated encephalomyelitis, but only rarely in multiple sclerosis. Although numerous studies have used different immunoassays for MOG-ab, there is no published blinded multi-centre validation experiments comparing MOG-ab assays. The aim of our study was therefore to compare the most frequently used assays for MOG-ab such as immunofluorescence cell-based assays (IF-CBA), flow cytometry cell-based assays (FACS-CBA) and enzyme-linked immunosorbent assay (ELISA). In phase one we compared 11 different MOG-ab assays (in-house and commercial; IF-CBA, FACS-CBA and ELISA) in a blinded fashion on 89 serum samples.
Methods: The clinical laboratories (Innsbruck, Mayo, Oxford and Sydney) sent coded MOG-ab positive sera (n=39), MOG-ab negative sera (n=40) and clinical documentation to the Institute for Quality Assurance (IQA), Lübeck, Germany. Euroimmun AG contributed 10 technical controls (humanized monoclonal antibodies) which were also sent to the IQA. All samples and controls were re-coded, aliquoted and distributed to the five testing centres. Upon completion of the testing, the assay results from each centre was entered onto a web-based database. The data were then unblinded, and analysed.
Results: We found a very good agreement between live IF-CBA and live FACS-CBA (kappa values > 0.9). There was a good agreement between live CBA (IF or FACS) and fixed IF-CBA (kappa values > 0.8). The agreement of ELISA and all CBA was very poor and our results indicate that ELISA is not useful for the detection of human MOG-ab. However, phase I only focused on clearly positive and negative samples, and we are therefore currently performing phase II using 100 additional samples (borderline and lower positive, healthy controls, and replicates from phase I) to compare the sensitivity and specificity of assays. We plan to perform a phase III to examine MOG-ab assays in routine diagnostic centres world-wide and are particularly interested in centres that can contribute sera to the study.
Conclusions: Large multicentre validation studies of antibody assay are important to evaluate assay reproducibility between centres and to help define the clinical phenotype associated with MOG-ab.

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Migraine and clinically isolated syndrome: the role of periventricular lesions.

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Introduction: Migraine may be a common diagnosis in patients initially referred to evaluate the possibility of multiple sclerosis (MS). On MRI, white matter hyperintensities (WMH) may be detected on the T2-weighted sequences in migraine patients. The periventricular region, traditionally considered a hallmark of MS, may be not so rarely involved, thus contributing to misdiagnoses. The number of periventricular lesions (PVLs) required to fulfill Dissemination in Space (DIS) requirements varies among different diagnostic criteria. 3 PVLs have been suggested by the MAGNIMS group while the Panel recently maintained the requirement for 1 PVL.
Objectives: To analyze the differences on WMH volumes and locations; to evaluate the involvement of periventricular region in two large cohorts of migraine and Clinically Isolated (CIS) patients.
Aims: to evaluate the impact of 1 vs 3 PVLs on sensibility and specificity of the DIS criteria according to the MAGNIMS group and the Panel in two large cohorts of migraine and Clinically Isolated (CIS) patients.
Materials and methods: White matter T2/FLAIR hyperintensities of 84 migraine and 79 Clinically Isolated Syndrome (CIS) patients were volumetrically and topographically assessed by using manual segmentation technique and, subsequently, by generating Lesion Probability Maps (LPMs) and Voxel-Based Lesion Symptom Mapping (VLSM). A logistic regression analysis based on lesion location was performed to evaluate the impact of 1 versus 3 PVLs on the sensibility and specificity of the 2017 revisions and the 2016 MAGNIMS criteria.
Results: CIS patients had a higher WMH number and volume in all the four locations analyzed. Interestingly, 10.7% of migraine patients showed infratentorial WMH, detectable through a careful evaluation of the posterior fossa on the T2-weighted images. Logistic regression analysis showed that PVLs were the best factor separating CIS from migraine patients with a 85% decrease in the probability to be migraineur for each PVL more than one (OR=0.156, 95% CI=0.076, 0.319, $p< 0.001$). MAGNIMS criteria demonstrated the highest specificity in differentiating CIS from migraineur (100% vs 87%) against a predictable lower sensibility (63% vs 72%).
Conclusions: PVLs play a key role in the differential diagnosis between migraine and CIS, particularly when they are ≥ 3. It might be prudent for the clinician to consider a higher number of PVLs, in order to avoid misdiagnosis.

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Multiple sclerosis and Sarcoidosis: a case for co-existence

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Background: Patients with sarcoidosis who develop neurologic disease are generally presumed to have Neurosarcoidosis (NS). However, possibility of a co-existing neurologic condition, such as Multiple Sclerosis (MS) should be considered as well. Incorrectly diagnosing MS patients with NS might not only deprive them of beneficial MS disease-modifying therapies (DMT) but also potentially expose them to NS therapies that may be harmful for MS (e.g., TNF alpha-inhibitors).
Objectives/Aims: To report a case series of 9 patients with biopsy-confirmed extra-neural sarcoidosis and specialist-diagnosed MS followed in tertiary MS centers, and to evaluate respective phenotypes, diagnostic determinants and treatment responses.
Methods: Inclusion criteria: biopsy-confirmed sarcoidosis outside the central nervous system; meets the Revised McDonald Criteria for MS; does not demonstrate any typical radiologic features of NS. A retrospective review of the patient charts was performed across 4 MS Centers to identify patients meeting the inclusion criteria.
Results: We identified 9 patients with systemic sarcoidosis and MS: 7/9 patients were women; average age was 46.8 years (range 37-54); average MS duration was 8.4 years (range 2-17); average sarcoidosis duration was 6.1 years (range 1-18 years). Sarcoidosis was confirmed by lung biopsy in 7/9 patients, mediastinal biopsy in 2/9 patients. All patients showed multiple MRI findings typical of MS (Dawson's fingers, U-fiber lesions, cerebellar white matter lesions, dorsal and lateral spinal short-segment lesions, etc.). None of the patients had MRI features suggestive of NS (persistent enhancement, cranial nerve enhancement, leptomeningeal involvement, pituitary lesions, etc.). Patients were followed by an MS specialist for an average 6.3 years (range of 1-17 years). All patients received DMT for MS. Typical additional MS-like lesions were seen on follow-up MRI in 6 out of 9 patients.
Conclusions: MS and sarcoidosis can rarely co-occur. If clinical and radiographic course is typical for MS and there are no radiographic features of NS, sarcoidosis should be viewed as a comorbid autoimmune disorder. Rigorous phenotyping and close clinical and MRI follow-up can help differentiate MS from NS.

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Multiple sclerosis new criteria are also more relevant in North Africans

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Development of the Mac Donald criteria (MDc) for Multiple sclerosis (MS) diagnosis and subsequent revisions were based on data from adult white European and North American populations. In North Africans (NAs), prevalence, clinical phenotype and differential diagnosis of MS are different. In 2017, the International Panel on Diagnosis of MS reviewed the 2010 criteria and recommended revisions. However, their relevance in NAs remains discussed. Data about the reliability of MS criteria in our region are scarce.
To study the sensitivity of 2017 MDc in a cohort of Tunisian patients with typical clinical isolated syndrome (CIS).
From 2003 to 2017, we collected patients with typical CIS followed in the department of Neurology of Razi Hospital. They had clinical follow-up of at least two years or until the development of definite MS. All patients were aged of 18 to 50 years and had baseline MRI obtained within three months of onset.
Seventy patients met inclusion criteria and consisted of 54 women and 16 men. Mean age was 36.6 ± 11.2 years with mean age when CIS occurred around 29.6 ±9.7 years. CIS was monofocal in 80.6%. It included spinal cord symptoms (40%), optic neuritis (32%), brainstem or cerebellar symptoms (18%) and supratentorial syndrome (10%). Only one patient remained diagnosed as CIS. At first attack, 2010 MDc were fulfilled in 38.5% while 64.4% with 2017 MDc thanks to CSF analysis in 11.4% and inclusion of symptomatic and asymptomatic lesions in 14.5%. The 2017 criteria had higher sensitivity compared to 2010 version in our population (74% versus 44.4%).
In our NA cohort, new criteria allowed the diagnosis of a higher rate of MS since first clinical event. More studies are urgently needed to really validate these criteria in our latitudes.

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Subclinical disease progression in NMO spectrum disorders suggested by full-field visual evoked potentials

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Background: In neuromyelitis optica spectrum disorders (NMOSD) relapse-dependent accumulation of central nervous system damage is key to our current understanding of fixed neurological deficits. However, little is known about possible chronic subclinical disease processes occurring independently of acute attacks such as optic neuritis (ON) or transverse myelitis. Visual evoked potentials (VEPs) provide objective functional measures of the visual pathway.

Objective: To investigate if subclinical disease progression occurs within the visual system of NMOSD patients independently of acute ON.

Design: Retrospective longitudinal multi-center study at 16 centers of the German Neuromyelitis optica study group (NEMOS) between May 1994 and May 2017.

Methods: Five hundred sixty-four full-field VEPs of 172 NMOSD patients were longitudinally assessed. For analyses, 209 eyes of 105 predominantly Caucasian (93.3%) and female (83.3%) NMOSD patients were eligible. Rates of change over time for P100 peak-latencies (RCL) and P100-N140 peak-to-peak-amplitudes (RCA) were analyzed for each individual eye using linear regression and compared using generalized estimating equation models.

Results: A median of three VEPs per patient were performed over a median interval of 32 months. The rates of change in the absence of ON during the interval were +1.951ms/year (N=101 eyes; SD=6.274; p=0.012) for the P100-latencies and -2.149µV/year (N=64 eyes; SD=5.013; p=0.005) for the P100-N140-amplitudes. The history of a previous ON, that had occurred >6 months before baseline VEP, had no influence on RCL and RCA. ONs during the observational period led to mean RCL and RCA of +11.689ms/year (N=16 eyes; SD=17.593; p=0.003) and -1.238µV/year (N=11 eyes; SD=3.708; p=0.308), respectively.

Conclusions: This first longitudinal VEP study provides evidence of subclinical disease progression within the visual pathway of NMOSD patients, occurring independently of acute ON attacks. These findings could have an impact on the disease prognosis and management of NMOSD patients and add novel insights into the pathophysiology of the disease.

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Patient satisfaction with the first talk about diagnosis and its impact on treatment decisions: a Swiss multiple sclerosis Registry study

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Introduction: Patient satisfaction with the first diagnostic consultation (FDC) might have an impact on treatment decision. Initiation of disease modifying treatment (DMT) in multiple sclerosis (MS) should be informed, shared with the patient, and consider all appropriate options.
Objectives: To investigate factors contributing to patient satisfaction with the FDC and to assess its association with DMT initiation.
Methods: Using retrospective patient-reported data of the Swiss MS Registry, we fitted ordered logistic regression models (outcomes: a. Satisfaction with FDC: 1(not at all, reference) to 5 (very satisfied); b. Start of DMT after FDC: no/yes), adjusted for period of diagnosis and other pre-specified confounders. Primary progressive MS was excluded.
Results: 421 persons with MS diagnosed after 1995 (clinically isolated syndrome (n=11), relapsing remitting (n=379) or secondary progressive MS (n=31) at diagnosis) were included. 54% of participants were satisfied with the FDC (levels 4-5), 24% were

not satisfied (1-2), and 22% were neutral (3). For 18% the FDC lasted ≤10 min, for 42% 10-30 min, for 32% ≥30 min, others did not recall. 84% perceived the diagnosis as clear. The most covered topics were the nature of MS (67%) and DMT (72%). 59% were suggested ≥2 DMT options, 22% 1 option, and 19% no DMT option. Of all patients, 70% initiated DMT within 3 months, 7% after 3 months, and 23% did not start any.

In the multivariable regression on satisfaction with FDC, involvement in the DMT choice (odds ratio 16, [95% confidence interval 4-59] vs. no involvement), the number of topics covered (1.4 [1.2-1.7] per additional topic), clarity of the diagnosis (3.5 [1.5-8] vs. a perceived unclear diagnosis), and high socioeconomic status defined by highest work position (2.1 [1.1-4]), were associated with better satisfaction. Worse satisfaction was associated with an interval from contacting a doctor to the diagnosis exceeding 3 months (0.48 [0.27-0.85]). Satisfaction with the FDC (6 [2-19]), diagnosis after 2010 (8.6 [2.1-35.6]), and FDC longer than 30 min (4.9 [1.1-20.7]), were associated with DMT initiation. Males were less likely to start DMT (0.3 [0.1-0.7]).

Conclusions: Satisfaction with FDC could be crucial for increasing DMT initiation in the MS population. In order to achieve that, physicians should aim to minimize the diagnostic process length, dedicate ample time to the FDC, provide clear information about MS, and involve patients in treatment decision.

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LB, MK, ML, VvW have nothing to disclose.

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CP has received travel support and participated to advisory board for Biogen Idec, Genzyme, Novartis and Roche.

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Myelin oligodendrocyte glycoprotein (MOG) antibody-associated demyelination: comparison between onset phenotypes

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Introduction: As a broad spectrum of disease entities, variable signs of onset potentially pose a challenge to early identification and treatment of MOG antibody-associated demyelination.

Objective: To analyze the clinical and prognostic features of MOG antibody-associated demyelination with different onset phenotypes.

Aims: To investigate the implication of first demyelinating event to whole disease course and future prognosis.

Methods: A total of 52 MOG-IgG seropositive patients identified by cell-based assay were divided into four groups: (i) ON at onset (MOG-ON$^+$, n=23); (ii) TM at onset (MOG-TM$^+$, n=12); (iii) pure brain symptoms at onset (MOG-ON$^-$TM$^-$, n=14); (iv) both ON and TM at onset (n=3, not included into analyze). Data were collected through medical records and regular follow-up.

Results: MOG-ON$^-$TM$^-$ had the youngest age of onset. Patients with MOG-TM$^+$ tended to relapse more frequently, with a longer interval to first relapse compared to those with MOG-ON$^+$ and MOG-ON$^-$TM$^-$. Throughout the course, 21%-33% of patients had clinical evidence of other attack localization except their initial ones. High MOG-IgG titers were associated with increased CSF leukocytes. There was a trend towards greater likelihood of haboring transient, low MOG-IgG titers in MOG-TM$^+$ vs the other groups. The majority of MOG-TM$^+$ and MOG-ON$^+$ had radiologic brain involvement, but the frequency of abnormal MRI and large brain lesion were predominately lower than the MOG-ON$^-$TM$^-$. After a median disease duration of 20 months, most cases exhibited a favourable outcome, but not always, with 13% developing severe visual deficits, 2% becoming wheelchair dependent and 6% developing cognitive impairment. The onset phenotype appeared to be an important predictor of disability type. Having ON at onset (OR 2.27, p=0.047) was more likely to achieve a complete recovery, while having high MOG-IgG titers (OR 0.14, p=0.025) was less likely to recover fully.

Conclusions: Onset phenotype may influence long-term presentation, MOG-IgG status as well as the outcome. Further large and prospective studies will be required to better clarify the clinical relevance of MOG-IgG and the first demyelinating attack.

Disclosure

Name: nothing to disclose

P337

Leucopathy-like acute demyelinating syndromes with anti-MOG-antibodies in children

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Acute demyelinating syndromes (ADS) are frequently associated with anti-MOG antibodies in children. Clinical phenotypes are heterogeneous and may delay the diagnosis, especially when they relapse and are wrongly considered as multiple sclerosis (MS). Here, we describe three children with progressive cognitive and motor impairment, epilepsy and behavior disorders. The brain MRI showed diffused bilateral white matter injuries including optic nerves, periventricular regions, corpus callosum, cerebellum and spinal cord. Cerebrospinal fluid (CSF) analysis showed high levels of proteins in two cases and meningitis with a majority of lymphocytes in two cases. There were no oligoclonal bands. Metabolic and inflammatory blood markers were all negative. Due to their atypical presentation, brain biopsies were performed in two children and showed white matter lesions with no argument for histiocytosis nor for tumor. Steroids were ineffective, clinical and radiological improvement and stabilization were obtained after active immunotherapy associating Mitoxantrone in two patients and Natalizumab in one of them. After nine years of follow up, all three children have cognitive impairment. A retrospective analysis for anti-MOG antibodies in these children at onset of disease was positive, and two children turned seronegative after treatment and during follow-up. Leucopathy-like ADS with anti-MOG-antibodies display distinct phenotypes and have a severe neurological prognosis. Early diagnosis and appropriate treatment may improve outcome in these children.

Key words: Acute Demyelinating Syndromes (ADS), leucopathy-like, anti-MOG antibodies, Multiple Sclerosis (MS), immunotherapy

Disclosure

No conflict of interest

P338

Neuromyelitis optica spectrum disorders: the evaluation of 66 patients followed by Istanbul Bilim University, department of neurology

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Background and objectives: Neuromyelitis optica spectrum disorders (NMOSD) are relatively rare disorders when compared to multiple sclerosis (MS). We aimed to evaluate clinical characteristics and disease course of the NMOSD patients followed at our department.

Patients and methods: All the patients with the diagnosis of NMOSD according to the Wingerchuck diagnostic criteria 2015 followed since the establishment of our MS clinic in April 2011, were evaluated.

Results: There were 66 patients (51 female, 15 male) with NMOSD followed at our MS unit. The mean age of the patients was 44,1±16,8 (17-84) years. The mean age of the patients on disease onset is 32.5± 16.9 (11-82) years. The disease duration was 8.1±6.5 years. The disease course was relapsing in 55 patients (83%). The attacks were triggered by infection in 2 patients and by vaccines in 3 patients. The first attack was optic neuritis (ON) and transverse myelitis (TM) in 12 patients (6 patients had bilateral ON (BON)), TM and area postrema syndrome (APS) in 4 patients (2 patients had also ON; one had BON and the other had ON), ON in 30 patients (BON in 5), TM in 17 patients (1 patient had also diencephalic syndrome), APS in 3 patients. The mean EDSS score was 3.5±2.1(1-8) at the last visit. NMO IgG was positive in 43 patients (65%). MOG was evaluated in 17 out of 66 patients and were all negative. Oligoclonal band was positive in 13 out of 33 patients (39%). In NMOSD patients, cranial magnetic resonance imaging (MRI) showed no abnormality in 31; nonspecific lesions in 22; chiasmal lesion in 1, brainstem lesions in 5, large hemispheric lesion in 2 and hypothalamic lesion in 1 patient. In spinal MRIs, 43 patients had longitudinally extensive transvers myelitis (LETM); 12 had short segment TM (STM) and in 11 patients it was normal.

Conclusion: This is one of the largest single center series collected over 7 years. NMOSD seems to be over-represented in our center since it is one of the few where NMO IgG/MOG testing is available. In NMOSD, early diagnosis and treatment, as well as differentiation from MS, is important to prevent the patient from the permanent disability.

Disclosure

there is no conflict of interest and nothing to declare.

P339

A comparative analysis of diagnosis delays when applying the 2017 McDonald criteria to patients with recurring-remitting multiple sclerosis

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Background: Multiple Sclerosis (MS) diagnosis remains a challenge because of the heterogeneity of the clinical presentation and the interindividual evolutivity among patients. Throughout the years, scientific and technological progress in multiple fields such as imaging, biology and pathology contributed to better define MS diagnosis. In 2017, new elements were added to the previous MS definition, the 2017 McDonald criteria.
Objective: To evaluate the impact of the 2017 McDonald criteria on MS diagnosis delay and on direct medical costs by studying a hundred recurrent-remitting MS patients.
Methods: We analysed the last hundred patients included in the European Database for Multiple Sclerosis (EDMUS) cohort by our Neurology department at the University Hospital of Rouen (France). Demographic (sex, age), clinical (Expanded Disability Status Scale - EDSS), imaging (lesion load on brain Magnetic Resonance Imaging - MRI), biology (oligoclonal bands in the Cerebrospinal Fluid - CSF) and economical variables were evaluated.
Results: Application of the 2017 McDonald criteria were associated with a mean decrease of MS diagnosis delay of 28.58 weeks *eg.* about 7 months (p=0,0002 ; CI 95%=[16,1 ; 40,3 weeks]) among 12 patients. All of these patients had received a lumbar puncture and had positive oligoclonal bands in the CSF. 2 of them had symptomatic lesions and 2 had cortical lesions on the MRI. The mean EDSS score was 1,38 [0 ; 5] . In comparison, among the patients whom MS diagnosis was not shortened by the 2017 McDonald criteria, 30 patients had a lumbar puncture, among which 16 (53%) had positive oligoclonal bands. 23 of these patients had symptomatic lesions and 2 had cortical lesions on the MRI. The mean direct medical costs during the delayed diagnosis period is under calculation. Further data will be presented at the ECTRIMS.
Conclusion: Applying the 2017 McDonald criteria can reduce diagnosis delay when oligoclonal bands are positive in the CSF and can contribute in treating MS patients earlier than with the previous Revised 2010 criteria.

Disclosure

Nothing to disclose

MS Variants

P340

Tbet positive B cells discriminate active neuromyelitis optica spectrum disorder

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Background: Neuromyelitis optica spectrum disorder (NMOSD) is a severe, recurrent autoimmune inflammatory disorder of the central nervous system (CNS) associated with a pathogenic antibody response against aquaporin-4 (AQP4). AQP4 serum titers, however, are a poor prognosticator of NMOSD disease activity. Biomarkers of NMOSD activity would be valuable for predicting treatment response.
Methods: We evaluated changes in pro-inflammatory, regulatory, and anergic B cell populations in NMOSD patients using fluorescence activated cell sorting (FACS). We obtained and purified peripheral blood B cells from active (< 1 month from acute clinical attack) and quiescent (> 90 days from acute clinical attack) AQP4-seropositive NMOSD patients. NMOSD patients were either untreated or naïve to B cell-depleting therapy. We determined the relative fractions of naïve, memory, double negative (DN), plasmablasts, B10 regulatory and anergic B cell subsets. Functional variants within the memory and double negative B cell populations were further assessed using surface and intracellular markers.
Results: The number of naïve, memory (CD27+IgD-), double negative (CD72-IgD-, DN) memory, B10 regulatory, and anergic B cells failed to distinguish active from inactive NMOSD patients. Cell surface markers of B cell activation (CD86, HLA-DR2, CD24, CD148) also failed to correlate with disease activity. We identified a novel B cell subset ($CD11c^{+}CxCR5^{-}$) within both the memory and DN memory B cell populations, that was significantly elevated in active NMOSD patients. This unique B cell subset expressed CD21, FcRL5, and the transcription factor T-bet.
Conclusions: Our studies have identified an expanded population of memory and DN memory B cells ($CD11c^{+}CxCR5^{-}CD21^{+}FcRL5^{+}T\text{-}bet^{+}$) in active NMOSD patients. This population shares surface markers identical to B cells that are expanded in systemic lupus erythematosus patients. Fluctuations in circulating Tbet+ B cells may be a useful marker for monitoring NMOSD patients.

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Clinical and MRI features of onset myelitis in MOG-antibody disease

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Introduction: Myelin oligodendrocyte glycoprotein (MOG)-antibody disease has recently been recognised. Transverse myelitis

at onset is a significant predictor of long-term disability, particularly sphincter dysfunction. Few data exist about the MRI features and their clinical association.

Methods: Adult MOG-antibody-positive patients, attending our specialist service, with onset myelitis and appropriate imaging were identified. MRI scans were reviewed and associated with clinical outcomes and CSF findings.

Results: Of the 22 patients included; 77.3% had LETM; 22.7% had short TM; 9.1% had isolated cervical cord lesions, 40.9% had involvement of the thoracic cord (18.2% thoracic without conus extension, 22.7% thoracic and conus). The remainder involved both cervical and thoracic cord. In total, 47.8% of patients had lesions involving the conus. 52.2% had >1 lesion at onset (range:2-6).

Median EDSS at nadir was 6 (range:1-9). Nadir EDSS scores correlated with total lesion length (r=0.3532,p=0.0119). Median EDSS at recovery was 1 (range:0-6). Lesion length did not correlate with recovery EDSS. One patient was left severely disabled (EDSS 6) and was the oldest (70 years at onset). Lesion number, GAD enhancement and swelling did not associate significantly with clinical outcomes, nor did CSF findings. All patients requiring long-term catheterisation had conus lesions and this proportion was significant when compared to those not requiring catheters (p=0.0373). The presence of brainstem lesions was significantly higher in patients whose residual EDSS was ≥3 (p=0.035).

16/22 had follow-up scans. 56.3% showed complete resolution (mean follow-up=29 months), 43.7% showed some resolution or were stable (mean follow-up=26 months). The mean improvement in EDSS was greater in those with complete resolution (p=0.0339).

Conclusion: MOG-antibody disease myelitis commonly presents as LETM, although short lesions are not uncommon. Patients may present with more than one lesion. Lesion length correlates with nadir EDSS but not with recovery EDSS as most patients recover well despite long lesions at onset. Brainstem lesions may contribute to residual disability. Long-term catheter requirement is significantly associated with conus involvement and MRI resolution associates with better recovery.

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M. Leite reported being involved in aquaporin 4 testing, receiving support from the National Health Service National Specialised Commissioning Group for Neuromyelitis Optica and the National Institute for Health Research Oxford Biomedical Research Centre, receiving speaking honoraria from Biogen Idec, and receiving travel grants from Novartis.

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Subclinical visual loss may be associated with MOG- IgG associated longitudinally extensive transverse myelitis

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Background: The natural history of MOG-IgG associated monophasic longitudinally extensive myelitis (LETM) has not been previously highlighted

Objective: To evaluate clinical course and afferent visual functions in a subset of MOG-Ig+ patients ,diagnosed by cell based assay(Tohoku University,Japan) and presenting with myelitis alone during their clinical course.

Methods: In this retrospective analysis 17/ 42 (40.5%) MOG-IgG+ patients diagnosed at a single center in south India satisfied the inclusion criteria. There were 14 patients with monophasic and 3 with recurrent LETM. Afferent visual functions including high contrast visual acuity testing and visual evoked potential (VEP) were recorded at disease onset . Ten patients could be retested after a median interval of 29 months (range 24- 72 months). The latter underwent optical coherence tomography (OCT) also.

Results: In all, 13/17 (76.5%) were male. Median disease duration was longer (p< 0.02) in those with RTM (144 months,range 72-236) as compared with LETM (38months, range12-104). At disease onset ,visual acuity (VA) was normal in all and VEP was prolonged (P100 latency ≥ 111.8 msec) in1 patient. On repetition, VA was normal in all but VEP was abnormal in 6/10 (60%). Seven patients (70%) had an abnormal OCT. These patients had a significant reduction of peripapillary retinal nerve fibre layer (pRFNL) thickness (*p* - 0.05) and macular ganglion cell complex (mGCC) volume (*p*- 0.005) when compared with healthy controls. No patient had microcystic macular edema.

Conclusion: Our study for the first time showed evidence of subclinical visual dysfunction in MOG-IgG associated myelitis. Our findings support the notion that there may be silent disease progression in MOG-IgG associated disease, similar to the subclinical optic atrophy reported among MS patients. These new findings suggest that this subset of patients may need long term follow up with frequent visual function monitoring, which may in turn, influence treatment decisions.

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Early treatment in neuromyelitis optica spectrum disorders

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Introduction: Neuromyelitis Optica (NMO) is a severe inflammatory disease of the CNS. We report the impact of an earlier treatment in clinical practice.
Methods: We included in our cohort only patients in which, at the end of a thorough investigation, other alternative diagnosis were excluded. Overall 70 patients reached a diagnosis of NMO. We evaluated how treatment approach changes overtime. We divided patients in "early treatment group" if the treatment was started after 1 or 2 relapses and "late-treatment group" if it started after more than 2 relapses.
Results: Overall the number of patients who received an "early treatment" was significantly higher for patients with a disease onset after 2007 (23% vs 50%, p< 0,001). In order to test the beneficial effect of an earlier treatment, we excluded 20 patients because they reached a severe disability status within the second relapses. Overall 16 patients were treated "early" and 34 patients were treated "late". The proportion of patients who reached a severe disability was significantly higher in the "late treatment group" (59% vs 6%; p< 0.05). The same results were observed evaluating the proportion of patients developing a permanent EDSS score of at least 6.0 (32% vs 0%; p< 0.05) or a permanent severe ipovisus (32% vs 6%; p< 0.05).
Conclusions: In the last years our treatment approach has significantly changed leading to an improvement in patients management. An early treatment allowed a better outcome changing the natural history of the disease.

Disclosure
M. Radaelli, F. Sangalli, L. Moiola, B. Colombo, M. Comola, M. Romeo report speaking fees and/or travel expenses from Biogen, Merck Serono, Genzyme, Novartis. F. Esposito received honoraria from Almirall and Genzyme, G. Comi has received compensation for consulting services and/or speaking activities from Biogen, Novartis, Teva Pharmaceutical Ind, Sanofi, Genzyme, Merck Serono, Biogen, Bayer, Actelion and Serono Symposia Int. Found, outside the submitted work. Dr. Martinelli reports consultancy, speaking fees and/or travel expenses from Biogen, Merck Serono, Bayer Schering, Novartis, Sanofi-Aventis, Genzyme Europe, Teva Pharmaceuticals, outside the submitted work. S. Guerrieri, G. Greco, P. Preziosa, U. Pensato have nothing to disclose

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Do concomitant autoimmune diseases affect neuromyelitis optica spectrum disorder (NMOSD) course?

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory demyelinating disease of the central nervous system that causes lesions in the optic nerve, spinal cord and brain.Literature data shows an ever-growing list of autoimmune diseases associated with NMOSD.
Aims: The aim of this study was to identify and compare the basic and clinical features of NMOSD patients with and without concomitant autoimmune diseases.
Methods: We conducted a case-control study among patients with a definite diagnosis of NMOSD, referred to Sina hospital, a tertiary care referral center in Tehran, from April 1, 2015 to April 1, 2016. Seventy nine NMOSD patients, both with concomitant autoimmune diseases (n = 18, case group) and without concomitant autoimmune diseases (n = 61, control group) were enrolled. The demographic data consist of gender, current age, NMOSD onset age, disease duration, family history of MS and NMOSD, smoking habit, passive smoker, and also clinical and laboratory data including Expanded Disability Status Scale (EDSS),Annual Relapse Rate (ARR) and positivity or negativity of NMO-IgG were collected. Data were processed using the Independent t-test and the Logistic regression was applied to evaluate association among variables.
Results: The female to male ratio was 8:1 in case group and 4.54:1 in control group. Our results revealed a significant relationship between case and control groups in NMOSD onset age (37.50±9.84 vs 30.72±10.87, P value = 0.02, 95%CI = 1.08-12.47). We found no significant differences in other characteristic variables between case and control groups. NMO-IgG positivity was 52.9% and 53.4% in case and control group respectively. The mean EDSS was 3.27±1.89 in case group and 2.89±2.11 in control group but this difference was not statically significant (P value>0.05), even after adjusting for gender, age and disease duration. The mean ARR was calculated 1.18±0.88 in cases and 0.87±0.71 in controls (P value>0.05).
Conclusions: Basic and clinical studies of the NMOSD associated with autoimmune diseases are limited and there is no consensus about that. Results of our study demonstrate that several autoimmune diseases may co-exist with NMOSD and this co-existence may enhance the NMOSD onset age and may also worsen the disease course. Further studies are needed to investigate the effect of concomitant autoimmune diseases on the course of NMOSD.

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Decision-making on radiologically isolated syndrome among Argentinean neurologists: a survey based on clinical experience

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Background: Although management of radiologically isolated syndrome (RIS) is still a challenge in clinical practice, in the absence of evidence-based guidelines, opinion of experts might give neurologists some guidance to optimize clinical decision-making. Our aim was to know current RIS management opinion of Argentinean neurologists based on their clinical experience.
Methods: A cross-sectional web-based anonymous voluntary survey was performed by Argentinean neurologists. We developed questions based on a hypothetical patient with RIS (4 periventricular white matter and 1 juxtacortical lesions on magnetic resonance imaging -MRI- gadolinium negative). General agreement was defined as at least 75% of coincidence in the answer to each particular question.
Results: Sixty-six participants completed the survey. There was general agreement to follow-up patients, perform further examinations and not to treat RIS patients at presentation. In addition, participants agreed to perform a lumbar puncture to evaluate the presence of oligoclonal bands (OCB, 82%) and to order a spinal cord MRI (75.4%). They did not agree to obtain visual evoked potentials (VEP, 50.8%), Brief International Cognitive Assessment for MS (BICAMS, 13.1%) or brain volume measures (9.4%). In case of positive OCB, altered VEP, BICAMS, brain atrophy or the presence of both Gd-negative or Gd-positive lesion on spinal MRI at follow-up, a few participants would prescribe treatment to these patients (13.1% to 46.7%). In addition, if a brain Gd-positive lesion is observed at onset, 43.6% would prescribe treatment. At follow-up, there was agreement to perform brain (100%) and spinal (80%) MRI. During the follow-up, only 15.4% would not initiate treatment in absence of clinical symptoms, regardless of the examinations results. In those cases in which a treatment was prescribed, there was agreement in using injectable drugs (78.7%).
Conclusion: These findings give us a first idea about Argentinean neurologists decision-making on this entity and may help in the development of a practice guideline.

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Pediatric MS

P346

The central vein sign in paediatric-onset multiple sclerosis

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Background: The diagnosis of paediatric-onset multiple sclerosis (POMS) has remained challenging and may thus delay treatment decisions. Recently, the central vein sign (CVS) was proposed as an additional diagnostic imaging biomarker in adult-onset multiple sclerosis (AOMS).
Objective: To evaluate the diagnostic value of the CVS in POMS.
Methods: We analysed 26 patients with POMS (median age at disease onset 14.8 years (range 7.2 - 17.1 years), median disease duration 12 months (range 4 - 73 months), median EDSS 1.0 (range 0 - 3.5)) for the existence of a central vein within lesions on highly resolving and co-registered 3D FLAIR and 3D susceptibility weighted imaging (SWI) at 3 Tesla.
Results: 232 lesions were analysed in total. A central vein was detectable within 96 (41%) lesions. All patients with POMS presented with at least one lesion containing a central vein, while 21 (81%) had at least two, and 17 (65%) had at least three lesions with a central vein. 17 (65%) patients with POMS had 40% or more lesions with a central vein.
Conclusion: The majority of all patients with POMS presented with cerebral white matter lesions containing a distinct central vein, suggesting a high potential of the CVS to improve POMS diagnosis in the future. CVS detection may be further improved by the selection of dedicated T2*-weighted sequences. Our findings are in line with previous reports in AOMS, and thus underline similarities between AOMS and POMS.

Disclosure

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Macular changes in pediatric multiple sclerosis

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Background: Neuroaxonal damage in the retina occurs dependent and independent of clinical optic neuritis in patients with multiple sclerosis (MS). In adult MS patients retinal imaging markers measured by optical coherence tomography (OCT) are promising biomarkers for disease course and severity.
Objective: To investigate retinal changes in pediatric MS.
Aims: To elucidate the role of retinal imaging with OCT as a potential diagnostic marker in pediatric MS.
Methods: Baseline data from a prospective and ongoing study following children with MS at the German Center for Multiple Sclerosis in Childhood and Adolescence Göttingen. Controls were recruited from healthy volunteers and from patients admitted to the hospital for conditions not affecting the retina. Spectral domain OCT was performed with Cirrus HD-OCT. Macular retinal nerve fiber layer (mRNFL), ganglion cell and inner plexiform layer thickness (GCIP) and outer retinal layer (ORL) volumes were investigated.
Results: The study included 115 children with MS (age 182±29 months, 75 female) and 68 controls (age 165±35 months, 41 female). In controls mRNFL, GCIP and INL were not significantly associated with age or sex.
When comparing all MS patients with controls and correcting for age and sex, MS patients had an on average −2.4 mm^3 lower mRNFL volume (29.66±5.31 mm^3, SE=0.621, $p=1.215\times10^{-4}$) than controls (31.79±2.57 mm^3). Similarly, MS patients had an on average −6.5 mm^3 lower GCIP volume (78.07±10.39 mm^3, SE=1.245, $p=5.215\times10^{-7}$) than controls (84.14±5.01 mm^3). In contrast, ORL volume did not differ between MS patients and controls (125.25±13.40 mm^3 vs. 125.99±8.75 mm^3, B=−0.507 mm^3, SE=1.828, p=0.782).
Eyes from MS patients with previous optic neuritis (ON) showed significantly reduced GCIP in comparison to control eyes (B=−6.981 mm^3, SE=0.827, p=0) and eyes from MS patients without prior ON (B=−9.074 mm^3, SE=1.983, $p=4.753\times10^{-6}$). GCIP volume was also reduced in MS eyes without prior ON compared to control eyes (B=−3.087 mm^3, SE=1.257, p=0.014).
While ORL volume was similar between eyes with history of ON and those without, two eyes had greatly increased ORL volumes in the context of microcystic macular edema (MME).
Conclusion: GCIP in pediatric MS patients is reduced both after ON but also without previous ON suggesting covert retinal neurodegeneration in the context of MS also outside of clinically defined optic neuritis attacks. Further, children occasionally also present with MME after ON.

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Adults with MS show earlier cognitive changes than those with pediatric MS

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Introduction: Cognitive impairment is common and often disabling in multiple sclerosis (MS), but the risk factors and mechanisms underlying cognitive decline remain poorly understood. Pediatric MS (MS onset < 18 years of age) is unique due to the demyelinating process occurring in the context of development.
Objectives: To compare cognitive functions in newly diagnosed patients with either adult- or pediatric-onset MS (AOMS vs. POMS).

Aim: To test performance in newly diagnosed MS patients using the Symbol Digit Modalities Test (SDMT) and a computer-based measure sensitive to processing speed deficits (Cogstate).
Methods: As part of an ongoing multi-center longitudinal cognition trial, AOMS and POMS participants were recruited from outpatient visits and matched by years of disease. At the baseline evaluation, all participants were administered the Wide Range Achievement Test-4 (WRAT-4), the SDMT and the Cogstate Brief Battery, which includes three measures of information processing speed tasks:simple (DET) and choice (IDN) reaction time and working memory (ONB). Cogstate scores were converted to z-scores and then averaged for one composite z-score.
Results: A total of n=64 participants completed baseline assessments with n= 32 in the AOMS group (mean age 33.36 ± 5.82) and n= 32 in the POMS group (mean age 11.31 ± 3.64). All participants had relapsing remitting disease and the groups were matched for disease duration (4.91 ± 3.05 years for AOMS vs. 6.38 ± 3.54 for POMS). The POMS group had higher estimated premorbid IQ (WRAT-4 reading 112.7 ± 18.5 vs. 105.4 ± 13.4), though the result did not reach significance (p=0.07).
Neither group's cognitive performances fell into the impaired range relative to age-normative means. However, the AOMS compared to the POMS group consistently performed significantly worse on the SDMT (mean z-score -0.26 ± 1.15 for AOMS vs. 0.68 ± 1.53 for POMS, p=0.01) and slower on the Cogstate composite (mean z-score of -1.04 ± 1.09 for AOMS vs. 0.35 ± 1.15 for POMS, p=0.04). Estimated premorbid IQ was correlated with SDMT, but not Cogstate performance (r=0.56 p=0.001 and r=0.13 p=0.35, respectively). Age of disease onset was significantly negatively correlated with cognitive processing (SDMT: r= -0.32, p= 0.01 and Cogstate DET: r= -0.33, p=0.02), further indicating that older age of onset is associated with greater cognitive impairment.
Conclusions: Adult MS is associated with larger cognitive involvement than pediatric MS.

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Perspectives on clinical trials in pediatric MS: results of an international survey

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Introduction and objective: For the first time in the past 5 years, pediatric multiple sclerosis (MS) trials have been launched, with some fully enrolled or completed. The experience of investigators with these recent trials has provided new insights on the feasibility and challenges of studies in pediatric MS, which are important to understand for future trials.
Method: We conducted a survey of the International Pediatric Multiple Sclerosis Study Group membership regarding barriers to pediatric MS clinical trials, using a web-based tool.
Results: 58 care providers from 18 countries answered the survey of which 38 had participated in a clinical trial. Top challenges for providers included the time to set up the trial and obtain local ethics approval, the frequency of study visits and difficulty balancing such effort with clinical time, and limited access to part-time clinical trial coordinator support. The frequency of study visits proved a barrier to patient recruitment and retention. Ethical concerns, raised by both providers and families, included the use of placebo, or comparator trials using a drug shown to be inferior to study drug in adult MS trials. Providers recommended strategies to reduce the number of in-person visits, shorten the time of research visits, enable laboratory sampling at sites close to home, and to limit the number MRI scans required.
Conclusions: This study highlights important barriers to success in pediatric MS clinical trials, and provides suggestions for study design that would be more practical for families and clinical trial staff.

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Juvenile multiple sclerosis (SOKIDMUS study): evaluation of factors associated with socio-professional performances in adulthood

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Background: To date, no studies about factors associated with socio-professional performances in adulthood in patients with juvenile multiple sclerosis (MS) (onset before 18 years of age) have been performed, despite studies showing cognitive impairments in these patients.
Goals: We aimed to assess these associations in two subgroups: patients with juvenile MS, and patients with ´non-juvenile MS´ (aged 18-22 years at MS onset).
Patients and methods. A cross-sectional study nested in the ´Observatoire Français de la Sclérose en Plaques´ (OFSEP) survey was conducted with inclusion of 445 patients with a confirmed MS diagnosis: 211 with juvenile MS (70.1% female) and 234 with non-juvenile MS (75.6 % female). Patients were 25 to 35 years at inclusion in 2015. The variables collected concerned baseline demographic, disease and therapeutic characteristics, social status, academic level, fatigue status (Modified Fatigue Impact Scale 5-item, MFIS5), mental health status (K6 scale), recovery level (Recovery assessment scale), self-esteem status (Rosenberg´s self-esteem scale) and socio-professional performance (´Work and social adjustment scale´, WSAS). The outcome was poor socio-professional performance defined as WSAS≥20. Descriptive analysis was completed by multivariate analysis with logistic regression in the two groups.
Results: In the juvenile MS group, patients were mostly between the ages of 15 and 18 at onset (71.1%), 92.8% had a relapsing-remitting course (92.7% in the non-juvenile group) and 64% were working (69% respectively). In multivariate analysis, Expanded Disability Status Scale (EDSS) at inclusion > 3 (62 patients out of 211 ; odds ratio (OR) : 5.1, 95% confidence interval (95% CI) : 2.1-12.3, p< 0.001), significant fatigue (MFIS5 ≥ 10, 89 patients; OR : 14.9, 95% CI : 5.6-39.5, p< 0.001) and risk of depression (K6≥13, 43 patients; OR : 3.4, 95% CI : 1.3-9.1, p=0.01) were significantly associated with poor socio-professional performances in patients with juvenile MS onset. The same factors were found for non-juvenile MS patients, in addition to a longer disease duration and a lower recovery level. No interaction was found statistically significant for the two groups.
Discussion: For both groups, factors associated with poor socio-professional performances are related to disease severity. Social interventions could be helpful in these patients.

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Obesity is associated with increased risk of developing pediatric multiple sclerosis and frequent failure of first-line therapy

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Background and Objective: Obesity has been linked to an increased risk of pediatric multiple sclerosis (MS) but little is known about its influence on disease activity. Analyzing a large German pediatric MS cohort, we assessed if obesity is associated with greater disease severity.
Methods: Retrospective single center study of patients enrolled in the Göttingen pediatric MS database. Radiologic disease activity, time interval to second clinical event, annual relapse rate on first-line therapy and EDSS progression were analyzed and compared with respect to body mass index (BMI).
Results: 453 pediatric MS patients were included in the study, 27.8% were overweight (>P90) and 14.8% obese (>P97) at first presentation. Obesity was found to increase risk of pediatric MS two-fold in girls and boys. Increased MS risk was related to high BMI in both childhood and adolescence. Analyses revealed no influence of BMI on severity of disease activity on MRI, time interval to second clinical event and short term EDSS progression, however, obese subjects were found to experience significantly more relapses on first-line treatment with interferon-b and glatiramer acetate compared to non-overweight patients and had a higher switch rate to second-line therapy.

Conclusions: Obesity in childhood and adolescence increases risk of pediatric multiple sclerosis, however, we found no indication that obesity also leads to a more inflammatory course of the disease. In spite of this, obese patients appear significantly more likely to respond poorly to first-line agents and subsequently require more frequent escalation of therapy. Normalizing weight of pediatric MS patients would therefore significantly alleviate disease burden and reduce therapy associated costs.

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Natural course

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Disability outcomes in patients with early cerebellar symptoms in multiple sclerosis

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Introduction: Cerebellar symptoms are a common feature in multiple sclerosis (MS). A proportion of patients present with these symptoms at or early after their first clinical presentation. Whether early cerebellar symptoms have any prognostic value in MS is unclear.
Objectives/Aims: The aim of this study was to investigate long-term disability outcomes in patients presenting with early cerebellar symptoms.
Design/Setting: This retrospective cohort study used prospectively collected data from the MSBase registry, a large international observational cohort of MS patients. The studied outcomes were cumulative hazard of relapses and disability worsening events, confirmed over 6 months with Expanded Disability Status Scale (EDSS) scores.
Methods: Inclusion criteria consisted of: diagnosis of relapsing MS with ≥1 relapse recorded, first EDSS assessment within 2 years of patients' first MS symptom, ≥3 recorded EDSS scores and EDSS frequency ≥1/year. Patients with a relapse with cerebellar symptoms or an EDSS score with cerebellar functional score ≥2 were identified as having early cerebellar presentation. Cox proportional hazards models were used to describe and compare the probability of remaining free from (i) relapse and (ii) disability worsening between patients who presented with early cerebellar symptoms and those who did not. Andersen-Gill models were used to estimate the cumulative hazard of (i) relapse incidences and (ii) disability worsening events. The models were adjusted for demographic and clinical factors.
Results: The study cohort consisted of 10,929 eligible MS patients, including 2,723 patients with early cerebellar symptoms. Shorter median times to first relapse (0.6 vs 1.1 years respectively, hazard ratio HR=1.09, $P< 0.001$) and to first confirmed disability worsening event (14.1 vs 17.5 years respectively, HR=1.44, $P< 10^{-13}$) were observed for patients with early cerebellar symptoms.

Patients with early cerebellar symptoms also had a greater cumulative hazard of relapses (HR=1.15, $P< 10^{-7}$) and of disability worsening events (HR=1.37, $P< 10^{-11}$).

Conclusions: The presence of early cerebellar symptoms in MS is associated with poorer prognosis. Therefore, early cerebellar symptoms could potentially be used as an early indicator of the need for more aggressive therapeutic approach.

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Factors affecting mortality and causes of death among MS patients

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Introduction: People with MS have increased mortality, compared to the general population, but only half, on average, die from causes directly related to the disease.
Methods: Among 324 dead patients from the London Ontario database (PP = 111; RR = 20; SP = 193), we used Kaplan Meier and Cox regression analyses to explore factors, affecting mortality and causes of death.
Results: The median time to death from onset was 24 years and the median age at death was 60 years. The majority of patients (n=210; 64.8%) died from causes related to MS; respiratory diseases (n=116; 55.2%), MS (n=48; 22.8%) and infections (n = 19; 9%) were the commonest immediate causes of death. In the group of dead from causes unrelated to MS (n=114; 35.2%) most of patients died from malignancies (n=42; 36.8%), cardiovascular (n=31; 27.1%) and cerebrovascular (n=15; 13.1%) diseases. In the two subgroups, of dead due and not due to MS, the distribution of disease phenotypes (relapsing onset patients: 65.7% vs 65.8%; p=0.98), sex ratio (females: 57.6% vs 56.1%; p=0.79) and disability at last assessment (median DSS = 8 in both subgroup) were similar. Those who died from causes related to MS were younger at the disease onset (33.0 vs 36.7 mean years; p=0.03), attained death in similar time (23.9 versus 26.0 mean years; p=0.075) and were younger at death (57.0 versus 62.7 mean years; p< 0.001). Therefore, older age at onset associated with a higher probability of dying from MS unrelated causes (OR=1.04; p=0.004), as patients grew older and were exposed to a higher risk of developing comorbidities, such as malignancies, cardiovascular and cerebrovascular diseases. Among the dead due to MS, the time to death was not affected by sex, the clinical phenotype, the age at onset or by the type of symptoms at clinical presentation. In contrast, among the dead not due to MS, time to death was shorter in males (males=23.3, females=28.1 mean years; p=0.03), in those with a PP course (PP=21.9 versus RR/SP=28.2 mean years; p=0.02) and in those older at onset (age ≤ 20 = 30.7, age 21-30 = 31.0, age > 30 = 23.9 mean years, p = 0.02).
Conclusions: Dead due and not due to MS have similar disease duration and disability immediately preceding death, but differ in the age at clinical onset, which is associated with different death causes. These data question the validity of differentiating whether death is directly related to MS or not, and the utility of using DSS 10 as MS-specific landmark status.

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Epidemiology

P354

Pregnancy outcomes in Teriflunomide exposed men and women. A nationwide Danish registry-based study

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Introduction: The majority of persons diagnosed with multiple sclerosis (MS) experience their first MS symptoms in the reproductive age.

Teriflunomide (TFL, Aubagio â) 14mg, was first released in Denmark for relapsing-remitting MS in December 2013. Treatment with TFL is contraindicated in women of childbearing potential who are not using reliable contraception. TFL can be transmitted via semen and a low risk of male-mediated embryo-foetal toxicity is described.
Objective: To report pregnancy outcomes of TFL exposed women and partners to TFL exposed men: gestation week < week 37, abortions and congenital malformations, the frequency of caesarean section, live born and stillborn, birth weight and Apgar score.
Methods: Prospective cohort study comparing pregnancy outcomes of TFL exposed men and women, matched on age at conception, 1:4 with controls from the background population. Data on TFL treated patients treated 1st of January 2014 to 31st of December 2016 for at least 30 consecutive days prior to conception, and with conception occurring up to two years after treatment discontinuation were extracted from The Danish Multiple Sclerosis Registry and merged with several national reproductive registries. Logistic regression was used to analyse the association between TFL exposure and any adverse event.
Results: A total of 31 pregnancies were recorded, 18 of partners to a TFL exposed man and 13 women. Among these, all 18 partners of men exposed to TFL completed their pregnancies: livebirth (18), gestation time >37 weeks (17), gestation time 33-36 weeks (1), birth weight normal in relation to gestation week (18), spontaneous and elective abortion (0), congenital malformation (plagiocephali/flat head syndrome) (1), normal delivery (14), induced delivery (2), caesarean section (2), Apgar score ≥7 (18). Among the 13 pregnancies in women exposed to TFL: elective abortion (11), spontaneous abortion (0), livebirth (2), gestation time >37 weeks (2), birth weight normal (2), congenital malformations (0), normal delivery (1), induced delivery (1), Apgar score ≥7 (2). The TFL group was associated with a 22% reduction in the odds of any adverse event relative to controls, although this association was not significant (OR 0.78; 95% CI 0.16-3.72, p=0.753).
Conclusion: Pregnancy outcomes were consistent with those of the background population. The malformation reported of the partner to a TFL exposed man is comparable to the rate of plagiocephaly reported in Denmark.

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P355

Robust evaluation of MS prevalence in Sweden based on the National Patient Registry data by modelling of a distribution of inpatient and outpatient care events, reported with MS diagnosis

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Background: Each medical care event (mce) with a diagnosis assigned to a patient is mandatory registered in the National Patient Registry (NPR). NPR includes all inpatient MS care events since 1969 and outpatient visits since 2001. Accurate evaluation of MS prevalence is a time consuming task. It involves validation of MS diagnosis and access to individual patient's records. Early symptoms of different neurological disorders can be misclassified with MS, and patients can possibly get a false MS diagnosis under the early clinical period.
Objectives: Evaluation of the actual MS prevalence using NPR data by analysing the frequency- and time- distribution of all reported MS diagnosis. Assessment of a fraction of false positive MS diagnosis in inpatient and outpatient care and analysis of its distribution in time.
Methods: NPR includes all the registrations of MS diagnosis (mce) based on a medical examination of a patient. Number of mce covers a range from 1 to over 100 per patient, dependently on MS duration. We analysed the actual mce-distribution using Gaussian fit with calculations of residuals of a fitted model. For the patients with 1 or 2 confirmations of MS diagnosis we investigated the time distribution. We checked when patients got MS-diagnosis without any further confirmation of MS in later years. Such diagnosis were considered as false positive MS-diagnosis and excluded from the final evaluations.
Results: We got 20814 living patients with reported MS diagnosis until 2013. The distribution of mce showed that the number of patients with 1 or 2 diagnosis extended strongly beyond the observed distribution for the rest of patients. This suggested that false positive MS diagnosis belong almost exclusively to the patients having only one confirmation of MS (61% misclassified) or two (20%). Analysis of a time distribution of a subgroup with mce=1 revealed, that for inpatient care, the number of patients with misclassified MS was stable with time with the mean of 27±7 patients per year and for outpatient care 101±12 per year. Total number of patients with misclassified MS in NPR was 2495 i.e.12% of all registered patients. They were excluded from the calculations of MS prevalence. The procedure resulted in 18320 prevalent MS patients in 2013 i.e. 191/100,000.
Conclusion: New method for evaluation of MS prevalence based on MS diagnosis registered in NPR appeared to be a robust one. It gave new insights on the level of false positive MS cases reported in early MS.

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P356
Inflammatory activity in the cerebrospinal fluid a decade after acute infectious mononucleosis

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Introduction: The risk of MS subsequent to acute Epstein-Barr virus (EBV) infection manifested as serologically defined infectious mononucleosis (IM) is 2.5 - 3 times higher than expected from population data. While association between EBV and MS was amply confirmed, the reason for the post-IM surplus risk is unknown. Both direct causality from persistent reactivity after IM, and reverse causality due to EBV specific immunodeficiency were proposed, but no hard evidence has been produced in support of any of these hypotheses. The immunological condition of persons who previously experienced acute IM has not been investigated.
Objectives: To reveal persistent inflammatory activity or neurodegeneration several years after IM. Markers which recently showed increased values in MS were selected.
Aims: To examine a direct rather than reverse causality between EBV and MS.
Methods: We examined healthy individuals who had serologically determined IM between 2003 and 2007. Follow-up including a questionnaire, a neurological evaluation and a CSF analysis was performed. The levels of NFl, CXCL13 and YKL-40 were determined with immunochemical methods in the post-IM group (n=22), and in MS control (n=23) and healthy control groups (n=19) with mean age 30, 36 and 26 years.
Results: The CSF level of YKL-40 was increased in the healthy post IM Group, 76.5 (SE 6.21), compared to healthy individuals not reporting previous IM experience, 57.7 (SE 6.88) (p t-test = 0.049, Kruskal-Wallis 0.084). The levels of NFL in the post IM group, 283.8 (SE 20.5) did not deviate from those of the healthy controls, and CXCL13 was below the detection level in most individuals. The NFL, CXCL13 and YKL-40 levels were markedly increased in the MS patients ($p < 0.001$), practically acting as positive controls.
Discussion: The higher levels of YKL-40 a decade after acute IM was suggestive of a direct rather than inverse link between EBV infection and subsequent inflammatory state, which may be comparable to inflammatory preclinical stages known from MS and other autoimmune diseases. YKL-40, which plays a role in inflammation, proliferation, and angiogenesis, has been evaluated in many inflammatory diseases and is a potential marker for a post IM stage, as IM is known to be a risk factor for several mainly inflammatory conditions including MS. Thus, further studies on the post IM state are warranted.

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P357
Increased risk of MS after organic solvent exposure

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Background: Several studies have previously indicated an increased risk of multiple sclerosis (MS) after exposure to organic solvents. Scientific results, however, have been contradictory and there has been debate on this issue. We sought to examine the association between exposure to organic solvents and MS risk adjusted for other known risk factors.
Method: Reports on prior occupational organic solvent exposure were provided by 1197 MS cases and 2361 population-based frequency matched controls from Norway and Sweden within the multinational case-control study on Environmental Risk Factors in Multiple Sclerosis (EnvIMS).
Results: Exposure to organic solvents was associated with an increased risk for MS with an OR of 1.46 (CI 95%: 1.16-1.83). The association remained similar in multivariable analyses adjusted for other established risk factors including smoking, having had infectious mononucleosis or low outdoor activity during adolescence as indication of low vitamin D status. In subgroup analyses, we found that the risk associated with organic solvents was only seen among persons who had smoked (OR=1.53 vs 1.11 for non-smokers; test for interaction p=0.06) and among those who had indication of low vitamin D status during adolescence (OR=2.28 vs 1.08 for higher vitamin D-status; test of interaction p=0.002).
Conclusion: In this study, we found that prior exposure to organic solvents was associated with an increased risk of MS. Interestingly,

the increased risk seems to be present only in individuals at increased risk by smoking and low vitamin D-status. Potential mechanisms include increased permeability of the blood brain barrier through solvent exposure, which enables access to the CNS for immune competent blood cells triggered in the lungs due to tobacco smoking.

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P358
Differential multiple sclerosis treatment allocation between Australia & New Zealand impacts on clinical course but not quality of life

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Background: Differential treatment allocation may impact on clinical phenotype in MS and in turn upon quality of life (QoL).
Objectives: (a) Investigate the association between disease-modifying drugs (DMDs) use and relapse frequency, disability, clinically significant fatigue, and physical & mental health-related QoL among participants with MS residing in Australia and New Zealand (NZ); (b) assess whether these associations differed significantly between Australia & NZ.
Methods: Disability and fatigue were measured by PDDS and FSS, respectively. QoL was assessed by MSQOL-54. Associations were assessed by binomial and multinomial logistic regression, as appropriate, adjusted for relevant covariates. Multivariable models were adjusted for demographic and clinical covariates, as appropriate.
Results: 837 participants (627 from Australia; 210 from NZ) using DMDs were identified from an online cohort of people with MS. First- and second-generation DMD use was associated with significantly higher adjusted-odds of fatigue and disability, though not with 12-month relapse number. DMD use was not associated with physical or mental QoL. The association of first-generation DMD use with moderate disability significantly differed between nations, such that treatment was associated with lower odds in Australia but not in NZ; a similar difference was found for severe disability but did not reach significance. No differences were seen in the DMD association with relapse number, nor with fatigue or QoL, between Australia & NZ.
Conclusion: The differential treatment allocation associations in NZ are evident in the DMD-disability association, but there is no evidence that this treatment regime has negative associations with fatigue, mood, or QoL.

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P359
Risk of mortality in immigrants with MS in Ontario, Canada

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Objective: To investigate whether mortality rates differ in immigrants compared to long-term residents with MS in Ontario, Canada after controlling for other known risk factors for mortality.
Background: There is little knowledge concerning how long-term outcomes in MS may differ based on sociodemographic conditions such as immigrant status. This study was conducted in Ontario, Canada a region with universal, publicly funded health insurance, a large immigrant population, and high MS prevalence.
Methods: We applied a validated algorithm to linked, population-based immigration and health administrative data to identify incident cases of MS among adults aged 20 to 65 years between 1994 and 2014 . Index date was defined by the first demyelinating disease claim. Long-term residents with MS were matched against immigrants in a 1:3 ratio by age and sex. Mortality from MS onset was calculated annually from 1994-2014 in immigrants and long-term residents. A Cox proportional hazards model was used to estimate risk of mortality in immigrants compared to long-term residents, controlling for age at diagnosis, sex, urban residence, neighbourhood income quintile, and co-morbidity burden.
Results: There were 1,372 incident cases of MS in immigrants and 21,870 in long-term Ontario residents. Unadjusted survival was slightly better in immigrants, with 93% of immigrants alive by year 15 versus 88% of long-term residents. After adjusting for confounders, the risk of death in immigrants with MS was similar to long-term residents with MS at all time points except in the first

year after the index date, when the risk was higher in immigrants (HR 1.66; 95% CI: 1.05-2.63; p= 0.03). Other significant predictors of mortality risk were older age at diagnosis (HR 6.47 for 51-65 vs. 20-35 years, p< .0001), male sex (HR 1.42, p< .0001), lower neighbourhood income quintile (Q1 vs. Q5 HR 1.40; p< .0001), and co-morbidity burden (HR 1.54, p < .0001).

Conclusions: In this large immigrant population with universal access to health insurance, risk of mortality did not differ in immigrants with MS compared to long-term residents except in the first year after presentation. The reason for the difference in the first year is unknown, but could be due to later clinical presentation, poor social supports, and/or more severe first relapse in immigrants. This finding warrants further investigation as some of these early deaths may be preventable.

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P360

Hospital admission, discharges and in-hospital mortality in multiple sclerosis patients: nationally representative data

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Introduction: Patients with MS are at risk for hospitalization. Tools to risk-stratify or identify patients vulnerable to admission, long hospital stays and adverse outcomes would be beneficial to clinicians. **Objectives:** To investigate the causes and rates of hospital admission, factors associated with discharge status, and prevalence of in-hospital mortality in patients with Multiple Sclerosis (MS).

Aims: To identify causes of hospital admission and factors associated with poor outcomes.

Methods: We examined the 2013 National Inpatient Sample, a large inpatient care database from the Healthcare Cost and Utilization Project, and used ICD-9 code 340 in any diagnosis position to identify MS. Age-, sex-, race- and chronic condition number-matched admissions without MS were randomly selected in a 2:1 ratio (80,781 admissions total). We used discharge disposition location as a proxy for morbidity. Primary reasons for admission were examined, and survey-weighted multivariate logistic regression models were used to calculate odds ratios (OR) and determine factors associated with discharge disposition and in-hospital mortality.

Results: Out of 26,927 MS admissions, 73% were female, mean age was 54.8 years (standard error 0.12), with 1,364 (5%) in-hospital deaths. Mean length-of-stay was 5.3 days and mean comorbidities 6. Non-neurologic causes of MS admissions were most commonly sepsis (9.3%), urinary tract infections (5.1%), and device/implant/graft complications (4.5%). Compared to controls, MS admissions had lower odds of discharge home (OR 0.584, Confidence Interval (CI): 0.562-0.607, p< 0.0001). Other factors associated with discharge to a facility included small hospital size (OR 0.84, CI: 0.804-0.877, p< 0.0001), longer length-of-stay (OR 0.931, CI: 0.927-0.935, p< 0.0001) and rural hospitals (OR 0.771, CI: 0.721-0.823, p< 0.001). MS admissions had lower odds of in-hospital mortality (OR 0.738, CI: 0.656-0.83, p< 0.0001). Patients with non-Medicare insurance had higher odds of discharge home (Medicaid vs Medicare, OR 2.118, CI: 2.004-2.239, p< 0.0001; Other insurance vs Medicare, OR 2.772, CI:2.657-2.893, p< 0.0001). Elective admissions also had higher odds of discharge home (OR 1.494, CI: 1.421-1.572, p< 0.0001).

Conclusions: After hospitalization, MS patients are at greater odds of not being discharged home and the non-MS reasons for some of these admissions may be preventable. Increased awareness of these risks may help prevent some hospital admissions.

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P361

Prevalence of multiple sclerosis within a healthcare delivery system in Northern California: a retrospective, electronic, health records-based study from 2010 to 2016

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Introduction: Given the role of both environmental and genetic factors in the aetiology of MS, quantifying the local prevalence of this condition in geographically distinct regions is important to understand its true burden, especially across diverse racial/ethnic populations residing in the same region and with access to the same healthcare.

Aims: To quantify the prevalence of MS in a healthcare delivery system in Northern California, USA.

Methods: We used an electronic health records database from a healthcare delivery system in Northern California, USA to quantify the prevalence of MS in adults ≥18 years of age. Individuals who had an International Classification of Disease 9/10 diagnosis of MS between 2010 and 2016 were identified. Overall and annual prevalence rates were calculated based on the total number of patient encounters during the entire study period and during each year, respectively. Rates were expressed per 100,000 of the population with 95% confidence intervals (CI). For comparisons by year, gender, and racial/ethnic groups, rates were age-adjusted using logistic regression.
Results: Among 1,508,102 adult patients in the Northern California healthcare system between 2010 and 2016, MS prevalence was 311 (95% CI: 300 to 321) per 100,000 population. There was a significant increase in age-adjusted prevalence from 259 (95% CI: 249 to 271) per 100,000 in 2010 to 358 (95% CI: 344 to 372) per 100,000 in 2016 ($P< 0.0001$). A 2.3-fold higher age-adjusted MS prevalence was observed for women compared with men (385 and 164 per 100,000, respectively; $P< 0.0001$). The highest age-adjusted MS prevalence was found among black women (677 per 100,000), whereas Asian men had the lowest prevalence (50 per 100,000). The age-adjusted prevalence of MS showed a numerical increase from 2010 to 2016 across all gender and racial/ethnic subgroups; however, only non-Hispanic white women, the largest subgroup, showed a significant linear increase in prevalence by year (27 additional cases per 100,000 population per year; $P< 0.0001$).
Conclusion: In a healthcare practice-based setting in Northern California, the prevalence of MS differed by gender and race/ethnicity, and was highest among black women. This study suggests that the prevalence of MS in the US is increasing, most notably among non-Hispanic white women.

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P362
Factors associated with therapeutic inertia in multiple sclerosis care: results from a cross-sectional study in Argentina

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Introduction: Therapeutic inertia (TI) is a common phenomenon in multiple sclerosis (MS) care defined as the lack of treatment escalation despiteevidence of disease progression. TI may lead to poor patient's outcomes. However, we have limited information on factors associated with TI
Objectives: To evaluate factors associated with TIamong neurologists caring for MS patients.
Design: Cross-sectional study comprising 117 neurologists with expertise in MS who were invited to participate in an online study. Participants answered questions regarding their clinical practice, risk preferences,management of 10 simulated case-scenarios, and complications associated with disease modifying agents. TI was defined as lack of treatment initiation or escalation when evidence of clinical and radiological activity(8 case-scenarios, 720 individual responses). We created a score defined as the number of case-scenarios that fit the TI criteria over the total number of presented cases (score range from 0-8).Candidate predictors of TI included demographic data, MS specialist vs. general neurologist, practice setting, years of practice, volume of MS patients, and risk preferences.
Results: Overall,90 participants completed the study (completion rate 76.9%). The mean age (SD)was 46.4 (10.3); 47.7% were female neurologists and 34.4% were MS specialists.Overall, 153 (21.3%) responses that exhibit TI.Participants with aversion to ambiguity were more likely to exhibit TI (mean TI score 5.6 vs 4.3; $p< 0.05$). Higher TI scores were observed among general neurologists ($p=0.003$). The multivariable analysis revealed that older age ($p=0.02$), higher aversion to ambiguity ($p=0.04$), being a general neurologist ($p< 0.001$) and lower years of practice ($p< 0.01$) were independent predictors of TI. The adjusted R^2 was 0.28.
Conclusions: TI was observed in one out of five therapeutic decisions in MS care. Most common associated factors include older age, being a general neurologist with lower years of practice and having aversion to ambiguity.

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Observatoire Français de la Sclérose en Plaques (OFSEP): an update

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Introduction: The Observatoire Français de la Sclérose En Plaques (OFSEP) is a French national cohort of patients with multiple sclerosis (MS) and related disorders (neuromyelitis optica spectrum disorders 'NMOSD'…), aiming at collecting clinical and MRI data and biological samples in a routine clinical setting, to foster clinical, basic and translational research in MS.

Objectives: To update the OFSEP description.

Methods: Patients are followed longitudinally by their neurologist involved in the OFSEP network, who collects clinical data in a computerized medical file, EDMUS. Since June 2013, this collection is standardized, including demographic and socioeconomic characteristics and disease and therapeutic description. Since April 2016, serious adverse events are also systematically collected. A standardized imaging protocol has been developed and is currently implemented in MRI centres nationwide; raw data are stored in a server interfaced with Shanoir software. Biological samples (blood, cerebrospinal fluid, urine and stool) are collected in seven specific subgroups of interest. OFSEP has implemented a strategy to improve the quality of its data and samples.

Results: On 15 December 2017, clinical data from all French MS expert centres and networks were aggregated: data from 59,477 patients were available (65% RRMS, 20% SPMS, 13% PPMS, 2% NMOSD) with mean disease duration of 13.6 ± 10.6 years. Standardized MRIs were produced by 24 MRIs centres and 12,482 cerebral (3D FLAIR, 17%; 2D DP T2, 17%; 3D T1 GADO, 12%) and 2,332 spinal sequences (SAG T2, 44%; SAG T1 GADO, 31%) from 856 patients were available with 319 (37%) patients with sequences at several temporal point. Biological samples were collected in 12 centres from 771 patients.

Conclusions: Over the last 7 years, OFSEP has improved his data quality and extended the patients followed and the variables collected. Its data and samples are open to physicians and researchers, public and private entities, in France and abroad. The ultimate goal of OFSEP is to answer questions about causes and mechanisms of MS, effectiveness of treatments, prognostic factors of disease progression, etc.

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Diet quality is associated with mobility and cognitive function in people with multiple sclerosis

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Background: People with multiple sclerosis (MS) are at increased risk of metabolic disorders like diabetes and hyperlipidemia. Aspects of diet are important determinants of metabolic comorbidities in the general population and influence mechanisms relevant to MS (immune/mitochondrial function, oxidative stress and action of gut microbiota). However, evidence linking diet with objective MS outcomes is sparse.
Objective: To assess the association between diet quality and disability and neurological function in people with MS.
Methods: We conducted an observational study of people with MS who completed MS Performance Test-based (MSPT) assessment of neurologic function and a 153-item food frequency questionnaire. For each individual, we calculated the Healthy Eating Index-2010, which is a composite measure of dietary quality favorably weighting an individual's intake of fruits, vegetables, legumes, seafood/plant proteins, whole grains, mono/polyunsaturated fat, other proteins and unfavorably weighting intakes of sodium, added-sugars and refined grains. Scores ranged from 0 (poorest quality) to 100 (optimal quality). We evaluated the association between diet scores and MS outcomes including disability (Patient Determined Disease Steps [PDDS]) and objective neurological outcomes (walking speed, manual dexterity and processing speed) using generalized linear models, as appropriate and adjusting for age, sex, disease subtype and duration, years of education and body mass index (BMI).
Results: We analyzed data from 277 participants (78% female, mean age: 48.2y [standard deviation; SD: 12.7y], mean BMI: 28.2 [SD: 7.5]) who completed MSPT and diet assessments. Participants in the highest quartile of dietary quality had significantly higher processing speeds, faster 25-foot walking speeds and marginally faster manual dexterity speeds relative to individuals in the lowest quartile (Q4 vs. Q1: adjusted mean difference for processing speed 3.87 [95% CI: 0.19-7.55]; P=0.02; for walking speed: 14% faster [95% CI: 4%-23%]; P=0.009; for manual dexterity: 6% faster; 95% CI: -2%-14%; P=0.08). Individuals in the highest quartile were also at a significantly lower risk of moderate vs. mild disability (OR: 0.25; 95% CI: 0.07-0.84; P=0.03).
Conclusions: High dietary quality was associated with lesser disease severity using measures of disability, mobility and cognitive function. Longitudinal studies should evaluate if high quality diets predict slower rates of disability accrual.

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Three dietary patterns consistently demonstrated over five years of follow-up in early multiple sclerosis: results from the AusLong Study

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Background: Diet may be relevant in multiple sclerosis (MS) onset and progression.
Objectives: To examine dietary patterns in a cohort of participants in the first five years following symptom onset.
Methods: We used the Cancer Council Victoria Food Frequency Questionnaire to evaluate dietary intake at baseline and 5-year review in a cohort of participants (n=260) in the early stages of CNS demyelination. Using iterated principal factor analysis, dietary patterns were identified and determinants thereof evaluated using linear regression.
Results: Three reproducible dietary patterns which we labelled 'Western', 'Mixed' and 'Prudent' were independently found at baseline and 5-year reviews, these patterns explaining 42.5% & 41.4, 32.0% & 29.1%, and 30.2% & 37.6% at baseline and 5-year reviews, respectively. The Western pattern was positively influenced by processed meats, takeaway, fried foods, confectionary, beer and spirits. The Mixed pattern was positively influenced by fried and sweet foods and some vegetables. The Prudent pattern loaded positively on whole-grains, non-fried fish, some vegetables, fresh fruits and wine. Those who were overweight or were current smokers had on average a higher Western diet score, whereas females and those who were middle-aged had a lower Western Score. Those using omega-3/6 containing supplements, middle-aged adults and those most physically active had higher Prudent diet scores. During follow-up, the Western and Mixed diet pattern scores decreased, whereas Prudent diet pattern scores increased. The change in Western diet score was significantly lower among females and those who decreased their BMI, whereas the change in Prudent diet score was significantly less among those who were current smokers at baseline or who increased their BMI.
Conclusion: Although all three dietary patterns persisted during follow-up, there was evidence that some participants improved their diet whereas others did not. These findings have implications for the health improvement efforts of people in the early stages of living with MS.

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Patient-reported loneliness and pessimism are associated with EDSS progression after discontinuation of disease modifying therapies in multiple sclerosis

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Background: The large armamentarium of disease modifying therapies (DMTs) available to treat multiple sclerosis (MS) has contributed to more stable disease. However, there is insufficient data available to determine whether DMTs should be discontinued in persons with MS (pwMS) with an apparently stable disease course.
Objective: To examine whether any clinical or patient-reported outcomes (PROs) were associated with time to disability progression after DMT discontinuation.
Methods: Participants who discontinued DMT, did not resume treatment, and had at least three follow-ups, were extracted from the New York State Multiple Sclerosis Consortium (NYSMSC). A change in Kurtzke Expanded Disability Status Scale (EDSS) score of $\geq$1.0 points, if baseline EDSS < 6.0, or of $\geq$0.5 points, if baseline EDSS $\geq$6.0, constituted disability worsening. Time to event was defined as the duration in months between study enrollment and disability worsening, or date of most recent follow-up in case EDSS scores remained stable. Mobility, physical and psychosocial limitations were assessed the follow-up before treatment discontinuation using the LIFEware™ system. Kaplan-Meier

survival curves and log-rank statistics were assessed to determine differences between patient-reported outcomes (PROs) or other clinical outcomes before DMT discontinuation and time to disability progression. These analyses were followed by Cox proportional hazards modeling to adjust for age at DMT discontinuation and EDSS before DMT discontinuation.
Results: A final sample of 96 participants were included in this analysis. Mean age at DMT discontinuation was 49.6 (SD=12.6) years and mean disease duration was 16.0 (11.0) years. During the study (mean of 6.1 years ±3.4 years), 24 patients progressed in EDSS scores and 72 remained stable. Participants who reported moderate to severe loneliness and pessimism before discontinuing DMT were more likely to reach EDSS progression sooner than participants who reported no or mild loneliness and pessimism (Adjusted Hazards Ratio for loneliness = 3.00, 95% CI: 1.22-7.35 and Adjusted Hazards Ratio for pessimism = 3.31, 95% CI: 1.27-8.61).
Conclusion: Participants who reported loneliness and pessimism before DMT discontinuation were more likely to reach EDSS progression sooner after DMT discontinuation. This suggests that psychosocial PROs, and symptomatic treatment, should be taken into consideration when patients and clinicians are contemplating DMT discontinuation.

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Katelyn S Kavak has nothing to disclose.

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Prognostic value of Anti-AQP4 and Anti-MOG antibodies in acute idiopathic transverse myelitis group

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Introduction: Acute idiopathic transverse myelitis (MTAI) is an inflammatory demyelinating disease, with monophasic or recurrent evolution. It may occur as an isolated clinical syndrome or CORE syndrome of the Neuromyelitis Optica (NOM) spectrum disorders. The presence of anti AQP4 in MTAI characterizes it as NOM spectrum disorders, and this reclassification allows the beginning a specific treatment. Another autoantibody has been studied as a biomarker in patients with NOM and high risk AQP4 syndromes, is the anti-MOG (oligodendrocyte myelin glycoprotein).
Objective: To test anti-AQP4 and anti-MOG antibodies in a cohort of patients with MTAI and to describe the clinical, demographic, laboratory and neuroimaging characteristics, analyzing the prognostic values.
Methods: Thirty patients with MTAI (Transverse Myelitis Consortium Working Group, 2002) attended in Rio de Janeiro / Brazil, whose anti-AQP4 and anti-MOG investigations were performed using the Cell Based Assay (CBA) method, from January 2016 to December 2017. Clinical, demographic, laboratory, and neuroimaging data were analyzed. The Expanded Disability Status Scale (EDSS) analyzed the disability in two years from diagnosis.
Results: The majority of the cases were women (83.3%), Afro-descendant (63,3%). Recurrent clinical course was the most prevalent (60%). Neuroimaging studies, observed 60% with extensive lesions (LEMT) and 40% of small lesions (NEMT). In group of LEMT, 44,5% was AQP4 positive patients and one case of LEMT was anti-MOG positive and AQP4 negative. This case is a male, afro-descendant, young age, monophasic course with completely recovery and EDSS zero. A clinical evaluation was analyzed by the median of EDSS; in the group of LEMT, AQP4 positive was 1,5; AQP4 negative, was4,0. In the group of NEMT, de median was 1,0.
Conclusion: In Brazilian patients MTAI, the median of EDSS in the group of LEMT AQP4 positive was lower than AQP4 negative group. Finally, the only case with anti-MOG positive was the best EDSS.

Disclosure
Nothing to disclose.

MS and gender

P368
Disease-modifying therapies for multiple sclerosis in association with pregnancy: a Swedish nation-wide cohort study

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Background: Multiple Sclerosis (MS) predominantly affects women of childbearing age. Disease-modifying therapies (DMTs) reduce the risk of future neurological disability, but data on potential negative effects on birth outcomes for more novel DMTs is still limited. While interferons and glatiramer acetate are considered safe at time of conception, discontinuation before planning pregnancy is typically recommended for more effective oral and biological DMTs. Hence, women may be at risk of relapses during the period between DMT discontinuation and the expectedly protective effects of pregnancy.
Objective: To describe DMT use, birth outcomes and relapse rates among women treated with DMTs shortly before pregnancy in a nation-wide cohort.
Methods: MS disease characteristics including treatment episodes given within 2 weeks preconception and relapses were extracted from the Swedish MS Register and data on pregnancies and birth

outcomes from the Swedish Medical Birth Register. We identified women who had undergone pregnancies until at least 22 weeks of gestation during the period of Jan 1st 2011 - Dec 31st 2016.
Results: Out of 1211 pregnancies, 446 were exposed to DMTs during the observed time period. Eight pregnancies were exposed to 2 different DMTs, contributing to 2 exposed pregnancies each. Thus, the number of exposed pregnancies amounted to 454, of which 200 were exposed to injectable interferons, 122 to natalizumab, 58 to rituximab, 49 to glatiramer acetate, 13 to dimethyl fumarate, 4 to fingolimod and 2 to alemtuzumab. The remaining 6 pregnancies followed hematopoietic stem cell transplantation at some point before the defined time period.
Conclusions: Along with first-line injectable DMTs, natalizumab and rituximab were the most commonly prescribed DMTs in women shortly before pregnancy. With regard to rituximab this represents the largest cohort reported so far. Data on safety aspects, including neonatal and delivery outcomes, and disease activity parameters will be included in the final presentation. Findings will be of importance for risk-benefit assessments in relation to pregnancy planning for women exposed to MS DMTs.

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P369
What is the impact of natural menopause on multiple sclerosis? An Italian, multicentre, retrospective, observational study

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Introduction: it is still not clear what happens to women with multiple sclerosis (MS) during menopausal transition: some studies have shown a worsening of subjective symptoms after menopause (MP)[1, 2], while one found a higher disability accumulation after MP[3].
Objective: Last year we presented data on 84 patients, now we present data of a larger population.
Methods: we included women with MS and a natural MP onset after 2005. Exclusion criteria: MS onset < 3 years pre-MP, primary progressive MS, date of MP uncertain, previous use of cyclophosphamide/mitoxantrone, hysterectomy/endometrial ablation, neoplasm/HIV, use of hormonal replacement therapy (HRT) < 3 years pre-MP. The observation period was set at 2-4 years pre and post-MP. Main outcomes were comparisons of ARR and EDSS scores pre/post-MP (ANOVA repeated measures). Possible confounders included in the analyses were: age at MP, MS duration, cigarette smoking, nulliparity and HRT post-MP. The analyses were repeated excluding women who suspended natalizumab (NAT) or fingolimod (FTY) during observation (confounder effect due to iatrogenic disease reactivation/rebound).
Results: we included 148 women from 16 centres in Italy (age at MP: 50.3±3.8 years, MS duration: 14.9±8.1 years). Observation period was about 3.5 years pre/post-MP. Cigarette smokers were 43 (29%), nulliparous were 39 (26%), 5 received HRT post-MP. At MP median EDSS score was 2.0. The majority of patients (93%) received DMTs during the observational period: 101 (68%) only first-line drugs (IFNs, glatiramer acetate, dimethyl fumarate, teriflunomide), 4 only second-line drugs (FTY, NAT, alemtuzumab), 31 (21%) both types of drugs. Most of subjects (78%) started DMTs before MP (6.6±3.9 years pre-MP). Twelve patients suspended NAT/FTY treatment during observation. ARR significantly reduced after MP with respect to pre-MP period (0.13±0.24 Vs 0.22±0.31, p=0.002). EDSS score increased significantly during the whole observation (p< 0.001), but the main differences were found after MP (p< 0.001), especially after excluding women with NAT/FTY interruption (EDSS score increased of 0.27 points and 0.46 points 2 and 4 years after MP). No interactions were found adjusting for possible confounders.
Conclusion: after MP ARR significantly decreases, while disability significantly increases. These results are in agreement with our previous work and literature[3]. Natural MP could be a turning point to a less inflammatory, progressive phase of disease.

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P370
Pregnancy and obstetrical outcomes in women with RRMS

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Introduction: Multiple sclerosis (MS) commonly affects young women of childbearing age who also frequently face issues related to becoming pregnant. There are some myths and doubts about pregnancy, newborns and progression of MS, causing many patients to fear becoming pregnant.
Objective: To study the pregnancy and obstetrical outcomes of RRMS patients in a prospective spanish cohort
Methods: Observational study. We followed-up prospectively those MS patients who wanted to become pregnant, their pregnancies and twelve months post-partum for four years. We collected information about concomitant diseases, contraceptive methods, artificial reproductive techniques (ART), DMTs, anaesthesia, kind of delivery and outcomes of the newborns. We compared these data with data of the Spanish population.
Results: From a cohort of 1166 patients, 60 pregnant (patients?) with 76 pregnancies were followed in the last 4 years. The Mean age was 35 (25-43) , mean BMI 20, mean disease duration 75 months, 65% were treated with DMTs before pregnancy. 22% were smokers and 15% moderate alcohol consumers. 17% received ARTs. 20% (verb: e.g. had/experienced) spontaneous abortion in the first trimester and 9% (verb: e.g. had/developed gestational diabetes. Mean duration of pregnancy was 39 + 1,7 weeks. C-sections was performed in 23% of the patients. 18% of patients didn´t receive anaesthesia during vaginal birth. All pregnancies resulted in live births, with no complications. Only 2% of malformations in newborns were reported. The mean birthweight was 3120 gr. Newborns of patients with moderate alcohol consumptionbefore the pregnancy has a trend of less weight at birth (300mg less). When we compare these data with the national and obstetrical spanish register there were no significant differences.
Conclusions: MS patients have very similar pregnancy and obstetrical outcomes as the generalSpanish population. Newborns have similar outcomes as the newborns of the spanish population register, In conclusion there are no obstetrical or neurological reasons to avoid pregnancy in MS patients

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MS symptoms

P371
Characteristics and treatment of multiple sclerosis - related trigeminal neuralgia: an Italian multi-centre study

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Background: The prevalence of trigeminal neuralgia (TN) in Multiple Sclerosis (MS) patients is higher than in the general population. Patients whose pain is insufficiently relieved by medication require invasive treatment, although studies on outcomes of surgically treated MS-related TN patients suggest higher recurrence rates and lower pain-free responses compared to idiopathic TN.
Objective: Aim of this retrospective, multicenter study was to gather information on the characteristics of MS patients with TN and on their medical and surgical treatments.
Methods and Materials: Neurologists members of the RIREMS (Rising Researchers in MS) group, were asked to identify patients with TN from their available clinical records and to fill out a database comprising their clinical data, and information on medical and surgical treatments carried out in each patient.
Results: Patient population consisted of 298 patients (179F, 119M, mean age: 57 +/-11 years) with a mean age at TN onset of 48 +/-11 years, and a mean EDSS at onset of 4 +/-2. Pain was most frequently located in the territory of the third trigeminal branch and was bilateral in only 4% of cases. Carbamazepine was the most frequent preventive treatment, prescribed as a first choice in 52% of cases, followed by oxcarbazepine (20%), gabapentin (14%) and pregabalin (10%). The first-choice treatment was mostly discontinued due to inefficacy (48%) or adverse events/tolerability issues (40%), with only 12% of patients discontinuing it due to pain remission. A second, third or fourth preventive treatment was prescribed, either in combination or sequentially, in 43, 12 and 4% of patients, respectively. First-choice symptomatic treatments were intravenous steroids (44%), NSAIDs (20%) and opioids (17%). Surgery was performed in 81 (30%) patients, most commonly gamma knife stereotactic radiosurgery (37%), followed by microvascular decompression (22%) and radiofrequency thermocoagulation (21%). A second surgical procedure was carried out in 32% of these, and a third procedure in 10%. The majority of patients (77%) are currently being treated for TN; of these, 19% require a combination of at least two medications.
Conclusion: Long-lasting pain remission in MS-related TN was uncommon in our study population, with over one third of surgically treated patients undergoing a repeat surgical procedure and with 77% of all patients requiring at least one preventive medication after a mean period of 9 (+/-7) years from TN onset.

Disclosure

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P372

Thoracic flexion provokes and localizes thoracic lesions in multiple sclerosis: a new clinical sign

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Objective: Determine whether local spine flexion can discriminate thoracic from cervical MS lesions.
Background: Lhermitte's sign/symptom indicates there is a cervical cord lesion due to an MS plaque or other cause. New lesions may not be apparent on cervical MRI, the Clinical/MRI paradox, although there may be prior MRI activity. Some MS patients have thoracic symptoms such as a sensory band, usually at T6-8, the "MS hug." Is it due to cervical or thoracic lesions?
Design and methods: 25 MS patients with potential thoracic cord lesions performed two maneuvers: 1) Rapid neck flexion, with flexion maintained briefly, and also rapid neck extension, and 2) Rapid thoracic flexion with the neck straight and immobile.
Results: Thoracic flexion was positive in 9 of 15 patients with recent onset thoracic cord symptoms such as a thoracic sensory band. Their pain or dysesthesia was provoked or worsened and radiated around the chest or from the thoracic spine then down to the legs. There was no cervical Lhermitte's sign elicited by this maneuver, even when it could be provoked with neck flexion. The thoracic flexion symptom was seldom positive when cord symptoms had appeared in the remote past, as in 10 additional patients. The maneuver is difficult when patients are corpulent, physically inactive, or have abdominal muscle weakness.
Conclusions: Thoracic flexion, a thoracic "crunch," can elicit an electrical sensation. This is usually associated with recent thoracic cord lesions and is likely to be independent of cervical pathology. As with cervical cord symptoms on neck flexion, this sign may help localize MS plaques, even when MRI is negative.

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AT Reder: nothing to disclose

P373

Assessing fatigue in multiple sclerosis: psychometric properties of the 5-item MFIS questionnaire

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Introduction: Fatigue in multiple sclerosis (MS) is a key symptom associated with work-related problems and poor quality of life outcomes. The 5-item Modified Fatigue Impact Scale (MFIS-5) is a brief self-assessment tool for measuring the impact of fatigue on cognitive, physical and psychosocial function. However, limited information is available on the psychometric performance of the MFIS-5 in patients with MS.
Objective: To assess the factor structure and construct validity of the MFIS-5 in the management of MS.
Methods: A multicenter, non-interventional, cross-sectional study in adult patients with MS (McDonald 2010 criteria) was conducted. A non-parametric item response theory (IRT) procedure, Mokken analysis, and confirmatory factor analysis (CFA) were performed to assess the factor structure of the MFIS-5. A graded response model (GRM or Samejima's model) was conducted to determine items characteristics.
Results: A total of 302 patients were studied (mean age = 42.3 ± 10 years, 64.2% female, 90.4% with relapsing-remitting MS). Mean Expanded Disability Status Scale (EDSS) score: 2.6 ± 1.9. The Mokken analysis found the MFIS-5 is a strong one-dimensional scale (overall scalability index H = 0.67) with high reliability (Cronbach's alpha = 0.90). The CFA model confirmed the one-dimensional structure (Comparative fit index = 1.0, RMSEA = 0.035). Samejima's model fitted well an unconstrained model with different item difficulties. The item characteristic curve showed all items presented appropriate shape and difficulty parameters. Items #2 (*"limited to do things away from home"*), #3 (*"had trouble maintaining physical effort for long periods"*), and #4 (*"less able to complete tasks requiring physical effort"*) represent 80.4% of the total information.
Conclusions: The MFIS-5 shows appropriate psychometric characteristics as a patient-reported outcome. MFIS-5 may constitute a valuable and easy-to-implement addition to measure in clinical practice the impact of fatigue in patients with MS.

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P374

Social support reduces the impact of chronic pain in individuals with physical disability: a longitudinal study

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Introduction: Chronic pain is common in individuals with multiple sclerosis (MS), and can have a negative impact on function. However, the presence of social support may buffer these negative effects. If social support is found to reduce the negative effects of pain on function, then social support could be a viable treatment target for individuals with MS and pain.
Methods: Individuals with MS endorsing at least some pain completed surveys assessing demographic variables (age, sex), pain intensity (0-10 NRS of average pain intensity), pain interference (Patient-Reported Outcomes Measurement Information System Pain Interference [PROMIS] item bank scales) and perceived social support (Multidimensional Scale of Perceived Social Support) on two occasions, separated by about 3.5 years (Timepoints 1 and 2). Regression analysis examined the ability of baseline social support to prospectively predict subsequent changes in pain interference, controlling for changes in pain intensity.
Results: 196 individuals (mean age: 53.87 years; 82% women) with MS and pain completed the measures. Change in pain intensity contributed significantly to the prediction of change in pain interference, controlling for demographic variables (*R-square* change = .19, *F-change* (1,231) = 44.66, $p < .001$). In addition, Timepoint 1 social support predicted change in pain interference over time, even after controlling for change in pain intensity (*R-square* change = .02, *F-change* (1,191) = 4.91, $p = .042$). Post-hoc tests found that those endorsing higher baseline social support reported subsequent decreases in pain interference (Mean PROMIS pain interference difference score = 2.08, SD = 9.20), while those endorsing lower baseline social support evidenced increases in pain interference (Mean = -0.90, SD = 8.55) over the next 3.5 years.
Conclusions: The findings indicate that higher levels of perceived social support is associated with subsequent improvements over time in pain interference for individuals with MS and pain, even when controlling for changes in pain intensity. On the other hand, lower levels of social support prospectively predict increases in pain interference. The findings are consistent with other research indicating multiple health benefits from the presence of social support. Research to develop and evaluate the benefits of interventions that enhance social support in individuals with MS and pain is warranted.

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P375

Fatigue and motor disability in African Americans with multiple sclerosis

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Objective: To investigate the impact of fatigue on motor disability in African Americans (AAs) with multiple sclerosis (MS).
Background: Fatigue is one of the most frequent (prevalence 50-90%) and burdensome symptoms of MS, adversely affecting patients' quality of life and ability to work. Although the disease course tends to be more severe in African American (AA) than in Caucasian (CA) patients, with increased occurrence of multifocal signs and symptoms, a greater risk for secondary progression and a poor response to disease-modifying therapies, the role of fatigue in modulating motor disability in AAs has never been explored.
Methods: Fourteen AA patients (13F, mean age 40.12 ± 11.25 yrs, mean disease duration 4.93 ± 4.16 yrs, median EDSS 1.7) and 9 AA healthy controls (3F, mean age 36.98 ± 8.07 yrs) were prospectively enrolled as part of an ongoing longitudinal study. In all subjects, fatigue and depression were estimated using the Modified Fatigue Impact Scale (MFIS) and the Beck Depression Inventory (BDI). An extensive motor evaluation was performed that included: 9-hole peg test (9-HPT), grooved pegboard test (GPT), 25-foot walk test (25-FWT), 2-minutes walk test (2-MWT), grip strength, arm muscle strength. Between- group comparison was performed with Mann-Whitney test, while correlations were tested with Spearman correlation coefficient.
Results: AA patients and controls did not differ in terms of MFIS or BDI scores (25.21 ± 17.17 vs 20.11 ± 17.93, p=0.44; 9.00 ± 8.71 vs 6.22 ± 5.97, p=0.35, respectively). Three AA patients and 2 HC presented a clinically meaningful MFIS score (total score>38). MFIS score was correlated with BDI score in both groups (r=0.70, p=0.006 and r=0.73, p=0.023, respectively), but a significant correlation between motor scores and MFIS was observed only in the patients' group (25-FWT rho=0.61, p=0.03; dominant hand 9-HPT rho=0.65 p=0.01; dominant hand GPT rho=-0.67, p=0.009; 2-MWT rho=-0.56, p=0.04).
Conclusions: These results suggest that even subclinical fatigue levels affect motor performance specifically in MS patients. We are currently enrolling CA MS patients and HC, thus allowing further evaluations of the differential impact of fatigue in MS patients in both ethnic groups.

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P376
Movement disorders in primary progressive MS: a prospective observational study

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Introduction: Movement disorders are thought to be rare in MS, however, many retrospective studies and review articles suggest that the prevalence is under-estimated. Moreover, the clinical characteristics of movement disorders have never been evaluated prospectively in patients with primary progressive MS (PPMS).
Objectives: To prospectively evaluate the prevalence and clinical characteristics of movement disorders in a sample of patients with PPMS.
Methods: A consecutive sample of PPMS was evaluated by a movement disorder specialist who carried out a standardized movement disorder questionnaire and performed a movement disorders-focused neurological exam. This study is still currently recruiting.
Results: Twenty PPMS were recruited so far (mean age 56.4 years, mean disease duration 12.2 years, 30% males). Movement disorders were present in 95% of the patients. the most common movement disorders were: action tremor 50%, tonic spasms 40%, focal dystonia 40%, myoclonus 30%, RLS 25%, spontaneous clonus 15%, demyelination-related parkinsonism 5%, fasciculation 5%, hemifacial spasm 5%. The movement disorders were spinal in origin in 60% of the patients, cerebellar in 25%, and ganglionic in 15%.
Conclusion: Movement disorders are very frequent in patients with PPMS and are often spinal or cerebellar in origin. Ganglionic movement disorders are much more common in PPMS compared to our previously-studied group of RRMS patients.

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Clinical assessment tools

P377
Spinal cord area as a cross-sectional predictor of gait related disability in multiple sclerosis

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Introduction: The timed-25 foot walk (T25FW) is an established measure of disability in multiple sclerosis (MS) A technology-enabled neuroperformance adaptation of the T25W, the walking speed test (WST) obtained via iPad® application has been implemented as part of routine clinical care at our center.
Objectives and aims: To determine the relationship of the WST and patient determined disease steps (PDDS) to other neuroperformance measures, patient reported outcomes (PROs) and quantitative MRI metrics in a large clinical cohort.
Methods: Demographics, MS disease history, iPad based neuroperformance tests, PROs, and quantitative MRI data were collected cross sectionally from the MS population at a single site between December 2015 and December 2017. Brain MRIs obtained +/- 90 days of a clinical encounter during which WST and PROs were collected were quantitatively analyzed via a semi-automated method to calculate T2 lesion volume (T2LV), normalized whole brain volume (BV), thalamic volume (TV), and cervical cord cross sectional area (CA). Spearman correlation coefficients were used to examine the relation of WST and PDDS with age, disease duration, PROs, neuroperformance measures and MRI metrics (significance set at $p < 0.001$). A linear regression model was designed to explore the contribution of disease measures and MRI measures to the WST and PDDS (significance set at $p < 0.05$).
Results: 944 patients (age 47.6 ± 11.4, disease duration 12.1 ± 9.4) underwent concurrent neuroperformance assessment and MRI. PDDS and WST showed a strong correlation ($\rho = 0.69$, $p < 0.001$). WST correlated with all PROs (strongest correlation were Neuro QoL lower extremity $\rho = -0.70$, $p < 0.001$). WST correlated with all MRI metrics (strongest correlations were T2LV ($\rho = 0.26$), CA ($\rho = -0.26$), and BV ($\rho = -0.25$). PDDS had the same pattern of correlations. Linear regression model incorporating age, disease duration, sex, and MRI measures demonstrated that CA, T2LV, and BV were significant cross-sectional predictors of WST ($p < 0.05$). For PDDS, significant predictors were age, CA, and T2LV ($p < 0.05$).
Conclusions: WST and PDDS correlated best with PROs capturing lower extremity physical function in a large clinical cohort with routine technology-enabled administration. Gait dysfunction is likely related to spinal cord injury as evidenced by the strong correlation of WST and PDDS with cross sectional spinal cord area.

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P378

Plasma neurofilament light levels are associated with risk of developing sustained disability in multiple sclerosis

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Background: Elevated levels of plasma neurofilament light (pNfL) have been associated with short-term disease activity, treatment response and prognosis in multiple sclerosis (MS). The long-term predictive value and clinical usefulness of pNfL measurement is yet to be determined.
Objective: To investigate the association between pNfL levels and risk of developing sustained disability progression in a large population-based sample of newly diagnosed MS patients.
Methods: Levels of pNfL were measured with the Single Molecule Array (Simoa™) NF-light® Advantage kit technology (detection threshold 1.95 pg/ml) in patients with a confirmed diagnosis of MS and in population-based healthy controls. We assessed the impact of age-stratified pNfL levels above 50th and 75th healthy controls percentiles (C50 and C75) on the risk of reaching sustained expanded disability status scale (EDSS) scores of 3.0, 4.0 and 6.0 using flexible parametric survival models while adjusting for potential confounders.
Results: pNfL levels were measured in 1026 healthy controls and 3765 MS patients. Median (interquartile range) pNfL was 7.5 (4.1) pg/ml in healthy controls and 10.5 (8.0) pg/ml in MS ($P < 0.001$). Median duration of follow-up was 5.1 years (interquartile range: 5.4). 2837 (75%) and 2156 (57%) of patients had age-stratified pNfL levels >C50 and >C75, respectively. There were no differences in the proportion of patients with levels >C50 and >C75 between sexes ($P = 0.9$ and $P = 0.5$). After controlling for sex, age and disease duration at sampling, conversion to progressive MS, and exposure to disease modifying treatments during follow-up time (as time varying covariate), the risk of reaching sustained EDSS score 3.0 was increased by 33% (95% Confidence Intervals (CI): 1.14-1.55) and 61% (95%CI: 1.41-1.84) for pNfL levels >C50 and >C75, respectively. Similarly, risk of reaching sustained EDSS scores 4.0 and 6.0 was increased by 65% (95%CI: 1.34-2.03) and 37% (95%CI: 1.05-1.77) for levels >C50 and by 70% (95%CI: 1.44-2) and 54% (95%CI: 1.23-1.92) for levels >C75, respectively.
Conclusions: High pNfL levels at diagnosis are associated with increased risk of developing sustained disability progression. Hence, pNfL may serve as a prognostic tool to assess the risk of developing permanent disability in MS.

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Brain and spinal MRI features can distinguish MS from NMOSD with different serostatus at disease onset in Latin American patients

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Background: Matthews's criteria (MC) were based on the shape and distribution of lesions on conventional brain magnetic resonance imaging (MRI) and they were able to differentiate multiple sclerosis (MS) from neuromyelitis optica spectrum disorders (NMOSD) in clinical practice. However, only positive aquaporin 4 antibodies (AQP4-ab) NMOSD patients were included and spinal cord MRI was not evaluated in this cohort.
We aimed to evaluate the MC in positive (P-NMOSD), negative (N-NMOSD) and unknown (U-NMOSD) AQP4-ab serostatus as well as assess the added diagnostic value of the spinal cord MRI at disease onset.
Methods: Medical records, brain and spinal cord MRI of patients with MS and NMOSD (diagnosed by current validated diagnosis) from Argentina, Brazil and Venezuela were reviewed by a blind rater and scored according to the Matthews criteria (lesions adjacent to the body of the lateral ventricle, lesions in inferior temporal lobe, S-shaped/curved U-fiber lesions and Dawson's fingers) adding short-segment transverse myelitis (STM, < 3 segment lesions) as a new criteria for the analysis. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) on MC adding STM were determined stratifying by AQP4 serostatus in NMOSD patients.
Results: Two hundred and eighty two patients were included (MS = 188 and NMOSD = 94, ratio 2:1). The Sensitivity, specificity, PPV and NPV of both the MC and MC adding STM for MS vs. P-NMOSD (n = 55) were 97.8%, 70.9%, 92.0% and 90.6%; and 100%, 58.1%, 89.0% and 100%, respectively. For MS vs. N-NMOSD (n = 28) were 97.8%, 82.1%, 97.3% and 95.1%; and 100%, 82.1%, 97.4% and 100%, respectively. For MS vs. U-NMOSD (n = 21) were 97.8%, 85.7%, 98.3% and 81.8%; and 100%, 76.1%, 97.4% and 100%, respectively.
Conclusion: This study showed that the MC are sensitive and specific for distinguish MS from all serostatus of NMOSD at disease onset. STM added to the MC did not raise the sensitivity and specificity for distinguishing MS from all serostatus of NMOSD.

Disclosure

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P380

Periodic limb movements in people with multiple sclerosis who report fatigue: polysomnography study in a large cohort

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Background: People with Multiple Sclerosis (PwMS) frequently report fatigue. PwMS Fatigue can be severe/disabling. Sleep Apnea is a common cause of fatigue in PwMS. Periodic limb movements during sleep (PLMS), not commonly reported in PwMS. PLMS are characterized by leg movements or jerks which typically occur every 20 to 40 seconds during sleep. PLMS adversely impacts sleep by both causing sleep fragmentation and increasing energy cost during sleep as well as causing daytime somnolence. PwMS reported fatigue is typically subjective or quantified by patient reported outcomes. People affected by PLMS may be distinctly unaware and not self-report symptoms suggestive of PLMS unless specifically questioned. PLMS can be treated pharmacologically which can then improve sleep and reduce daytime fatigue PLMS can be easily investigated with Polysomnography (PSG), however, prior studies investigating PLMS in PwMS have been limited by small sample size.
Objective: To investigate the incidence/degree of PLMS during sleep in PwMS who report fatigue.
Methods: Retrospective analysis of PwMS who reported fatigue, and were not previously diagnosed as having Sleep Apnea or PLMS, and agreed to overnight PSG study.
Results: 292 PwMS (average age 47.3 ± 10.7 years, 81.4% female). No PwMS had a diagnosis of PLMS prior to undergoing PSG. PwMS reporting fatigue: 41% (n=121) had PLMS index (PLMS per hour, PLMS-I) >0. Of those PwMS with PSG identified PLMS: 10% had PLM-I 5-10 per hour, 5% had 11-21 PLMS-I, 12% had >21 PLMS-I. 38% (112/292) of PwMS experienced arousal due to PLMS (PLMS-AI). 34% (n=38) had 0< PLMS-AI< 5, 31% (n=35) had PLMS-AI 5-20, 14% (n=16) had PLMS-AI 20-50, and 21% (n=23) had PLMS-AI >50.
Conclusions: PLMS commonly occurs in PwMS who report fatigue. A group of PwMS who report fatigue have both significant >5 PLMS/hour and PLMS related arousals/hour. These factors increase the "work" of sleeping. PLMS may contribute to daytime sleepiness and should be recognized and potentially treated. The etiology of fatigue related to sleep problems in PwMS is multifactorial and is not just due to Obstructive Sleep Apnea.

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P381

Baseline cognitive evaluation predicts one year disability progression in MS

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Background: Cognitive impairment affects 40-70% of multiple sclerosis (MS) patients and has a dramatic impact on their quality of life, performance at work and social life. Several early epidemiologic, clinical, para-clinical and imaging factors may predict future disability and disease progression, however, cognitive predictors are still lacking.

Objective: To assess the ability of specific computerized real-time cognitive tests to predict disability progression at 1 year after initiating immunomodulatory treatment for MS in comparison with the predictive value of the Expanded Disability Status Scale (EDSS).

Patients and methods: Fifty three relapsing-remitting (RR) MS patients (F=42, mean age 36.02±9.25, mean EDSS 2.18±1.27) underwent cognitive evaluation using a computerized real-time battery of basic neuropsychological tests ("CogScan"; Anima Scan LTD) before starting immunomodulatory treatment with glatiramer acetate or interferon beta preparations. Tests included Finger Tapping Test (FTT), Simple Reaction Time (SRT), Choice Reaction Time (CRT), Immediate and Delayed Memory for Pictures, Words and Faces and Digit Running Task (DRT or Speed-Accuracy Tradeoff, a test that assesses shift from speed of mental processing to working memory related error checking). EDSS was performed every 3 months. Univariate logistic regression analysis was conducted for each predictor and the most robust predictor was analyzed by receiver operating characteristic (ROC).

Results: At 1 year, 9 patients (17%) had 3-months sustained disability progression. Baseline EDSS did not predict disability progression. Real time computerized assessment of simple cognitive functions yielded four statistically significant predictors: Accuracy and latency in the DRT, and standard deviation (SD) in both FTT and DRT. The Digit Running-I SD showed the best predictive value for disability progression.

Conclusions: Baseline cognitive impairment, especially slow and highly variable performance on the Digit Running Task that measures the quality of complex information processing in time-limited situations, but not baseline EDSS, can predict the one-year progression of neurological disability in MS patients treated with immunomodulatory drugs.

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Semion Kertzman is an employee and head of the Research Unit at AnimaScan, Ltd.

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Variability in scoring the functional system scores of the expanded disability status scale at clinics from different countries

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The purpose of this study was to estimate the extent to which Expanded Disability Status Scale (EDSS) data from different MS clinics are inferentially equivalent and thus, can be pooled for research purposes. Data harmonization using Rasch analysis was performed on EDSS data from 12 clinics, each from a different country, obtained from the MSBase registry. Patients' most recent visit was used to estimate whether clinics scored the Functional System Scores (FSSs) items without bias such that the FSSs/EDSS are inferentially equivalent (have the same meaning). Bias factors are sex, onset age, age, disease duration, and country. A logit difference ≥ 0.5 and $p < 0.05$ on the Mantel-Haenzel test indicates item bias (differential item functioning (DIF)) between factors. The Expected Test Score Standardized Difference (ETSSD) estimates total score bias (differential test functioning (DTF)) among the clinics and is interpreted the same as Cohen's d effect size.

Total N=14536 (women = 69%, onset age = 31 years, age = 44 years, disease duration = 13 years). Clinic samples ranged from

236-3392. MS types were relapsing MS =78%, secondary progressive MS=12%, primary progressive MS=7%, and unknown=3%. Median EDSS was 2.5. All items fit the Rasch model after rescoring, with INFIT/OUTFIT mean square fit statistics within the acceptable range (0.5≥ and ≤1.7). Principal component analysis of residuals explaining 55% of variance, but no second component was identified and low response dependency (r< ~0.3) supporting unidimensionality of the FSS items.

FSS items were well distributed along a measurement continuum but were not a good match to the sample; the sample had low disability but there were few items in that measurement range, resulting in an 8.5% ceiling effect. Reliability (α=0.82) was good. All items had DIF (item bias) by clinic. Sensory FSS had the most DIF (7/12 clinics). Vision FSS had the greatest DIF range (> 2 logits). Despite item bias, there was minimal total score bias suggesting biases cancelled. The Rasch transformed FSS total score (EDSSrasch) correlated highly with the EDSS (0.92). Correlation plot shows EDSSrasch was more sensitive to change at the low disability end of the measure.

EDSSrasch, a modification of the familiar EDSS based on a strong statistical model, can better detect change at lower disability. Data harmonization results show that the EDSSrasch from different clinics are inferentially equivalent and can be pooled.

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Importance of patient reported outcomes: correlation of clinician-evaluated versus patient self-reported disability in multiple sclerosis patients

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Background: Multiple Sclerosis (MS) results in disability over time and is commonly measured by the Expanded Disability Status Scale (EDSS) in clinical trials. Scores range from 0 (no disability) to 10 (Death due to MS) in 0.5 increments representing higher levels of disability. EDSS has limited use in the clinic setting due to time constraints and need for a trained physician due to complex scoring guidelines. EDSS is heavily focused on ambulation with limited assessment on MS global impairment. Results from the MS-ADVANCE study may be used to assess the validity

of other measures of disability in MS patients and more accurately capture outcomes important to patients.
Objectives: To examine correlation between disability-related Patient-Reported Outcomes (PROs), SDMT and EDSS scores of patients in the MS-ADVANCE study.
Methods: MS-ADVANCE prospectively captures multiple PROs via web-based surveys and journals. Responses to the following PROs and assessments were analyzed for correlations vs. EDSS: Patient Determined Disease Steps (PDDS), Symbol Digit Modalities Test (SDMT), Modified Fatigue Impact Scale (MFIS), Activities of Daily Living (ADL), Mobility, and Sleep. Pearson's r and Fisher's exact test were performed to assess correlation.
Results: Baseline demographics of patients with an EDSS (n=293) were 81% female, mean age of 52 years, race (0.6% Asian, 25.4% African-American, 3.3% Middle Eastern, 1.7% native American, 68.5% white), 90.3% RRMS. As of March 2018, the following number of PROs or assessments were reported: PDDS (n=183), SDMT (n=507), MFIS (n=224), ADL (n=57), Mobility (n=44), Sleep (n=48). Significant correlations ($p< .0001$) were found between EDSS scores and PDDS (r=0.836, z=1.207), SDMT (r= -0.568, z= -0.644), MFIS (r=0.365, z=0.383), ADL (r=0.499, z=0.548), Mobility (r=0.602, z=0.697). Sleep was not significant (r=0.357, z=0.373). EDSS scores ranged from 0 to 8.5.
Conclusion: Proper assessment and treatment of disability is critical in MS care. Incorporating PROs in MS care can address limitations of the EDSS. The strong correlation between PDDS and EDSS in this study suggests use of PDDS as an alternative measure of disability in MS patients in the clinic setting. Global MS impairment may be more accurately measured by a battery of assessments including PDDS, SDMT, MFIS, ADL, and Mobility, which take less time to capture, but may also provide valuable insight to outcomes that matter to patients.
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Upper limb function assessed by an engineered glove correlates with motor and cognitive disability in progressive MS

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Introduction: The underrepresentation of upper limb function and cognition in EDSS results in its inadequacy in monitoring clinical disease status, particularly in patients with progressive MS. An engineered glove (Hand Test System, HTS) has been previously used to quantitatively measure impairment in finger movements in a cohort of relapsing remitting MS patients.
Aims: To assess the correlation of finger motor function assessed by the HTS system with clinical outcomes in a cohort of progressive patients.
Methods: We evaluated the finger motor function in 19 subjects with progressive MS enrolled in the European ERACoSysMed study (13 PPMS, 6 SPMS; F/M ratio 13/6; mean age 49 years (SD=8); median EDSS 5 (range 1.5-6.5); mean disease duration 13 years (SD=11). All the subjects performed 30-sec repetitive fingers-to-thumb opposition sequences with their dominant hand at maximal velocity and bimanually paced by a metronome. The HTS glove was used to calculate motor performance parameters such as the maximum movement rate (RATE) and the inter-hand interval (IHI), index of bimanual coordination. All the patients underwent a clinical assessment by EDSS, Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT) and Symbol Digit Modalities Test (SDMT). Correlations between finger motor impairment and clinical parameters were evaluated by the Spearman´s rank correlation coefficient.
Results: In this cohort of progressive patients, EDSS and SDMT were not significantly correlated (r=-0.21, p=0.37); the 9HPT was significantly correlated with EDSS (r=0.45, p=0.048) but not with SDMT (r=0.22, p=0.34). The RATE was found to be correlated with EDSS (r=-0.59, $p< 0.001$) but not with SDMT (r=0.24, p=0.32). The IHI was strongly associated with SDMT (r=0.73, p=0.003) but not with EDSS (r=0.19, p=0.51). In multivariate models including all the demographic and clinical variables, the RATE and the IHI were the parameters with the highest correlation with EDSS and SDMT respectively.
Conclusions: Tools to objectively assess disability in progressive MS patients are urgently needed. The sensor-engineered glove is a simple and quantitative device to assess upper limb function. RATE-EDSS and IHI-SDMT correlation may reflect glove parameters specificity in the detection of motor and cognitive networks impairment. Thus, the glove may represent a promising method to assess the different features of disability in progressive MS.

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Evoked potentials and white matter lesion volume to explain disability in early MS

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Introduction: Evoked potentials (EPs) have been part of the routine diagnostic workup in suspected MS for decades. However, with the broad availability of brain MRI, the role of EPs in clinical practice is under debate. We related EP and brain MRI results to disability (Expanded Disability Status Scale, EDSS) at the time of diagnosis to elucidate the differential contribution of both methods to objectify disease severity.
Methods: We studied 543 newly diagnosed MS and CIS patients (EDSS 1.6 ± 1.5) with both EP data and brain MRI available. Brain MRI followed a standardized protocol (3D FLAIR, 3D T1w, 3 Tesla). EPs comprised visually evoked potentials (VEPs) and somatosensory EPs (SSEPs) of the median and tibial nerve. Tibial nerve SSEP latencies were corrected for body height. Latencies of all VEPs and SSEPs were combined with amplitudes to one score. White matter lesion volume (WMLV) was derived from brain MRI by an automated tool (Lesion Segmentation Tool). EP results and WMLV were correlated with EDSS at the time of diagnosis by linear regression models.
Results: EDSS correlated with tibial nerve SSEPs ($R=0.495$, $p< 0.001$) and, to a lesser extent, with median nerve SSEPs ($R=0.356$, $p< 0.001$) and VEPs ($R=0.169$, $p< 0.001$). EDSS also correlated with WMLV ($R=0.345$, $p< 0.001$). Of 268 cases with normal tibial nerve SSEPs, only two showed abnormalities of median nerve SSEPs. Including all three EP measures and WMLV in a multiple linear regression model with EDSS as response variable, tibial nerve SSEPs and WMLV were the only significant explanatory variables.
Conclusions: With regard to EDSS, only tibial nerve SSEPs add information to brain MRI. Compared to tibial nerve SSEP, the value of median nerve SSEP seems to be low, if not negligible.

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Validation of the assessment of self-reported MS symptom severity using single-item 0-10 numeric rating scales

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Background: The assessment and tracking of symptoms is important for multiple sclerosis (MS) management. Current validated measurements of a single symptom often require multiple items, creating a significant high burden for patients when multiple symptoms are being assessed.
Objective: We developed a tool where patients rated the severity of 13 common symptoms on a numeric rating scale from 0-10. The aim was to validate six of the symptoms against commonly used scales (including walking difficulties, fatigue, pain, feelings of anxiety, depression and vision problems).
Method: Data were collected through the Australian MS Longitudinal Study (2015 Medical Survey: n=1,985; 2016 Baseline Economic Impact Survey, n=1,577). Validation measures included Patient Determined Disease Steps Scale (PDDS), Fatigue Severity Scale (FSS), Hospital Anxiety and Depression Scale (HADS), Assessment of Quality of Life (AQoL) (with subscores for mobility, fatigue, pain, anxiety, depression and vision problems), and European Quality of Life (EQ-5D) (with subscores for mobility, pain, anxiety/depression). Concurrent validity was assessed using Spearman rank correlations. Predictive validity was assessed by comparing the R-squared or pseudo R-squared from regression models.
Results: We observed a high correlation between walking difficulties and PDDS ($r=0.82$), a good correlation between fatigue and FSS ($r=0.72$), pain and AQoL-pain ($r=0.77$), feelings of anxiety with HADS-Anxiety ($r=0.68$), and feelings of depression with HADS-Depression ($r=0.63$), and a fair agreement between vision problems and AQoL-vision ($r=0.43$). In terms of predictive

validity, the R-squared (or pseudo R-squared) of associations with quality of life or work productivity were generally similar for our symptom severity assessment compared to the comparison measures. For example, the PDDS explained 23% of the variability of AQol, and our walking difficulties assessment explained 24% of the variability.
Conclusions: The assessment of self-reported MS symptom severity using single-item 0-10 numeric rating scales seems to have adequate concurrent and predictive validity.

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P387
Validation of bipedal hop test to detect subtle but meaningful impairment among people with mild multiple sclerosis

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Introduction: People with mild multiple sclerosis (MS) report difficulties with muscle strength, imbalance, and incoordination, but these impairments are often undetected by current clinical measurement tools. A recently developed bipedal hopping test was able to distinguish motor impairment in people with MS (PwMS), without gait disturbances, from controls.
Objectives: In order to consider using the hopping test in clinical research, construct validity should be assured.
Aims: We aimed to compare metrics on a bipedal hopping test with current gold-standard measurements to determine convergent and divergent validity.
Methods: Participants (n=56) with low disability MS (Expanded Disability Status Scale (EDSS) £3.5) completed tests of cognition (Montreal Cognitive Assessment; MoCA) and grip strength, as well as walking at self-selected walking speed and hopping on an instrumented walkway. Walking and hopping variables (e.g. velocity, length, variability) were extracted from the walkway software.
Results: As expected, hopping variables showed convergent validity with physical impairments and divergent validity with cognition. Longer hop lengths were strongly and significantly associated with decreasing EDSS (r=-0.36) and increasing grip strength (r=0.46). Walking variables used in clinical setting (such as stride length and velocity) were associated with hop length (r=0.44) and hop speed (r=0.34). There was no association between hopping variables and MoCA score. Lastly, hopping variables provided granularity within equivocal EDSS scores. For instance, hop length ranged from 29.28cm to 128.99cm in participants with an EDSS of 0.
Conclusions: Hopping, which is a more difficult task than walking, may be more sensitive when measuring balance and muscle strength among people in the low disability range. It showed good convergent and divergent validity with physical and cognitive measures and provided greater granularity among performance of patients who scored identically on the lowest range of EDSS. Bipedal hopping has the potential to be an important clinical measurement tool in tracking motor ability in the early stages of MS.

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P388
Real-life smartphone accelerometery is closer correlated with disability and mobility in MS than a commonly used wrist-worn activity and mobility tracker

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Introduction: Mobility in persons with multiple sclerosis (pwMS) can be assessed with clinical tests and surveys which have restricted ecological validity. Research-grade accelerometers (i.e. ActiGraph) are considered to measure real-life mobility. Smartphone accelerometery might be an easily accessible alternative.
Objectives: To explore the validity of smartphone accelerometery in comparison to clinical tests, surveys and the ActiGraph in free-living context of pwMS and controls.
Methods: 68 pwMS (EDSS: mean 3.3, median 3, range: 1.0-6.0, RRMS n= 33) and 70 matched controls (mean age: 42y, women: 65%) absolved 5-repetition sit-to-stand test (FTSTS test), timed 25 feet walk(T25FW), timed tandem walk (TTW) and 6-minute walk time (6MWT), Godin Leisure-Time (GLTEQ), Frenchay Activity Index (FAI) and the international physical activity questionnaire (IPAQ). pwMS underwent an examination for Expanded Disability Status Scale (EDSS) score and answered the 12 Item MS Walking Scale (MSWS-12). Real-life data were collected with a smartphone recording accelerometer and an ActiGraph over 7 days. Corrected for wear time, we computed correlation tests between ActiGraph (steps per minute), smartphone accelerometery (variance of vector magnitude/varVM), clinical tests and surveys. Moreover, we used t-tests to determine the ability to separate between patients and controls as well as between different disability groups.
Results: ActiGraph data correlated moderately ($r = 0.43$, $p< 0.05$) with smartphone outputs, low to moderately with clinical tests (TTW, T25FW, 6MWT, r=-.23, -.20,.31, p< .05) and some questionnaires (FAI, IPAQ and MSWS-12, r=.27, .30, -.33, p< .05). Smartphone showed overall higher correlations with age and waist (r=-.48, -.23, p< .05), clinical tests (TTW, F25WT, FTSTS, 6MWT, r= -.51, -.44, -.45, .49, p< .05) and most of the questionnaires (GLETQ, FAI and MSWS-12, r=.36, .25, -.51, p< .05). ActiGraph data only differed between pwMS and controls (p< .001) but could not differentiate disability groups. Smartphone could not only differentiate pwMS and controls ($p< 3*10^{-7}$) but

also RRMS and PP-/SPMS ($p< 2*10^{-11}$) and between participants with/without ambulatory impairment($p< .001$).
Conclusions: Smartphone accelerometery seems to provide better estimates of mobility and disability than a wrist-worn ActiGraph in free-living context for both controls and pwMS. It might thus be the first-choice measurement tool for real-life mobility.

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Categorising the multiple sclerosis impact score 29: performance over 7 years of follow-up in the UK MS Register

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Introduction: Registries are increasingly being used to answer some of the more complex questions in MS that randomised controlled trials (RCTs) are not able to address. Registries use larger numbers of subjects often less precisely characterised than those in RCTs. Registries have variable follow-up length and data capture events but can run for prolonged periods. To maximise the opportunities that registries provide we need to understand more about their performance.
Aims: UK MS Register subjects are asked to complete the MSIS-29 every 3 months. Here we determine how frequently the questionnaire was completed over 7 years; categorise the multiple sclerosis impact scale (MSIS)-29 physical sub-score and study category change as a measure of disease progression over 7 years.
Methods: the MSIS-29 physical sub-score was stratified into five equal categories based on a differing risk of death over the next 10 years (Raffel, 2017). Basic demographics in each category were determined and survival curves determined its performance over 7 years.
Results: The UK MS register has >6000 people with MS who regularly interact with the platform. The MSIS-29 was answered on average 0.7x every 3 months per person (range 0.072- 4.74 every 3 months). 3300 subjects had longitudinal data of over 3 years with 500 subjects with 7 years of data. Increasing MSIS-29 physical category from 1 to 5 was associated with increasing age (44.1 to 51.9 years), reducing %relapsing (79.8% to 48.6%) and increasing %progressive (5.1% to 36.7%) subjects but also with increasing unemployment (25% to 85%). Survival curves utilising category change demonstrated that there was a significant difference between the curves with the lowest (1) and highest (5) categories being associated with the slowest rate of change. Whilst categories 2-4 progressed at a similar rate.
Discussion: A significant subgroup of the MS Register engage regularly for a prolonged period and using the MSIS-29 physical category change registries can generate outcome measures that can be used over the longer term.

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Spinal cord atrophy but not brain atrophy measures, correlates with the Multiple Sclerosis Severity Score

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Background: Multiple sclerosis is an heterogenous disease, in which disability depends on the evolution time. Brain and spinal cord atrophy have been found to be predictors of the forthcoming disability.
Objective: To explore the relationship between brain and spinal cord atrophy with the disability, measured as the Expanded Disability Status Scale (EDSS) and as the time-related disability measured by the Multiple Sclerosis Severity Score (MSSS).
Method: The brain and cervical spinal cord atrophy were measured in 63 consecutive MS patients with 3T magnetic resonance imaging (MRI). Brain volume measures were calculated with FreeSurfer and spinal cord volumes were segmented manually. Clinical forms, the EDSS, and the MSSS were recorded at the time of the MRI scans and the correlation between brain atrophy measures, spinal cord atrophy, and clinical measures were obtained.
Results: Sixty-three MS patients were studied (73% females). Fifty-two relapsing-remitting MS and 11 secondary progressive patients. Mean age 40.1 (SD 10.6), evolution 12.1 years (SD 8.5), EDSS 2.6 (SD 1.4), MSSS 3.1 (SD 3.1). Brain parenchymal fraction, the cortical grey matter, cerebellum, brain stem, and cervical cord volumes correlated with the EDSS, but only the cervical spinal cord volume correlated negatively with the MSSS (Spermann Rank correlation -0.359, p=0.008). Similar results were found when excluding SPMS patients from the analyses (Spearmann Rank correlation -0.336, p=0.014).
Conclusions: Although several brain volume measurements correlate with the concurrent EDSS, only the spinal cord atrophy seems to encompass the disability adjusted by the time of evolution, reflected by the MSSS scale. Our results appoint to the necessity of measuring the spinal cord atrophy as a marker of continuous degeneration in MS.

Disclosure
The authors have not disclosures to declare

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Cerebellar grey matter damage associates with cognitive impairment, but not with fatigue and emotional changes in early relapse onset multiple sclerosis

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Background: Cerebellum has a main role in various sensory-motor networks and in cognitive-behavioural processes in patients with Multiple Sclerosis (MS), with a wide-range negative impact on their lives.
Aim: To investigate the association between cerebellar white (WM) and grey matter (GM) lesion burden and cognitive dysfunctions, fatigue and depression at MS diagnosis.
Methods: Fourty-five consecutive patients (F/M: 2.4; age 33.91±9.9 years; disease duration -DD- < 5 years) with relapsing remitting MS were enrolled. Clinical evaluation included: EDSS, Brief Repeatable Battery of Neuropsychological Tests (BRB-NT), Delis-Kaplan Executive Function System Sorting Test (D-KEFS ST), MS Neuropsychological Questionnaire (MSNQ), Fatigue Severity Scale (FSS), Beck Depression Inventory (BDI-II) and Brain 3T MRI, which included 3D T1, 3D FLAIR, 3D DIR and 2D PSIR. MRI analysis was achieved on 3DT1 using SUIT atlas, calculating lesion number and volume by manual segmentation (ITK-SNAP).
Results: Evidence of cognitive dysfunction was documented by BRB-NT and/or D-KEFS SR in 26.6% patients. Cognitively impaired (CI) patients showed a significant decrease in mental performance in almost all items of BRB-T ($p< 0.02$) and in D-KEFS SR ($p< 0.004$). No difference between CI and cognitive normal (CN) patients was observed regarding age, sex, DD and EDSS. CI patients had significantly more cerebellar GM lesions than CN ($p=0.04$). Cognitive dysfunctions observed by BRB-NT were associated with cerebellar GM lesion number ($r=0.42$, $p< 0.05$) and volume ($r=0.33$, $p< 0,05$). The more frequently compromised tests were SDMT and SRT-D. No correlation was found between cerebellar and supratentorial GM lesion load both on DIR ($r=0.08$ $p>0.5$) and PSIR ($r=0.29$, $p>0.05$). Moderate inverse correlations were observed between cerebellar pathology and MSNQ ($r= -0.44$, $p< 0.05$), FSS score ($r=-0.66$, $p< 0.05$), and BDI-II score ($r=-0.67$, $p< 0.05$). While only weak correlations were found between supratentorial WM and GM lesions number and volume and MSNQ (< -0.33, $p< 0.05$) and FSS (< -0.33, $p< 0.05$), no correlation was found between BDI-II and supratentorial lesions.
Conclusions: Our findings suggest that cerebellar pathology has an early and significant negative impact on cognitive functions in MS. The negative association with fatigue and emotional changes seems to indicate that these functions are not significantly influenced by cerebellar pathology in the early disease phases

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Assessment of the addition of an activities of daily living measure to the UK MS Register

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Background: The UK MS Register is one of the largest repositories of ´real world´ data from People with MS (PwMS) in the UK. Data are captured clinically and by Patient Reported Outcome Measures (PROMs) via the internet. Longitudinal data collection has been ongoing for 7 years. Amongst the ´core´ instruments is the Multiple Sclerosis Impact Scale 29v2 (MSIS29), and the EuroQol 5D (EQ5D). In 2017 the Extended Barthel Independence (EBI) instrument was added to assess participant dependence.
Objective: To examine the appropriateness of the EBI against the existing measures on the MS Register
Methods: Participants was ascertained by searching the UK MS Register datasets: Required complete demographics - date of birth, gender, age at diagnosis, MS type at diagnosis and current MS Type. The EBI, MSIS29v2 and the EQ5D had to be completed within a similar time point. MSIS and Barthel are calculated, the EQ5D allows for self assessment via a 0 -100 scale.
Results: 2649 participants satisfied all criteria, 72% were female. Mean age at diagnosis was 40.7(±10.7), mean age at response = 52.4(±11.4).
Mean response to the instruments with current MS Type:
PPMS RRMS SPMS Benign Unknown
MSIS 43.0. 55.5. 61.6 24.2 42.9
EQ5D 58.4 61.2 51.9 70.6 61.4
EBI 78.1 91.6 70.0 94.9 85.4
Conclusion: Previous work has shown that MSIS29 alone has been an excellent proxy for disability, fitting well across disease

types. The addition of self assessed quality of life on the Register illustrates that most participants rate their quality of life in the middle of scale suggesting a certain amount of self adjustment to their disability. EBI however shows despite disease status that most participants have a high degree of independence in most aspects of daily living.

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P393

Multiple sclerosis: brain atrophy and multi-domain computerized cognitive testing - a longitudinal investigation of changes in disease impact relating structure to function

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Background: Cognition is frequently impacted in people with Multiple Sclerosis (PwMS). Traditional evaluation of disease impact in PwMS by EDSS and MRI findings does not adequately identify/quantify cognitive impairment. MRI abnormalities in PwMS include demyelination, neuronal/axonal injury and atrophy. Quantitative analysis of MRI changes in PwMS is not commonly done in routine care. Investigating the relationship between regional atrophy measurements and multi-domain cognitive impairment might provide an important step to improved understanding of MS progression.
Objective: Explore the relationship between multiple individual cognitive domain scores, the number of impaired cognitive domains (#CDI), and the change in these individual approaches to analysis of cognitive function to specific regional brain atrophy measures as they both change over time in PwMS.
Methods: Retrospective review of PwMS who underwent both computerized cognitive screening battery (CAB-NT) at two different dates >1 year apart, and MRI performed < 3 months from each CAB-NT. A repeated measures analysis looked at correlations between 7 CAB-NT domains (global cognitive score, memory, executive function, visual-spatial (Vis), verbal function, attention, information processing speed, motor function, #CDI) with regional atrophy measurements [inter-caudate width -C, third ventricular width -TV, right thalamic width -RT, left thalamic width -LT right thalamic/cerebral peduncle width ratio -RTC, and left thalamic/cerebral peduncle ratio -LTC]. Significance was defined at $p< 0.05$.
Results: PwMS N=59, 81.4% female, average age = 47.3±10.7. VIS with RT p=0.02 and LT p=0.028; #CDI change correlated with change in RT volume p=0.009. Multiple individual cognitive domain scores as well as the change in these same cognitive domain scores individually over time did not correlate with a change in measured brain atrophy.
Conclusions: Change in #CDI is strongly correlated with the longitudinal change in degree of thalamic atrophy in PwMS. VIS is also significantly correlated with thalamic width bilaterally. GCS changes did not significantly correlate with any changes in regional atrophy measurements, supporting the notion that cognition is not a homogenous function and should not be solely measured with a single scale cognitive test. #CDI correlated with changes in thalamic volume, suggesting that change in cognitive network ability reflects both important structural changes and functional milestones.

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Quality of life among patients with multiple sclerosis at a specialized center in Colombia

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Background: Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease which produces multiple symptoms affecting quality of life (QOL). In Colombia, its effect on quality of life at the personal, family and social levels has not been explored extensively.
Objective: To describe the QOL of MS patients based on the domains of the generic instrument created by the World Health Organization (WHO).
Methods: An observational, descriptive study with a group of patients participating in an integral healthcare program from a specialized center between December, 2016 and February 2017. The WHOQOL-BREF instrument was applied, and each domain was scored from 0 to 100. The higher the score, the better the QOL. Likewise, a descriptive analysis of the instrument´s domains and the socio-demographic and clinical features was conducted. Categorical variables appeared as absolute and relative frequencies; continuous variables, in turn, appeared as the median and the interquartile range (IQR). The researchers adhered to the Declaration of Helsinki. Consequently, informed consent was obtained from the participants.
Results: A total of 173 patients were assessed, 80.3% (139) of which were women, with a median age of 43 years (IQR 35-51).

In addition, 39% (68) were single, 35.8% (62) were employed and 30% (52) reported a decrease in their job performance caused by the disease. *Relapsing-remitting MS* was the most prevalent phenotype (82.1%). The median for the disease´s duration was 7 years (IQR 3.6-14). Similarly, 73.4% of the patients experienced no relapse during the last year, and 88.2% received disease modifying treatment. The most frequent clinical manifestations were fatigue (71.7%), sensory symptoms (54.3%) and risk of depression for 90.8% (Zung test). Moreover, 66.5% had an EDSS between 0 and 2, which is indicative of minimal disability. The Physical, Psychological, Social Relationships and Environment domains had median values of 44 (IQR 34.5-56), 69 (IQR 50-81), 56 (IQR 44-94) and 69 (IQR 56-88), respectively. Additionally, the median was 4 (IQR 3-4) for overall QOL, and 3 (IQR 3-4) for satisfaction with health.

Conclusion: as previously reported, physical health domain QOL is the most affected in patients with MS even with low EDSS and no relapses in the previous year; despite having a chronic and potential disabling disease, most patients are satisfied with their overall QOL.

Disclosure

The researchers declared no conflicts of interests

P395

Manual dexterity and computerized cognitive testing in people with multiple sclerosis: motor domain reflects more than just what is in the hand

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Introduction: Cognitive impairment is common in people with multiple sclerosis (PwMS). The Neurotrax computerized multidomain cognitive assessment battery (CAB-NT) motor domain includes both time to plan and carry out movement as well as motor dexterity, inter tap interval/variance. EDSS is traditionally utilized as a measure of disease impact but relies on visible aspects of hand function and does not include cognitive impact as it relates to dexterity. Due lesion load/location variability, visible disability of hand function might be independent of cognitive impairment. Improved analysis of disease impact in PwMS can provide better understanding of perceived/reported. Better measurements that define the role of each aspect of disease impact separately are needed to objectify the trajectory of disability and treatment efficacy in PwMS.

Objectives: Explore the relationship of 9-hole Peg Testing (9hPT) as a measure of manual dexterity to the information obtained by a standardized CAB-NT in PwMS.

Methods: PwMS prospectively underwent standardized CAB-NT, MACFIMS and 9hPT. Correlations between CAB-NT motor scores of a Global Cognitive Summary (GCS) without the motor score (e.g. average of the other 6 domains) and the 9HPT of the dominant hand (DH) as well as individual cognitive domain scores were explored.

Results: 63 PwMS, average age 45+/8.1, 71% female**.** The NT motor domain significantly predicted cognitive impairment as determined by MACFIMS [using oral SDMT] with Area Under Curve AUC of 0.76 and P< 0.0001. Scores of 9hPT DH tracked with CABNT individual domains: GCS p=00096, executive function p=.00065, attention p=.00034, information processing speed p=.0046, motor p=.00071, GoNoGo response time normal p=.00012, Catch Game Time to make 1st move p=.0467.

Conclusions: Global cognitive summary score (excluding motor score) and 9hPT are significantly correlated with CAB-NT motor score. Even after controlling for 9HPT, GCS without motor is still associated with CAB-NT motor score implying that this score is associated with cognition as measured by other domains. For PwMS CAB-NT motor domain is not completely explained by primary motor modalities. Manual dexterity measurements must include understanding of cognitive impact on dexterity as well as non-cognitive aspects to better understand PwMS disability perceptions and impact on ability. Improved analysis of disease impact/progression can provide a path to more informed treatment decisions/timing of change.

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Economic burden

P396

New diagnostic criteria and the costs for treating multiple sclerosis

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Introduction: National healthcare systems are confronted by soaring costs for disease-modifying treatments (DMTs) in multiple sclerosis (MS). We aim to assess whether the introduction of new diagnostic criteria is associated with higher costs for treating MS, as a consequence of early diagnosis and increased number of people with MS eligible to DMTs.
Methods: The present cohort study retrospectively included 2229 RRMS patients (42.1±11.2 years; female 63.3%), followed up from 1997 to 2017 (mean follow-up 8.5±4.7 years). Costs for DMT administration and management were calculated, and referred to each year of observation (annual costs). An interrupted time-series analysis was employed to assess whether the introduction of new diagnostic criteria (2001, 2006, and 2011) had an impact in modifying the average annual patient cost for treatment. The DMT cost variable was log-transformed to reduce data skewness. To account for repeated measurements within each patient over the study period, a mixed-effect log-linear regression model was employed, with the covariates age, gender, disease duration, DMT type, year of treatment start and baseline EDSS included as fixed effects in the model. Interaction terms between time and inclusion of new diagnostic criteria were also included.
Results: Average annual cost per patient was 12356.50±6198.45 euros. We observed a 0.6% increase in the average annual cost per patient after the introduction of 2001 criteria (Coeff=0.006; 95%CI=0.003/0.009; p>0.001), no significant variations after 2006 criteria, and a 0.3% decrease after 2010 criteria (Coeff=-0.003; 95%CI=-0.006/-0.001; p=0.045). When we did not adjust for DMT type, average annual cost per patient increased by 7.9% after 2010 criteria (Coeff=0.079; 95%CI=0.059-0.099; p< 0.001).
Discussion: In RRMS, average annual costs per patient are mainly driven by the introduction of more effective and expensive DMTs in recent years. Costs have otherwise remained stable over time independently from the introduction of new criteria. Profiling RRMS patients towards the most appropriate treatment is needed to control DMT-related costs.

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Cost progression regarding healthcare, sickness absence, and disability pension among people newly diagnosed with MS: a register-based longitudinal study in Sweden estimating cost trajectories in four cohorts of incident MS cases over time

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Background: A chronic disease like multiple sclerosis (MS) involves not only suffering but also different healthcare and social security costs. Sweden has the 2nd highest MS prevalence in Europe, 189 cases/100,000 individuals. Still, most current studies on MS' cost of illness (COI) are based on small, highly selected, survey data. Larger, population-based studies are warranted, focusing on people with MS (PwMS) diagnosed after the introduction of new treatments. In addition, information on trajectories of healthcare, sickness absence (SA) and disability pension (DP) costs, over time, is scarce.
Aim: To explore the healthcare, SA, and DP cost trajectories among PwMS in Sweden over time, among newly diagnosed PwMS, linking the progression of costs with years since MS diagnosis.
Methods: All people living in Sweden, aged 25-60 years at MS diagnosis according to the National Patient Register, were included. Four different cohorts, based on year of MS diagnosis (2006-2009) were followed in nationwide registers prospectively for 5 years, up until 2013, determining 1) direct costs: healthcare utilization and out-of-pocket expenditure (in- and outpatient care), prescribed drugs, and 2) indirect costs: SA and DP. Average per patient costs were calculated in 2017 Swedish Krona (SEK). Descriptive statistics and group-based COI trajectories, stratified by year of MS diagnosis, were computed.
Results: 3272 new PwMS were identified. In all four cohorts, the majority had at least one inpatient stay and one outpatient visit during the follow-up (71% and 99%, respectively). Direct costs increased the 1st year after MS diagnosis; drug costs declined from 2 years after diagnosis and onwards (e.g. for the 2006 cohort, from SEK 35,191 to 60,737 one year after, to SEK 48,861 4 years after). Inpatient and outpatient costs increased again 2 years after diagnosis. While SA costs decreased over time (e.g. from SEK 14,970 to 4036, in the 2006 cohort), DP costs increased, indicating a shift, as disease progressed, from short-term to long-term social security benefits. Overall, direct costs were higher with each 1st year of MS diagnosis, while indirect costs were lower. Results were similar for both women and men in all four cohorts.
Conclusions: A decrease in total costs was observed 5 years after diagnosis; among other explanations, early MS diagnosis, allowing for early treatment, as well as new MS therapies, could lead to slowing disease progression, reducing costs over time.

Disclosure

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study. FY is currently employed by PAREXEL, HG is currently employed part-time by Statfinn & EPID Research, and KK has been employed by Quantify Research AB from October 2015 to February 2018; all three companies are contract research organisations that perform commissioned pharmacoepidemiological studies, and therefore are collaborating with several pharmaceutical companies.

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Analysis of the satisfaction of needs in multiple sclerosis

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Introduction: Measuring the satisfaction of needs is important for understanding the level of service coverage by public or private resources and is useful for service planning and for guiding optimization of care, especially considering an increase in multiple sclerosis (MS) prevalence.
Aim: To examine the satisfaction of health and social care-related needs, in relation to potential associated factors.
Methods: A total of 1,014 people with MS attending neurology outpatient clinics, rehabilitation units and MS Society branches participated in a cross-sectional study carried out in Italy during 2017. A questionnaire was specifically developed by a multi-disciplinary team. Separate logistic regression models (for health and social needs) were performed to determine the association between potential predictors and needs satisfaction.
Results: The study demonstrated significant gaps between perceived needs and service provision. The satisfaction of rehabilitation needs was more likely in subjects with the highest level of education (university degree vs. primary school) (OR=1.73, p=0.015). The geographic area of residence negatively influenced the satisfaction of needs related to psychological support (OR=0.55, p=0.043), technical aids (OR=0.15, p< 0.001), medications (OR=0.41, p=0.050) and psychological support (OR=0.55, p=0.043) (central and southern vs. northern Italy). Satisfying a need for technical aids was less probable for subjects currently employed vs. unemployed (OR=0.24, p=0.017). Transportation needs were less likely to be satisfied in subjects who were married (OR=0.43, p< 0.001). Satisfaction of financial support was less frequent for subjects with a higher level of disability (OR=2.56, p=0.031). Personal assistance was less likely to be satisfied in older subjects and those with a longer disease duration (OR=1.02, p=0.041 and OR=1.02, p=0.028, respectively). Career guidance was more frequently a met need for subjects who were currently employed (OR=3.34, p=0.013). Workplace adaptation was significantly less likely to be satisfied for subjects living in central vs. northern Italy (OR=0.15, p=0.018).
Conclusion: The type and relevance of health and social-related needs emphasize the necessity for an interdisciplinary approach to MS, essential for patient-centered care. The results of this study also provide the basis for advocacy priorities related to the rights of people with MS.

Disclosure

Ponzio M, Tacchino A, Brichetto G, Vaccaro C, Battaglia MA, and Messmer Uccelli M have no conflicts of interest to declare.

Neuro-ophthalmology

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Is there a relationship between oculomotor fatigability and perceived fatigue in multiple sclerosis?

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Introduction: In patients suffering from multiple sclerosis (MS), fatigue is one of the most common and disabling symptoms of disease. The exact pathophysiological mechanisms are not clear and objective measures to quantify and monitor fatigue and fatigability in MS are lacking, which makes targeted treatment difficult.
Objectives: This prospective study investigated if repeated saccadic eye movements enable measurement of oculomotor fatigability and can reflect perceived fatigue in MS.
Methods: A validated standardized infrared oculography protocol was used for quantifying saccades in MS patients and healthy controls (HC), which included a first pro-saccadic task (FPT) and a repeated pro-saccadic task (RPT). The protocol was designed to induce oculomotor fatigability between FPT and RPT. Saccadic peak velocity, latency and gain were calculated in both tasks. Fatigability was assessed by subtracting the parameters of RPT by those of FPT. The neurological fatigue index (NFI) sum score was used to assess perceived fatigue. The relationship between saccadic parameters and NFI sum score in MS patients was analysed using a linear regression model, adjusted for sex and disease duration.
Results: This cross-sectional study included 181 MS patients and 58 HC. The MS patients had a mean disease duration of 18.5 (±10.2) years. From FPT to RPT, there was a significant increase in latency and decrease in peak velocity and gain observed in both the HC and MS group, but changes were most prominent in the MS group (differences between tasks in MS group: latency 9.6 ±20.7 ms, peak velocity -18.4 ±21.6 deg/s, gain -0.06 ±0.20, p< 0.001). Latency in both FPT and RPT was related to NFI sum scores (β 0.03, p=0.05 and β 0.04, p=0.01, respectively). There was no relationship between peak velocity and gain of both tasks and the fatigability parameters with the NFI sum scores.
Conclusions: This study demonstrates significant oculomotor fatigability in patients with MS. There was however no simple relationship between objective oculomotor fatigability and subjective fatigue perception. This suggest that fatigability and fatigue in MS should be considered as different concepts which should be taken into account in patient care and MS treatment trials.

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Quantification of pupillary light reflex abnormalities in patients with neuromyelitis optica spectrum disorder and multiple sclerosis using automated infrared pupillometry

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Introduction: Both neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS) patients experience optic neuritis (ON) attacks and also a degree of pupillary light reflex abnormalities. NMOSD are characterized by devastating optic neuritis attacks causing more structural damage and visual impairment than in MS.
Objective: To differentiate pupillary response variation in RRMS from NMOSD and to evaluate the potential usefulness of manual quantitative pupillometry for assessing the magnitude of pupillary response alteration.
Methods: In this cross-sectional study, we investigated pupillometry parameters including neurological pupil index (NPi), pupil size (PS), minimum size of pupil (MinPS), percentage change of pupil size (CH), Constriction Velocity (CV), Maximum of Constriction Velocity (MCV), Dilation Velocity (DV) and latency (LAT) from 315 subjects(182 RRMS, 23 NMOSD, 110 Healthy Control). Regarding the observed association of age with disease progression in the sample population and pupillary responses, partial correlations for each group while holding effect of age constant were run. As optic neuritis may play a significant role in pupillary response, subclassification according to ON state of eyes was also applied. Finally, linear regression was run to model the relation between EDSS and pupillary parameters.
Results: EDSS was partially correlated with almost all pupillary variables. Different groups indicated a statistically significant increase in Latency with r=0.0.468, p< 0.005 for NMOSD and r=0.171, p< 0.005 for RRMS group, and further indicated a decrease for almost all other variables such as CH (r=-0.69, p< 0.001, NMOSD; r=-0.16, p< 0.005, RRMS), NPI (r=-0.49, p< 0.001, NMOSD; r=-0.21, p< 0.001 RRMS) and MCV (r=-0.59, p< 0.005, NMOSD; r=-0.31, p=0.56, RRMS). The linear regression also revealed that age might play the role of suppressor mediator in NPI-EDSS relation.
Conclusions: The results revealed that NMOSD and RRMS exacerbate the pupillary response in line with and similar to the aging process. The degree of this exacerbation might associate to the particular pathophysiologic process of diseases as indicated by results. Furthermore, pupillary light response are affected even in the absence of ON, and the alteration of pupillary response may be expressed in terms of EDSS. These observations may set the stage for applying very simple and available methods of pupillometry in MS or NMOSD, as a routine assessment.

Disclosure

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P401

Critical flicker fusion threshold test in MS population - is it a viable way of effective and quick monitoring of visual function?

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Introduction: Opticus neuritis (ON) is a frequent manifestation of multiple sclerosis (MS). Determining threshold frequency of a flickering light (critical flicker fusion, CFF) allows early detection of visual impairment due to demyelination, and thus might play a role in substantiating the suspicion of an incipient ON, enabling early treatment-modification.
Aim and objectives: The aim of this study is to correlate CFF thresholds with visual acuity/contrast sensitivity in a population of MS patients with and without ON. Furthermore, CFF will be correlated to loss of retinal neurons, as quantified by inner retinal layer thickness using optical coherence tomography (OCT).
Methods: In this pilot study, 114 patients with MS and with prior optic neuritis (MS+ON; n=40) or without prior optic neuritis (MS-ON; n=74) and 89 controls (N) were tested in the Multilple Sclerosis Clinic of Aalborg University Hospital, Denmark, using several smartphone visual function tests (Landolt C acuity, Landolt C contrast sensitivity, and CFF). Testing was performed with the patient wearing their glasses at a distance of 0.4 meters.

The results were analyzed utilising Kruskal Wallis test with pairwise multiple comparisons using Dunn's method.
Results: Each smartphone test took approximately 15 seconds to complete and was intuitive enough that patients were able to immediately perform the task. Findings showed that CFF threshold values were significantly reduced in MS patients with or without previous ON compared to controls. As the only visual test, CFF showed no significant difference between MS-ON and MS+ON.
Statistical Comparison of Smartphone Visual Function Tests in MS Patients and Normals
Contrast Sensitivity
N vs. MS-ON P = 0,0006*
N vs. MS+ON P< 0,0001*
MS-ON vs. MS+ON P< 0,0066*
Visual Acuity
N vs. MS-ON P = 0,016*
N vs. MS+ON P < 0,0001*
MS-ON vs. MS+ON P = 0,0005*
CFF 15 Hz
N vs. MS-ON P = 0,0011*
N vs. MS+ON P = 0,0017*
MS-ON vs. MS+ON P = 0,0331
CFF 30 Hz
N vs. MS-ON P = 0,0001*
N vs. MS+ON P < 0,0001*
MS-ON vs. MS+ON P = 0,1213
Conclusion: Critical flicker fusion, a test of visual speed of conduction, provided some of the greatest discrimination between eyes of MS patients with or without a previous diagnosis of ON compared to normal eyes. This finding motivates the importance of using a behavioral visual test of visual conduction speed, such as critical flicker fusion, which is resistant to optical blur, to monitor various causes of visual dysfunction including MS.

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Visual evoked potential in EAE and toxic demyelination: a pre-clinical model for remyelination efficacy that is predictive of human clinical trials

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Background: Therapies with potential to remyelinate the central nervous system constitute one of the most promising therapeutic developments in the pipeline to treat multiple sclerosis. We completed the first positive double-blind placebo-controlled human trial for a remyelinating therapy in MS using visual evoked potentials(VEP) as an outcome. We unequivocally demonstrated improvement in longstanding latency delay on VEP for patients during the period on treatment despite the chronicity of injury. A full understanding of visual system injury in animals could enhance the ready and robust adaptation of these techniques for additional human clinical trials - and the appropriate interpretation of trial results.
Methods: We obtained VEP from C57BL/6J mice using an Espion Diagnosys system (Diagnosys LLC, Littleton,MA). We induced EAE with myelin oligodendrocyte glycoprotein 35-55 in female 8-week-old mice using adjuvant-injected mice as controls. Toxic demyelination was induced with 5 weeks of cuprizone diet. IHC for CASPR was performed on optic nerve sections. Electron microscopy of mice optic nerves was performed using a JEOL1200EXII transmission electron microscope.
Results: We found that prolongation of VEP latency precedes clinical onset of disease in EAE. VEP latency is delayed from the 5th day after immunization. N1 delay increase till day 18, with a consequent conduction improvement. Quantification of optic nerve IHC for CASPR in EAE mice mirrors the VEP delay, showing the histopathologic substrate of N1 delay. Clemastine is effective in improving VEP in EAE 7days post immunization(p=0.0002), maintaining its effect at day 21(p=0.018)and day 28(p=0.03). Cuprizone diet also provokes N1 latency delay(p=0.003). Clemastine is effective in enhancing remyelination, more quickly than expected after suspending the toxic demyelinating diet(p=0.03). Optic nerve EM showed reduced unmyelinated axons and increased remyelinating axons in mice treated with Clemastine. CASPR staining of optic nerves shows a higher number of paranodes in treated mice.
Conclusions: Here, we show that VEP latency correlates with quantitative measures of myelin from histopathology in mouse models of both inflammatory and chemical visual pathway demyelination. Furthermore, VEP latency delay improves after treatment with a tool remyelinating compound in both models, mirroring quantitative/qualitative myelin assessment and providing support for use of this approach for screening other molecules

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New, diagnostic flicker test for optic neuritis shows changes in response following disease onset

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Introduction: Optic neuritis (ON) is primarily diagnosed clinically, but diagnosis may be complicated especially in the case of recurrent disease.
Objectives/aims: We present here the results of a new, digital flicker test. Our aim was to examine the diagnostic potential in ON and the pattern of the flicker test response during the course of ON and how this compared to that of other, commonly used diagnostic tests for ON.
Methods: The flicker test is a psychophysical test of the subjective brightness of a flickering field (0-60 Hz), the pathological response is a darkness enhancement(DE) at medial frequencies. DE was expressed a quantitative covariate. Standard visual evoked potentials (VEP) were recorded using 9 mm checkers. Optic coherence tomography (OCT) was performed on Cirrhus HD-OCT providing thickness measurements of both retinal nerve fibre layer (RNFL) and ganglion cell layer/ inner plexiform layer (GCL/IPL). 122 consecutively referred, untreated ON patients and 27 age-matched, healthy controls were examined. Patients were examined within 31 days. Follow up measurements were done at 3 and 6 months following ON onset.
Results: In acute ON 113 of 122 patients showed abnormal DFT (sensitivity 93%). The flicker test was performed 17.0 days (SD:10.5) following ON onset. During follow up the mean flicker test variable had improved by 43 % at 3 months and by 60 % at 6 months following ON onset. An abnormal flicker test response was shown in 67 % at 3 months and in 55 % at 6 months. VEP showed abnormal latency prolongation in 91% at first visit, 82% by 3 months and 78 % by 6 months. GCL/IPL thinning was shown in 29 % of ON patients at first visit (within 31 days), in 63 % at 3 months and 69 % at 6 months. RNFL thinning was apparent in 46 % by 3 months and 66 % by 6 months. Temporal RNFL thinning was shown 55% at 3 months and 70 % at 6 months.
Conclusion: We present a sensitive and easy-to-use new test for acute ON. Due to a more pronounced dynamic response than VEP following ON onset, and a higher sensitivity in the acute phase than OCT measurements, the flicker test may be of diagnostic value including in the case of recurrent ON.

Disclosure

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P405

Looking for new markers of therapeutic response: a functional structural study of the retina in multiple sclerosis

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Background: Development of markers for therapy response is a priority for therapeutic optimization in multiple sclerosis (MS). The retina represents an ideal model to investigate effects of DMTs using non-invasive technologies as multifocal electroretinography (mfERG) and optical coherence tomography (OCT), since it may mirror the inflammatory and neurodegenerative processes of MS. After DMT administration, functional changes may precede structural ones so neurophysiological retinal response deserves further evaluation.
Aim: To evaluate repeatability of first-kernel mfERG response and relationships between functional and structural retinal measures in relapsing remitting MS (RRMS).

Methods: RRMS patients who agreed to two visits before and 12 months after starting teriflunomide were evaluated using monocular 2.5% low contrast letter acuity (LCLA), OCT, mfERG, and EDSS. We performed baseline intra-session test-retest for mfERG. Analyses were done using a mixed linear effect models, with prior history of optic neuritis (ON) and age as covariates.
Results: 18 subjects (78% women; median 45 years), mildly disabled (median EDSS=2) were available for baseline analyses. Median (P25-P75) for average first-kernel responses: 5.8 (4.3-8.5) nV/deg^2 for N1 amplitude; 25.6 (24.6-26.6) ms for N1 peak time; 15.9 (13.1-21.3) nV/deg^2 for P1 amplitude; 45.2 (44.3-46.2) ms for P1 peak time. Intra-session changes were higher for amplitudes (N1: 34.7%; P1: 23.7%) than for peak times (N1: 2.3%; P1:3.8%). We did not find any association between ganglion cell plus inner plexiform layer (GCIPL) and thicknesses or first-kernel responses for bipolar cells (BP) and photoreceptors (PRL). We found a linear association between outer plexiform layer (OPL) thickness (synapsis between BP and PRL) and N1 amplitude (beta=0.846; p-value=0.004) but not N1 peak time (beta=-0.196 p-value=0.195). We did not find other associations between structural and mfERG markers of BP and PRL. GCIPL thickness (beta=0.828) was the only significant predictor for 2.5% LCLA.
Conclusion: Analysis of peak times, rather than amplitudes, is more reliable for mfERG longitudinal assessments. Absence of association between inner and outer retinal structures suggest that there is either an absence or a negligible retrograde trans-synaptic degeneration after ON. The significant structural-functional relationship between synapsis of bipolar cells and photoreceptors and N1 deserves further evaluation.

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P406

Corticotropin treatment of acute optic neuritis improves low contrast visual acuity in some asymptomatic eyes: repair of subclinical MS lesions

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Corticotropin is an approved treatment for acute optic neuritis as a presenting symptom of remitting-relapsing multiple sclerosis [RRMS] and during the course of RRMS. While the majority of patients recover high contrast visual acuity [HCVA] either spontaneously or with treatment, symptomatic deficits in low contrast visual acuity [LCVA] may persist.
25 patients with a clinically isolated syndrome of acute unilateral demyelinating optic neuritis were enrolled in an open label study within 14 days of symptom onset.
All participants were treated with subcutaneous corticotropin: 5 days of 80 IU; 10 days at 40 IU.
Participants underwent neuro-ophthalmologic exams seven times during the study: baseline, 4-7 days after the initiation of treatment, 6-10 days after completion of treatment, and then one month, three months, six months, and one year after treatment.
HCVA, 1.25% LCVA and optical coherence tomography [OCT] were evaluated at each visit using strict clinical trial protocols.
Significant improvement in LCVA in the clinically unaffected eye for seven subjects was the most unexpected, intriguing result.
LCVA improved in both the study eye and the non-study eye. Improvement in the non-study eye occurred over the 400 days of observation, while the study eye appears to improve rapidly in the first 50 days, and then continues to improve at a slower pace for the rest of the study.
This difference between the baseline and last observation for LCVA at 7 letters exceeds the threshold of a clinically significant change for clinical trials with wet age related macular degeneration, diabetic retinopathy, and retinal venous occlusive disease and the baseline variability in this study. All 7 eyes had normal HCVA in the "non-study" eye. In this small series, the retinal fiber layer and macular OCTs remained stable.
While it is has been known for years that clinically unaffected eyes may demonstrate increased latencies with evoked potentials, this study is the first to address longitudinal LCVA following corticotropin treatment.
The sustained improvement in the asymptomatic "non-study" eye suggests that corticotropin exerts an anti-inflammatory effect upon visual function. Larger randomized masked studies will be necessary to confirm these results.

Disclosure
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Adam A deBusk, DO - Mallinckrodt Pharmaceuticals

Comorbidity

P407
Comparative effect of tobacco versus non-tobacco use on disease outcomes and discontinuation of oral disease modifying therapies in clinical practice

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Objective: To compare disease outcomes in tobacco versus non-tobacco users treated with oral disease modifying therapies (DMT) in clinical practice at 24-month follow-up.
Background: Numerous studies demonstrated that tobacco exposure is a risk factor for early disability. However, studies evaluating the relationship between tobacco and multiple sclerosis (MS) disease activity and DMT persistence have yielded conflicting results. We sought to address this issue from routine clinical practice.
Methods: 659 MS patients using either dimethyl fumarate (DMF) or fingolimod (FTY) were followed for 24 months in a large academic MS center and were stratified by tobacco use. DMT discontinuation and measures of disease activity were assessed using propensity score (PS) weighting. Covariates used in the PS model included demographics and baseline clinical and MRI characteristics within 12 months of DMT initiation. Outcome measures included annualized relapse rate (ARR), and the proportions with discontinuation, new brain MRI lesions, absence of disease activity (defined as freedom from clinical relapses and MRI activity), and depression (PHQ-9 score $\geq$10) by 24 months on-treatment. After PS adjustment, odds ratio estimates were calculated as tobacco vs non-tobacco use. Based on clinical experience, we hypothesized DMF tobacco users would be more at risk of breakthrough disease.
Results: 164 tobacco users (DMF n=101; FTY n=63) and 495 non-tobacco users (DMF n=294; FTY n=201) were identified. PS weighting showed excellent covariate balance. By 24 months, tobacco (39.4%) and non-tobacco (34.4%) users were equally likely to discontinue their respective DMT [OR=1.17, 95% CI (0.79, 1.75)]. Tobacco users had decreased odds of absence of disease activity [OR=0.61, 95% CI (0.44, 0.83)]. Similarly, tobacco users trended towards a higher ARR [OR=1.38, 95% CI (0.97, 1.96)] and proportion with new gadolinium-enhancing lesions [OR=1.39, 95% CI (0.80, 2.60)], new T2 lesions [OR=1.62, 95% CI (0.94, 2.79)], and depression [OR=1.38, 95% CI (0.84, 2.27)], but did not reach statistical significance. Disease activity endpoints were not driven by either DMT alone.
Conclusions: In our study, tobacco users were less likely to achieve absence of disease activity compared to non-tobacco users in a population of patients treated with oral DMTs. This finding suggests that tobacco is a negative risk factor for inflammatory disease activity and warrants further exploration with larger studies.

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P408
Multiple sclerosis is associated with an increased risk of acute myocardial infarction

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Background: Cardiovascular diseases, including ischemic heart disease, are the leading cause of death in the general North American population. In some chronic immune-mediated diseases, including psoriasis and rheumatoid arthritis, there is an increased risk of ischemic heart disease as compared to the general population which is not fully explained by major cardiovascular risk factors, possibly reflecting a role of inflammation.
Objective: To examine the risk of incident acute myocardial infarction (AMI) in the multiple sclerosis (MS) population as compared to a matched population without MS, controlling for traditional vascular risk factors.
Methods: We conducted a retrospective matched cohort study using population-based administrative (health claims) data in British Columbia and Manitoba, Canada over the period 1984-2016. We applied a validated case definition to identify incident cases of MS in each province. For each case we identified up to 5

controls without MS matched on age, sex and region. We compared the incidence of AMI between the MS cases and matched controls using incidence rate ratios (IRR). We used Cox proportional hazards regression to compare the risk of AMI between cases and controls, stratifying on birth year, using age as the time scale, and adjusting for sex, socioeconomic status, diabetes, hypertension, and hyperlipidemia. We report hazard ratios (HR) and 95% confidence intervals (95%CI). We pooled findings across provinces using meta-analysis, and assessed the sensitivity of our findings to unmeasured confounding such as smoking status using the E-value.

Results: In total we identified 14,565 persons with MS and 72,825 matched controls. Women comprised 73% of the cohorts. The crude incidence of AMI per 100,000 population was 146.2 (95%CI: 129.0-163.5) in the MS population and 128.8 (95%CI: 121.8-135.8) in the matched population. After age-standardization, the incidence of AMI was higher in the MS population than in the matched population (IRR 1.18; 95%CI: 1.03-1.36). After adjustment, the hazard (risk) of AMI was 60% higher in the MS population than in the matched population (HR 1.62; 95%CI: 1.39-1.90). The observed HR of 1.62 could only be explained away by an unmeasured confounder that was associated with both MS and AMI by a risk ratio of 2.62-fold, which is unlikely.

Conclusion: The risk of AMI is elevated in MS, and this is not fully accounted for by traditional vascular risk factors.

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P409

Abdominal obesity is associated with more severe disability in a large population of people with multiple sclerosis

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Background: Metabolic syndrome and related vascular disorders such as diabetes and hyperlipidemia are overrepresented in people with multiple sclerosis (MS) and are associated with adverse MS outcomes. Excess visceral adiposity, approximated using waist circumference (WC),is a strong risk factor for metabolic comorbidity in the general population and is associated with poorer outcomes in other neurologic diseases. Whether abdominal obesity is associated with disability and symptom severity in people with MS is unknown.

Objective: To evaluate the association between abdominal obesity as measured by WC and disease characteristics in a large population of people with MS.

Methods: As a part of the Fall 2017 semi-annual survey, North American Research Committee on MS (NARCOMS) registry participants reported height and weight (used to calculate body mass index [BMI] as kg/m^2) and were mailed a tape measure with detailed instructions on how to measure WC. We considered WC as a continuous variable and used WC cut-points derived from the abdominal obesity criteria for the metabolic syndrome (men: WC≥102 cm; women: WC≥89 cm). We assessed the association between WC and disability status, as measured using Patient-determined Disease Steps (PDDS), and symptom severity (using Performance Scales© and NARCOMS depression and pain scales) using multinomial models (comparing moderate vs. mild and severe vs. mild disability or symptom severity), adjusting for age, sex, income, smoking status, disease-modifying therapy, and symptom duration.

Results: Of the 6231 responders with MS, 4309 (69%) reported WC in addition to BMI. Of these, 52% meet criteria for the abdominal obesity component of metabolic syndrome (men: WC≥102 cm; women: WC≥89 cm). In multivariable models adjusting for BMI, WC meeting this criterion was independently associated with a 61% increased odds of severe vs. mild disability (OR: 1.61; 95% CI: 1.30-2.01). In stratified models among normal weight individuals (BMI: 18.5-25), a 5 cm increase in WC was associated with 24% increased odds of severe vs. mild disability (OR: 1.24; 95%CI: 1.15-1.35). WC was not independently associated with depression, fatigue or pain severity in models adjusted for BMI.

Conclusions: Increased WC is associated with more prevalent severe disability, even after adjusting for overall obesity level. Longitudinal studies should evaluate whether excess abdominal obesity is a predictor of future changes in disability and symptom severity.

Disclosure

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P410

Impact of quality-driven interventions on screening for cognitive impairment and depression in multiple sclerosis (MS) patients

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Background: Through baseline assessments in a quality improvement (QI) initiative conducted in 2 large specialty MS clinics, we identified needs for improving approaches to screening for cognitive impairment (CI) and depression, and for making referrals to specialists.
Objective: Assess the impact of targeted quality-driven interventions on rates of CI and depression screening and referrals among MS patients.
Methods: The cohort comprised neurologists and clinical teams in 2 diverse, large specialty MS clinics in the Southeastern U.S. At baseline, we retrospectively reviewed consecutive charts of MS patients in each clinic. In a grand rounds format, the neurology teams then received feedback on their baseline rates of CI and depression screening, use of validated screening tools, and referrals to specialists. The teams developed action plans to improve screening and referral processes. Six months after the interventions and implementation of action plans, we retrospectively reviewed MS patient charts for the follow-up period. Chi-square tests assessed the significance of baseline and post-intervention differences in the study measures.
Results: The baseline (n = 300) and post-intervention (n= 300) patient samples were similar in median age (52 years), age at MS diagnosis (38 years), gender (77% female), and presence of ≥ 1 new or enhancing lesions in the previous 24 months (15%). From the baseline to post-intervention period, rates of chart documentation increased for CI screening (52% to 67%, $p < .001$); use of a validated CI screening tools (2% to 23%, $p < .0001$); and patient referral to specialists (28% to 55%, $p < .0001$). Post-intervention rates were also higher for depression screening (63% to 73%, $p < .01$); use of validated depression screening tools (4% to 10%, $p < .01$); patient referral to specialists (25% to 59%, $p < .0001$); and detection of clinical depression (42% to 54%, $p < .01$).
Conclusion: In 2 large specialty MS clinics in the U.S., targeted quality-driven interventions were associated with increased rates of CI and depression screening and referrals to specialists. These findings may inform the design and implementation of scalable QI initiatives to overcome common barriers in screening and referrals for CI and depression, and to thereby reduce the negative effects of these comorbidities on quality of life and function in patients with MS.

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Impact of comorbidity and DMT use by DMT group on quality of life in participants in the Pacific Northwest MS Registry

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Introduction: Among people with MS, comorbid conditions can diminish quality of life (QoL). Disease modifying therapy (DMT) for MS may moderate this effect.The relationship between DMT type and comorbidities, and its impact on QoL, has not been studied to date.
Aims: Determine the impact of DMT types and comorbidities on QoL in participants in the Pacific Northwest Multiple Sclerosis Registry in the USA.
Methods: The study used self-reported data from participants registering between 2011 and 2016. Comorbidities included cardiovascular disease (CVD), diabetes, cancer, depression, smoking, and respiratory, thyroid, and gastrointestinal disease. QoL

was assessed using physical and psychological scores from the Multiple Sclerosis Impact Scale. DMT users were grouped by self- injectable therapy (beta interferons, glatiramer acetate), oral therapy (teriflunomide, dimethyl fumarate, and fingolimod), and infusion (IV) therapy (alemtuzumab, rituximab, natalizumab, and ocrelizumab). Those not on a DMT were excluded. Multiple linear regression was used to analyse the impact of comorbidity and DMT type on physical and psychological QoL, adjusting for participant characteristics. Interactions between DMT type and each comorbidity were tested and post-hoc comparisons between DMT types for participants with the comorbidity were analysed.

Results: Of 908 participants included, 55.3% (n=502) were on self-injectable 34.1% (n=310) on oral, and 10.6% (n=96) on IV therapy. Physical QoL scores were significantly worse for those with CVD (regression coefficient [B]=1.86, *P*=0.006) and depression (B=2.94, *P*≤0.001), and suggestive for respiratory disease (B=1.67, *P*=0.051). Psychological QoL scores were significantly worse for depression (B=4.40, *P*< 0.001) and suggestive for diabetes (B=1.32, *P*=0.078). There was a trend toward significance for interactions between DMT type and diabetes (*P*=0.069) for physical score, and DMT type and CVD (*P*=0.061), cancer (*P*=0.079), and diabetes (*P*=0.061) for psychological score. Among participants with comorbidities, post-hoc analyses showed no differences by DMT type for QoL scores.

Conclusion: There was suggestive evidence for moderating effects of DMT type on the impact of comorbidities on QoL, but scores did not differ significantly by DMT type for those with comorbidities. Cohort sizes may have impacted results. These results emphasise the need for clinicians to maintain awareness of the overriding impact of comorbidities on QoL of MS patients.

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P412

Vascular disease risk factors and MS progression: a study of brain metabolism

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Introduction: There is growing evidence that vascular disease risk factors (VDRF), such as hyperlipidemia, hypertension, obesity, diabetes, and heart disease, can significantly increase the risk of disability progression in MS. Recent research has shown MS subjects with one or more VDRF at diagnosis required unilateral assistance to walk at earlier times than those without any VDRF. There also appeared to be a dose-response relationship between VDRF and MS disability with presence of a single VDRF increasing the risk of early gait disability by 51% and presence of 2 of these conditions increasing the risk by 228%.

Objectives: To study how VDRF affect cerebral blood flow and brain metabolism measured by DCE MRI and ^{31}P magnetic resonance spectroscopy and imaging (MRSI) in people with MS.

Methods: This is a 3-year long observational study with a single-site, mixed design (cross sectional and longitudinal) with two arms. The study includes prospective brain MRI and clinical disease progression outcome measurements. MRI data is collected at baseline, 12, 24 and 36 months. We enrolled a total of 60 MS subjects consisting of 35 subjects with VDRF (VDRFP) and 25 subjects without VDRF (VDRFN).

Aims: The outcome measures include changes in the VDRFP and VDRFN groups in the following: 1) cerebral blood flow and blood volume detected by 7T MRI and high energy phosphate metabolites in cerebral gray matter (GM) assessed by ^{31}P 7T magnetic resonance spectroscopic imaging (MRSI), 2) brain atrophy, 3) clinical impairment, disability, and quality of life.

Results: We preformed cross-sectional analyses of baseline data. Average age of the 50 subjects, whose MR data were analyzed, was 54.5 years (SD:7.5); 72% female). 28 subjects have VDRFP (average age 56.4years (SD:6.9); 82% female) and 22 subjects were VDRFN (average age 52.2 years (SD:7.8); 59% female). A volume of interest in parietal brain region was analyzed for changes in phosphate metabolites. Adenosine triphosphate (ATP) to total phosphate signal ratio is decreased in VDRFP subjects by 4.5% (P< 0.05). Brain parenchymal volume (normalized for head size) was assessed using SIENAX [1]. VDRFP female subjects showed a 3.9% decrease in normalized brain tissue (P=0.02, N1=13,N2=23,one-tailed Student's t-test).

Conclusions: Our preliminary results support the view of an impaired metabolic state in VDRFP MS subjects that may potentially increase risk of neurodegeneration.

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Arterial hypertension in patients with multiple sclerosis as a significant risk factor of disability progression

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Background: Recent studies have demonstrated the negative effect of vascular disease on disability progression in multiple sclerosis (MS). We analyzed the effect of arterial hypertension

(AH) on the rate of disability progression in relapsing-remitting MS (RRMS).

Materials: 595 subjects with RRMS entered the study. Retrospective data from the database of St. Petersburg City center for MS (CCMS) included the patients evaluated every 3 months for 2 to 6 years. Confirmed AH data included i) in-patient questioning, ii) BP and physical examination monitoring data and iii) health care services medical records.

EDSS was calculated by neurologists qualified to evaluate EDSS. Statistical analysis is performed with the program SAS 9.4 considering sex and age data as co-factors.

Results: AH was confirmed in 16.3% (97/595) RRMS patients. In AH(+) patients and AH(-) the period of time of EDSS progression to 3.0, 4.0 and 6.0 was documented. Using the Kaplan-Meier analysis, AH (+) patients revealed significantly more short time to reach established levels of disability compared to those AH(-), i.e. EDSS 3.0 (p 0.002), 4.0 (p 0.02) and 6.0 (p 0.103). These results are confirmed by Cox regression analysis. The risk of progression to score 3.0, 4.0 and 6.0 was higher in AH(+) vs AH(-) patients: RR 1.4, (p 0.016, CI 95% 1.06-1.88), RR 1.74 (p 0.013, CI 95% 1, 12-2.69), and RR 3.4 (p 0.03, CI 95% 1.12-10.48), respectively.

EDSS score progression at 5 and 10 years since the time MS diagnosis was confirmed, using the Wilcoxon and Mann-Whitney test revealed the disability in the AH(+) group increased more significantly than in the group AH(-).

Conclusions: AH appeared to be an independent factor in accelerating the disability progression in patients with RRMS. AH is associated with a higher risk of disability and reaching higher disability score in a shorter time.

Disclosure

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RLS is an important and frequent cause of depression and anxiety in patients with MS: striking results of the 'RELOMS-T'

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Introduction: Anxiety and depression are common psychological comorbidities that impact the quality of life of patients with multiple sclerosis(PWMS). Similarly, significantly greater anxiety and depression symptoms were observed among patients with restless legs syndrome(RLS) than in the control subjects. Many studies have assessed the relationship of depression and anxiety with MS, as well as with RLS. Nonetheless, there has not been an effort to show how the prevalence of RLS affects both depression and anxiety in PwMS. Furthermore, considering the comorbidities that accompany MS, RLS is one of the most common.

Objectives: We aimed to investigate the interaction between anxiety/depression and RLS in PwMS in a nation-wide, multicentre, prospective and cross-sectional survey.

Methods: Data were drawn from the Restless Legs of Multiple Sclerosis-Turkey project (RELOMS-T) which is designed to represent all of the PwMS throughout the country. All of the participants were assessed by using demographic and clinical parameters along with the Hamilton Anxiety and Hamilton Depression Scales (HAM-A and HAM-D) to explore the psychiatric burden of MS and RLS coexistence.

Results: Of the 1068 participants 173 (16,2%) experienced RLS [RLS(+)] and 895(83,8%) did not [RLS(-)]. The mean (SD) anxiety score of RLS(+) and RLS(-) patients were 12,7 (SD:4,5) and 7,9 (SD:3,5) respectively; and depression 22,4 (SD:6,8) and 19,6 (SD:5,8). The mean scores on HAM-A and HAM-D and the two subscales of HAM-A assessing the psychic and somatic functioning were found to be significantly higher in RLS (+) subjects than those of the RLS (-) ($p < 0.001$ for all variables). Our data also seem to provide initial evidence of a correlation between the severity of RLS and of anxiety and depression symptoms among PwMS.

Conclusions: This study is the first to examine the effects of the combination of the two neurological conditions with depression and anxiety as well as comparing their prevalence and severity to each other. According to our data the presence of RLS in PwMS may increase the occurrence of both anxiety and depression symptoms and this increase correlates with the severity of RLS. Treatment of RLS in PwMS could possibly reduce symptoms of psychiatric comorbidities originating from RLS. Thus, awareness of MS specialists about the psychiatric burden of this coexistence is important to improve the quality of life in PwMS.

Disclosure

Nothing to disclose

Pathology

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Neuroinflammation causes changes to the nodes of Ranvier in multiple sclerosis normal appearing white matter

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Introduction: In addition to the focal demyelinating lesions that are characteristic of multiple sclerosis (MS), both imaging and neuropathological analyses have demonstrated the presence of diffuse pathology in both white and grey matter, including changes to the structure of nodes of Ranvier in the normal appearing white matter (NAWM). The presence of axo-glial glial junctions of the myelin end loops and the proper clustering of sodium channels (Nav) at the node and potassium channels (Kv1.2) at the juxtaparanode are crucial for fast action potential conduction.
Aims: Study the structural and functional consequences of nodal pathology and the role of inflammation in them.
Methods: We have examined the spatial expression of Caspr1, NF155, Nav, Kv1.2 and SMI32 in NAWM areas from post-mortem progressive MS brains (n=20 cases comprising 34 blocks) compared to non-neurological controls (n=10 cases comprising 16 blocks). To determine axo-glial abnormalities, intensity profiles were measured for each nodal parameter. This axo-geometrical data was then integrated into an axon computational model, which was developed with NEURON incorporating published electron-microscopy data from human and macaque brains. To test our hypothesis, rats were injected into the cerebral subarachnoid space with lentiviral vectors for lymphotoxin-α and interferon-γ and nodal changes examined 3 months later.
Results: The paranodes in the MS NAWM tissue were 21.7% longer on average than in the control, and associated with stressed axons and microglia. In addition, we found a higher proportion of axons in MS NAWM with Kv 1.2 channels dislocated towards the paranode, which correlated with paranodal elongation. When these changes were inserted into the computational model, assuming that the observed increment of paranodal length corresponded to an increment in the peri-axonal space, we observed an exponential decrease in conduction velocity and an increase in metabolic cost as the peri-axonal space increases. Furthermore, we predicted a potential conduction failure when the peri-axonal is increased up to a certain threshold in axons less than 1μm of diameter. The same changes in paranodal length and Kv channel dislocation were observed in the corpus callosum of rats with meningeal inflammation and chronic microglial activation.
Conclusions: These results point to microglia/astrocyte secretion of cytokines, glutamate and ROS as possible factors that could trigger these nodal changes.

Disclosure

"Name: nothing to disclose"

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Differential expression of microglial TMEM119 and P2RY12 in white- versus grey-matter multiple sclerosis lesions; does the presence of leukocytes determine microglial responsivity?

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White-matter demyelination in Multiple Sclerosis (MS) is accompanied by a dysfunctional blood-brain-barrier leading to infiltration of leukocytes into the central nervous system (CNS). In post-mortem material of MS patients, these leukocytes and additional amoeboid-shaped, activated, microglia are present in white-matter lesions (WMLs). However, grey-matter lesions (GMLs) are almost devoid of infiltrating leukocytes and show only a modest microglial reaction. This clear difference in microglial reaction between WMLs and GMLs has raised questions about the responsivity of WM and GM-derived microglia in MS pathology.
In the present study, primary human microglia cultured from post-mortem MS patient-derived subcortical white- and cortical grey-matter were used to investigate the expression of microglia specific proteins TMEM119 and P2RY12 upon treatment of the cells with the pro-inflammatory stimuli IFN-γ+LPS, or with the anti-inflammatory cytokine IL-4. In addition, we studied TMEM119, P2RY12, IFN-γ and IL-4 immunoreactivity in human post-mortem MS WMLs and subpial GMLs.
TMEM119 and P2RY12 mRNA levels in human primary microglia were down-regulated when cells were treated with IFN-γ+LPS. In addition, P2RY12 mRNA level was enhanced when stimulated with IL-4, whereas TMEM119 mRNA level was equal to control. These responses were similar in white matter derived microglia and in grey matter derived microglia. In addition, this pattern of mRNA regulation was reflected in TMEM119 and P2RY12 immunoreactivity in WMLs where, if CD3 and CD20 positive lymphocytes, and IFN-γ positive cells were present, less TMEM119 and P2RY12 immunoreactivity was present. When lymphocytes and IL-4 immuno-positive cells were present, P2RY12 immunoreactivity could be observed, but not TMEM119. In subpial GMLs, where infiltration of leukocytes, including lymphocytes, and IL-4 and IFN-γ immune-positive cells were absent, TMEM119 and P2RY12 immunoreactivity was similar to normal appearing white and grey matter.
These results suggest that the difference in microglial response in demyelinating WMLs and GMLs could be driven by the presence or absence of leukocytes, respectively. Further studies to determine the microglial subtypes present in WMLs and GMLs, are warranted.

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Cortical neuronal loss and white matter demyelination in multiple sclerosis: a retrospective study

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Introduction/Objectives: MS was traditionally considered to be a disease primarily affecting the white matter (WM), although the importance of grey matter (GM) demyelination has now been firmly established. Demyelination of cerebral WM is thought to drive neuronal degeneration and permanent neurological disability in individuals with MS. Brain magnetic resonance imaging (MRI) studies, however, support the possibility that demyelination and neuronal degeneration can occur independently. This study investigated postmortem MS brains for pathological evidence of cortical neuronal loss that is independent of cerebral WM demyelination.

Methods: In our post-mortem MS cohort of 100 brains, we identified 12 brains that lacked cerebral WM demyelination. We matched these 12 brains with 12 typical MS (TMS) cases that included cerebral WM lesions. Cases were matched based on age, sex, disease duration, post-mortem interval, postmortem MRI protocol, and disability. Demyelination was quantified histologically in cerebral WM, cerebral cortex, and spinal cord and compared between the two groups. Neuronal densities in 5 cortical regions not directly connected to spinal cord were compared between the two groups and with aged-matched postmortem control brains. Cerebral MRI metrics were compared between the two groups and with controls. Pathological correlates of brain WM MRI abnormalities were investigated in the group lacking cerebral WM lesions.

Results: Cases without cerebral WM demyelination exhibited demyelination in spinal cord and cortex. Despite the lack of cerebral WM demyelination, cortical neuronal densities and cortical thickness were significantly decreased compared to control brains and similar to TMS brains. Surprisingly, cerebral WM MRI abnormalities were similar to those found in TMS. Swollen myelinated axons were the pathological correlate of cerebral WM MRI abnormalities found in the MS brains without cerebral WM demyelination.

Conclusions: A subtype of MS, which we call myelocortical multiple sclerosis (MCMS), is characterized by demyelination of the spinal cord and cerebral cortex, but not of the cerebral WM. Cortical neuronal loss occurs independent of cerebral WM demyelination in MCMS. Future studies should investigate mechanisms of primary neuronal degeneration in MS.

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Persistent TNF and IFNγ production induced in the cerebral meninges in a rat model of MS gives rise to neuronal loss

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Introduction: The progressive phase of multiple sclerosis (MS) is characterised by accumulating grey matter (GM) pathology. The presence of immune cell infiltrates in the meninges is associated with lymphoid tissue development, greater cortical demyelination, shorter disease duration and significant neuronal loss. Analysis of isolated meninges of MS cases has shown increased gene expression for the pro-inflammatory cytokines: tumour necrosis factor (TNF) and interferon-γ (IFNγ).
Aims: We aimed to test the hypothesis that chronic production of these cytokines in the meningeal compartment and diffusion into underlying GM can drive MS GM pathology.
Methods: To do this we stereotactically injected HIV-1 based VSV-g pseudotyped lentiviral transfer vectors into the sagittal sulcus (SS) of DA rats to deliver continuous transgene expression (TNF + IFNγ) in the meninges. Rats were either immunised with MOG peptide or IFA as a control. A neuropathological analysis was conducted at chronic time points up to 2 months.
Results: Injection of these vectors induced the formation of lymphoid follicle-like structures in the meninges by 28 dpi, which remained at 2 months, containing CD4+ and CD8+ T-cells, CD79a+ B-cells and Iba1+ macrophages, and MadCAM+ channels. Subpial demyelination underlying these aggregates was accompanied by widespread microglial activation and was partly dependant on MOG immunisation. Quantification of NeuN/HuCD co-staining showed a 23-48% decrease in neuronal numbers in cortical layers II-IV at 2 months post injection. Neuronal loss occurred in both MOG and IFA immunised animals and in the absence of demyelination. TNF/TNFR1 interactions can initiate cell death by activating pathways involved in necroptosis. Immunostaining showed TNFR1 expression by neurons. RT-PCR on cortical RNA at 28 dpi and 2 months showed an increase in expression of TNFR1 and downstream necroptotic genes, RIP3, MLKL, cIAP2 and Nox2 compared to eGFP vector control animals. RIP3+ and MLKL+ immunopositive cells with the morphology of neurons were present in TNF + IFNγ vector injected animals. Membrane staining for phosphorylated MLKL in neurons was suggestive of the final stages of necroptosis.
Conclusions: Our results suggest that TNF in the presence of IFNγ is a potent inducer of meningeal inflammation and can activate TNF signalling pathways in cortical cells leading to neuronal death and subpial demyelination and thus may contribute to clinical progression in MS.

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Synaptic pathology and plasticity in grey matter inflammation in multiple sclerosis

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Introduction: Synaptic pathology is emerging as an important feature of MS. Alterations of synaptic transmission have been described in detail in active demyelinating lesions in animal models of MS, and some evidence of diffuse synaptic loss in MS brain tissue has been provided by postmortem studies.
Aim of this study was to further investigate the hypothesis of an inflammatory synaptopathy in MS grey matter.
Methods: This study was performed on postmortem samples of MS and control brains (9 MS and 10 controls), supplied by the MS Society Tissue Bank. MS brain samples were selected for presence of active inflammatory demyelinating grey matter lesions (GML). Synapses were identified in confocal microscopy with immunofluorescence for synaptophysin, and further characterized as glutamatergic or GABAergic using immunofluorescence for presynaptic vescicular transporters of glutamate (VGLUT1, VGLUT2) and GABA (VGAT). Markers of inflammation, M1/M2 microglia phenotype, oxidative damage, neuronal pathology, axonal pathology and synaptic plasticity were assessed using immunohistochemistry.
Results: An important reduction of synaptic density was observed in active demyelinating GML if compared to the normal appearing grey matter (NAGM) (-64.04%, $p< 0.0001$), with recovery of synaptic density in chronic inactive GML. The density of glutamatergic presynaptic terminals was reduced (-17.7%; $p=0.0013$) in active demyelinating GML, and increased (+27.21%; $p< 0.0001$) in chronic inactive GML, if compared to the NAGM. The density of GABAergic presynaptic terminals was approximately unchanged in active demyelinating GML if compared to the NAGM, and reduced in chronic inactive GML (-15.8%; $p=0.008$).
Conclusion: This study provides direct evidence, in MS brain tissue, of synaptic damage/loss during active grey matter inflammatory demyelination and of synaptic reorganization/remodelling in chronically demyelinated grey matter.

Disclosure
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Experimental models

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In vivo confocal imaging and single-cell transcriptomic analyses reveal early activation of retinal microglia during experimental autoimmune encephalomyelitis

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Background: In MS, chronic activation of innate immune cells of the central nervous system (CNS) is thought to be a significant contributor to neuronal loss and disease progression. However it is unclear if innate immune activation drives or is a consequence of neuronal dysfunction and death. Furthermore, even if innate immune cells do contribute to injury, the relative importance of resident vs. infiltrating cells is uncertain. The retina exhibits neuronal injury and shows innate immune activation, and is devoid of myelin. This may permit to study an anatomically separate "gray matter" structure, capable of disentangling the effects of innate immune activation from directly proximate damage to myelin as is seen in the cortex. It also provides a means to study the direct localized effect of innate immune activation on neuronal function and health.
Objective: To characterize the timing of innate immune activation in the retina during EAE.
Methods: We used confocal scanning laser ophthalmoscopy (CSLO) to monitor changes in the density and morphology of retinal innate immune cells in 6 adult CX3CR1 +/- GFP mice during two months after direct immunization against MOG_{35-55}. We scored EAE severity daily. Mice were then sacrificed and surviving ganglion cells (GC) were counted through Brn3a staining of retinal flat-mounts. In a separate study, we performed single-cell RNAseq of retinal CD11b+ cells sorted by flow cytometry 6 days after immunization (n=25 immunized vs. 25 healthy controls), using canonical markers to distinguish between microglia, macrophages, NK cells and circulating monocytes.
Results: Density of retinal $CX3CR1^+$ cells increased progressively during the first weeks after immunization, reaching a two-fold change compared to baseline levels around day 30, slowly decreasing thereafter. Morphology changes were consistent with immune activation. Mice with more severe EAE had a higher peak of retinal CX3CR1+ cell density ($r^2 = 0.48$; P=0.003), which was also associated with worse GC loss ($r^2= 0.29$; P=0.031). Transcriptomic profiling revealed activation of retinal microglia and macrophages at day 6 after immunization, before any clinical signs were observed.
Conclusions: Retinal innate immune activation is local to the site of neuronal loss, and precedes clinical onset in EAE. Flow cytometry and single-cell RNAseq can be used to distinguish cell subsets and identify pathways that are activated during EAE and that contribute to neuronal loss.

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Multicolor 19F-MRI for in vivo imaging of immune cells activity in a model of multiple sclerosis

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An non invasive imaging modality capable of quantifying inflammation, axon injury and myelin loss is highly required to monitor multiple sclerosis (MS) progression and to support disease modifying interventions. In this context, MRI is a suitable imaging tool for in vivo investigation and with the use of fluorine probes, active inflammation could be detected. We extended MRI towards multicolor imaging using two formulations of fluorine nanoparticles (19F-NPs) with two different fluorocarbons (FCs) having distinct resonance frequencies. 19F-NPs were produced by direct sonication of FCs with a surfactant including also a fluorescent dye for cytometric analysis (FCM). Both 19F-NPs were clearly differentiated in vivo allowing multicolor 19F-MRI without overlaps or artefacts. Thus we exploited multicolor 19F-MRI to monitor in vivo the dynamics of immune-cells infiltration in the experimental

autoimmune encephalomyelitis (EAE), a mouse model of MS. All in vivo experiments were performed on a 7T-MRI scanner, in healthy (n=6) and in EAE (n=14) in C57BL/6 mice immunized with a MOG peptide and received two dose of pertussis toxin at 0 and 2 days post immunization (dpi). Pathological mice showed different levels of motor impairments from weakness to complete paralysis of hind limbs. Longitudinal MRI was performed at different dpi and after a first dose of 19F-NP given at the onset of EAE (16dpi) and a second dose at disease peak (20dpi). Interestingly, with the 19F-NP given at the onset of EAE, a low fluorine signal was found in the CNS. While with the second FC given at the peak of motor disability, a strong signal was observed all over the spinal cord and in the brain. At the last MRI (26dpi), animals were sacrificed and several organs were collected and processed for FCM to identify 19F-labeled cells. Importantly, our results showed that 19F-NP uptake was proportional to the level of EAE severity. Furthermore, 19F signal was associated with the increase of leukocytes infiltration in the CNS as measured by FCM. In particular, monocytes and neutrophils were the main cells positive to 19F-NPs that were also increased in EAE mice with a severe motor disability.

In conclusion the present work demonstrates the potentiality of multicolor 19F-MRI with gain in sensitivity to track immune cells activity in vivo during neuroinflammation. In the future, the proposed multicolor imaging method could also be used to monitor the efficacy of new anti-inflammatory molecules.

Disclosure

All listed authors are in agreement and have no conflict of interest to declar.

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Are B cells attracted by T follicular helper cells in the EAE animal model of MS?

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T follicular helper (T_{FH}) cells are a subset of $CD4^+$ T cells homing to germinal centres (GCs) of secondary lymphoid organs. They are crucial for B cell maturation into plasma cells and thus antibody production during physiological immune responses. Pathological structures, morphologically similar to GCs called ectopic lymphoid tissue, can develop in the meninges of multiple sclerosis (MS) patients. We here speculated that T_{FH} cells interact with B cells in a 'pathological GC reaction' locally in the meninges and may promote MS pathology.

We induced the experimental autoimmune encephalomyelitis (EAE) animal model of MS in T_{FH} cell-deficient ($CD4^{Cre}Bcl6^{flox/flox}$) mice and found the severity of MOG_{35-55} peptide induced EAE decreased compared to controls. This correlated with a significantly reduced amount of pathogenic T cells and total B cells infiltrating in the central nervous system (CNS) of T_{FH} cell-deficient mice. To further characterize these B cells in the CNS, we performed transcriptomic profiling. We also performed an adoptive transfer (AT) EAE using MOG-specific T cells derived from T_{FH} cell-deficient mice transgenically expressing a MOG-specific T cell receptor and their wildtype littermates. In fact, we found abundant GC-like ectopic lymphoid tissue in the spinal cord in these mice and $CD4^{Cre}Bcl6^{flox/flox}$ myelin-reactive T cells induced less severe AT-EAE than wildtype-derived T cells. We are further characterizing ectopic lymphoid tissue to understand local T/B-cell interaction in this model. Taken together, our data suggest that T_{FH} cells contribute to CNS autoimmunity by promoting B cell infiltration in the CNS.

Disclosure

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P423

Modeling neuroinflammation in human neural stem cell niches with induced pluripotent stem cell-derived cerebral organoid reveals altered migration and neurogenetic programs: implications for neurogenesis in multiple sclerosis

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Despite a past study describing adult neurogenesis in individuals with multiple sclerosis (MS), mounting evidence from mouse models of MS and human postmortem MS tissue indicates otherwise.

Above settling this debate, understanding the mechanisms by which human neural progenitors respond to neuroinflammation remains a critical issue in MS and may shed light on these conflicting data. Pursuit of these questions, however, has been experimentally inaccessible until the recent development of human cerebral organoids, 3D cultures that model the spatiotemporal dynamics underlying human corticogenesis. By implementing cerebral organoids derived from healthy induced pluripotent stem cells (iPSCs), we investigated the effect of a single inflammatory cytokine, IFN-g, on the developmental dynamics of the human stem cell niche, which largely reflects the requisite events activated during repair. Continuous exposure of organoids to IFN-g for 42 days at 5, 10 and 100 ng/mL led to significantly less growth in organoid size starting at day 21. We observed increased apoptosis only in organoids exposed to IFN-g at 100 ng/mL while lower IFN-g doses showed similar levels of apoptosis and proliferation. Immunostaining revealed a premature displacement of stem cells from the subventricular-like zone, resulting in a smaller central progenitor pool and a reduction in mitotic outer radial glia, the cell type responsible for the dramatic expansion of the human cortex. In spite of a reduced progenitor pool, organoids exposed to IFN-g maintained the proper emergence of early born neurons. qPCR analyses suggest aberrant migration of progenitors, as indicated by increased *DAB1* and *CDH2* expression in IFN-g organoids. Our work provides insights into how neuroinflammation in MS disrupts the developmental processes enacted during repair and paves the way, as a novel paradigm, for future studies to interrogate human neurogenesis in the presence of inflammation from MS patient-derived cells.

Disclosure
Nothing to disclose.

P424
Automatic segmentation of white matter and detection of active lesions in multiple sclerosis

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Introduction: Disability can be prevented by early detection of multiple sclerosis lesions. Computer aided MS lesion detection via brain MRI segmentation is more efficient than time consuming manual methods. Yet, automatic segmentation is considered a challenging task due to the complexity in structures and similarity of normal tissues and lesions.
Methods: This paper proposes an automatic method of segmentation and active lesion detection for MS MRI images. The main method consists of three steps which includes image normalization and enhancement, region growing segmentation with gaussian contour enhancement and Hough transform. First, normalization of intensity is performed which is essential for the quantitative texture analysis of images. Then histogram normalization is implemented, which has better results compared to other methods. Later, region growing segmentation with gaussian contour enhancement is applied to segment white matter. It is a process which makes clusters of image regions according to image intensity of seed points. After selecting the initial seed, a statistical approach is used to grow the region. After this step, edges are detected by using the canny edge detector which helps us to apply Hough transformation. Edge points are taken as centre with a radius and then a circle is drawn across the lesion. The proposed method was evaluated on Gd-enhanced MRI data, taken from John Hunter Hospital of four patients with active MS. A total of 1973 MRI slices were used with each patient's scan yielding 665 to 800 slices. The auto-detection of lesions were compared to manual results from an expert radiologist.
Results: For evaluation, our algorithm consisted of four classes which are true negative, false negative, false positive and true positive, then overlap metric, structure similarity index (SSI) and precision were measured quantitatively. Overlap metric, SSI and precision were quantified as 0.91, 0.96 and 0.94, respectively. After auto-segmentation, active lesions were detected with an accuracy of 0.99 for examined images.
Conclusion: The proposed locally developed algorithm was able to and efficiently perform segmentation of white matter and accurately detect active MS lesion with high accuracy. This robust method will help radiologist to segment and detect active lesions automatically.

Disclosure
nothing to disclose

P425
Visual evoked potentials and optical coherence tomography to detect optic neuritis in C57BL/6

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Experimental autoimmune encephalomyelitis (EAE) is induced through myelin oligodendrocyte glycoprotein (MOG) injection. C57BL/6 mice develop chronic EAE, a common disease model of multiple sclerosis (MS). This animal model permits to study optic neuritis, an acute inflammatory disorder that causes demyelination of the optic nerve, thinning of the retinal nerve fiber layer (RNFL), and death of retinal ganglion cells (RGCs). We aimed at testing the usefulness of non-invasive visual evoked potential (VEP) and optical coherence tomography (OCT) in detecting optic nerve involvement in this model. Ten C57BL/6 were immunized, and VEPs were recorded before the day of immunization and at different time points until 37 dpi. Clinical score was measured daily and healthy control group (n=5) was monitored at the same time points.
In EAE, VEP latency was significantly increased at 11 dpi ($p=0.026$) until 37 dpi ($p< 0.0001$), with partial recovery at 23 dpi

(p=0.195). Amplitude was significantly decreased only at 31 dpi (p=0.006). In EAE, NGCC (neuronal ganglion cell complex) decreased significantly at the last time point compared to healthy (p=0.008). VEP latency was significantly correlated with NGCC thickness (Pearsons' r=-0.661; p=0.007). VEP delay preceded clinical EAE motor symptoms (16dpi) and neuroaxonal retinal thinning at OCT. These findings suggests that VEPs can be used as an early biomarker of demyelination in EAE to test new remyelinating treatments, while OCT is suitable for monitoring subsequent neuroaxonal loss for testing neuroprotective strategies.

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P426

Fusiogenic property of virus determines the mechanistic aspects of axonal loss concurrent with demyelination

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Mouse hepatitis virus (MHV) infection in mice causes meningoencephalitis and myelitis with subsequent axonal loss and demyelination which mimics certain pathological feature of human neurological disease multiple sclerosis. MHV induced neuroinflammation can follow "inside-out" mechanism, where pathology initiates within axons and leads to damage to its outer myelin covering. Previous study demonstrated spike protein (S) (host attachment protein) is one of the major genomic determinants of pathogenic properties and viral spread from brain to the spinal cord as well as from grey to white matter and causes white matter myelin loss and axonal degeneration. Fusion peptides (FP) in S are key players that mediate intercellular viral spread. A central proline residue of FP has been alluded to have a distinctive role in spread from one cell to another. The MHV S from strain RSA59 (PP) contains two central consecutive proline(s) in the FP. When one proline is deleted, RSA59 (P) produces significant differences in neural cell syncytia formation and viral titer post infection *in vitro*. NMR studies of 16-mer FP fragment from RSA59 (PP) shows a more ordered *cis* isomeric helix-turn-helix structure in methanol than its *trans* counterpart in water. Comparative molecular dynamics studies on the trimeric spike fusion domain and the FP reveal a dual role for the central proline, wherein in aqueous environment it imparts conformational rigidity to the fusion apparatus and facilitates the same by promoting a more ordered structure in the membranotropic environment through ready isomerization to a *cis* peptide form. RSA59 (PP) and RSA59 (P) infection studies with C57Bl/6 mice by transcranial inoculation produces distinct patterns of injury at day 3 post-infection. Both cause similar degrees of necrotizing hepatitis and meningitis, but only RSA59 (PP) produces widespread encephalitis that extends deeply into the brain parenchyma with extensive apoptosis of neurons and glia. In contrast, RSA59 (P) infection is limited with minimal extension of viral antigen from the meninges and the inoculating needle tract. By day 6 post-infection, both viruses are mostly cleared from the brain despite considerable residual microglial activation. Interestingly, RSA59 (P) produces significantly reduced demyelination at chronic stage of the disease compared to RSA59 (PP). Our work provides a premise for understanding the mechanism of virus induced demyelination and axonal loss.

Disclosure

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P427

Age and chronicity of demyelination determine motor impairment in a model of multiple sclerosis

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Background: Epidemiological studies have identified age as a risk factor for transition from the relapsing to the secondary progressive phase of multiple sclerosis (MS) and evidence suggests that age-related neurodegenerative processes drive disability progression in the progressive forms of MS.
Objective: To test the hypothesis that age and chronic demyelination determine neurological impairment in a model of toxic demyelination.
Design/methods: The cuprizone model was used to induce demyelination in young (9 week-old) and aged (48 week-old) mice. CNPase, Iba-1, GFAP and APP immunohistochemistry were used to quantify demyelination, microglial/macrophage activation, astrogliosis and axonal damage in the corpus callosum, in a blinded manner using image analysis software. The rotarod test was used for weekly functional assessments. Multiple linear regression analysis was performed with latency to fall off the rotarod as the dependent variable and demyelination, time from onset of feeding with cuprizone and mouse age (young vs. aged) as independent variables.
Results: Histological examination showed that all young and aged mice fed with cuprizone had developed demyelination by week 4. Quantification of demyelination revealed significantly less extensive myelin loss in the aged cuprizone-treated, compared to the young cuprizone-treated mice (P= 0.008) after 4 weeks of cuprizone feeding, but no differences after 8 or 16 weeks of treatment, indicating that ageing may be associated with delayed onset of demyelination. Univariate logistic regression revealed that age (P< 0.0001), demyelination (P< 0.014) and time

from onset of cuprizone feeding (P< 000.1) all correlated significantly with latency to fall off the rotarod. A multivariate regression analysis model with these factors as covariates could explain 52% of the variance in latency to fall of the rotarod (R^2= 0.521, P< 0.0001). There was a significant Interaction between age, demyelination and time from onset of feeding in the model (P=0.036).
Conclusions: Our study provides evidence of an effect of age and chronicity of demyelination on neurological impairment in an animal model of MS.

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Genetics/Epigenetics

P428
Evaluating the distribution and haplotype structure of multiple sclerosis risk loci across populations

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Differences in multiple sclerosis (MS) prevalence and clinical presentation across populations provide some evidence that allele and locus heterogeneity may exist. Currently, 200 non-MHC autosomal risk variants in 153 loci have been identified as conferring risk for MS in >100,000 ancestral Europeans. To evaluate the distribution of risk alleles across populations, we computed a genetic risk score of the 200 variants in 1000 Genomes populations of Europe (N=441), Africa (N=323), Asia (N=166), and the Americas (N=258). European populations include CEU: Utah, IBS: Spain, GBR: Britain, FIN: Finland, TSI: Italy; African include ACB: Barbados, ASW: SW US, LWK: Luhya, YRI: Yoruba; Asian include CHB/CHD: China, JPT: Japan; and the Americas include CLM: Colombia, MXL: Mexico, PEL: Peru, PUR: Puerto Rico. The mean risk score ranges from 18.8 in Asians to 19.8 in Africans (~13 more risk alleles in Africans), with Europeans and people of the Americas demonstrating intermediate scores of 19.4 and 19.3 respectively. When comparing the mean risk score across the four populations, differences ($p \leq 0.05$) were observed for each of the pairwise combinations except Europeans and people of the Americas; indicating differences in the distribution of MS risk variants across ancestral groups. We further evaluated the genetic risk score in admixed (3 or 2-way European, African, and Native American ancestry) Hispanics (1398 cases; 1386 controls) and African Americans (1305 cases; 1155 controls). The mean risk score was 19.4, 20.0 (p=8.12E-58) and 19.7, 20.03 (p=3.51E-23) in Hispanic and African American controls, cases. The increase in cases indicates the utility of the risk score in characterizing risk among diverse populations. In each data set, we compared risk scores in the top 5th percentile of the distribution to those in the interquartile range and found that being in the top 5th percentile indicates greater odds of disease in Hispanics than in African Americans (3.16 vs. 2.39) despite higher mean risk scores observed in African Americans. Utilizing local ancestry analyses to compute of the odds of MS for those with 0, 1, and 2 alleles of European, African, and Native American ancestry (derived from Karitiana, Maya, Pima, and Surui peoples of HGDP) for each risk variant; we find evidence that for some risk loci, haplotype structures differ across populations and the identified risk variant may not be the best tag for the true causal variant in all populations.

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P429
Molecular signature of brain lesion evolution and fate in progressive MS

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Hypothesis: We hypothesized that the different lesion types in the brain of progressive multiple sclerosis (SPMS) patients can be characterized by specific transcriptome signatures. These could unmask complex mechanisms that drive the evolution and fate of lesions, and lead to discovery of biomarkers and potential drug targets that can halt progression.
Methods: With immunohistochemistry, we classified 98 brain areas: NAWM and active lesions representing lesion evolution, and inactive, chronic active and repairing lesions representing the fate of lesions, and also control white matter tissue from 10 MS and 5 non-neurological control brains. We carefully dissected the lesion types out and created the transcriptome profile of each lesion type by next generation RNA sequencing, and normalized

the expression against the control tissue. We produced clusters and networks of significant genes using KeyPathwayMiner and TiCoNE. We also extracted key molecules that could influence either the maintenance or halt of active inflammation.

Results: Out of the detected 18000 genes, over 4000 were differentially expressed between MS and controls (FDR< 0.05). Here we found *CD26* in NAWM as a potential early marker of lesion evolution. By unsupervised clustering, we observed a gene cluster (n=580) representing the evolution of active lesion from NAWM. The co-enriched network was related to cellular trafficking and immune activation as *ICAM, VCAM, HLA-DRs, CD4, CD11c*. As for fate of active lesions, we retrieved genes uniquely expressed in each lesion type and mapped them to protein-networks to reveal stage-specific mechanisms. The repair-specific network was related to genes participating in tissue recovery/remodeling and cytotoxic immune response, the inactive-specific network was related to coagulation and homeostatic control, and the chronic active-specific network was related primarily to metabolic changes with *ENO1* as a major hub in chronic active subnetworks.

Discussion: Our data support lesion type specific transcriptome signatures. We observed high transcriptional changes across lesion evolution and fate emphasizing the importance to study each lesion type separately not to misinterpret temporal differences. With an unsupervised approach, we created *de novo* biological pathways containing major hubs and molecules that may control the mechanisms of active lesion evolution, and its fate into inactive, chronic active, or repairing lesion.

Disclosure

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P430

Multiple sclerosis-associated microRNA-548ac targets immunologically relevant genes including SDC4, SEL1L and TNFAIP3

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MicroRNAs (miRs) play an important role in regulating gene expression by degrading transcripts and/or repressing translation. The miR-548ac-encoding sequence is located in the CD58 gene locus. Genetic variants in this locus have been linked to an increased risk of multiple sclerosis (MS) and also to different expression levels of miR-548ac. This molecule may play a causal role in MS pathogenesis.

The specific function of miR-548ac has not been investigated before. We aimed at identifying the target genes of this miR to enhance the understanding of the contribution of this molecule to the development of MS.

HeLa cells were transfected with mir-548ac precursor-encoding plasmids to overexpress mature miR-548ac. With real-time PCR assays, the levels of mature miR-548ac were measured 24 h and 48 h post transfection. Transcriptome profiling analysis was used to identify significantly downregulated transcripts. The most likely direct targets of miR-548ac were verified bioinformatically and experimentally validated with luciferase reporter assays.

In response to overexpression of miR-548ac, 257 (24 h) and 99 (48 h) transcripts were found to be significantly downregulated. Bioinformatically, ten were determined to be the most likely direct targets of miR-548ac, including the transcripts of SDC4, SEL1L and TNFAIP3. Luciferase assays confirmed a direct interaction of miR-548ac with the 3'ends of these molecules, which have been associated with immunomodulatory processes before.

To conclude, our findings imply that miR-548ac modulates immunological mechanisms. Other miRs map to genetic MS susceptibility loci as well. Investigating their functional roles will provide further insights into the molecular mechanisms underlying MS. Such efforts might also be of relevance for the identification of novel biomarkers for the disease.

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P431

Parent-of-origin genetic effects in multiple sclerosis

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Introduction: Parent-of-origin effect describes a phenotype that depends on whether a causative allele was inherited from the mother or the father.

Objectives: We aimed to investigate whether any parent-of-origin effects are observed in multiple sclerosis (MS) susceptibility.

Methods: We utilized a genome-wide single nucleotide polymorphism (SNP) dataset of 931 family trios (consisting of an affected child and both parents) of European origin. After strand phasing and SNP imputation, parent-of-origin effects were analyzed with the PREMIM/EMIM software. For each SNP, p values for maternal and paternal inheritance effects were assessed and those with $p < 0.05$ were evaluated.

Results: Out of 198 MS risk-associated non-MHC SNPs available on the chip, 24 had nominal statistically significant maternal parent-of-origin effects, whereas 21 had nominal paternal

parent-of-origin effects. None of them passed the genome-wide significance threshold. However, in the *EVI5* region in chromosome 1 where multiple independent MS risk-variants were identified, a SNP closest to *GFI1* previously shown to be paternally expressed, displays paternal parent-of-origin effect for MS risk (rs58394161, $p = 0.0099$).

Conclusions: We analyzed parent-of-origin effects in MS and identified MS-associated variants with potential parent-of-origin effects on disease susceptibility. Parent-of-origin effects in regions with multiple independent MS variants may provide important clues on the functional mechanisms that contribute to MS risk and could partially explain the missing heritability in MS.

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P433
Increased microRNA-146a circulating levels in Portuguese multiple sclerosis patients

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Introduction: Multiple sclerosis (MS) is an autoimmune disease of the CNS characterized by a multifocal inflammatory immune response mediated by lymphocytes and macrophages. Its pathogenesis is conditioned by the interaction of multiple genetic and environmental factors.Recent reports highlight the role of microRNAs in the control of various immunological processes, including the development and maturation of T and B lymphocytes, the presentation of antigens, and cytokine production. In this context, the differential expression of some miRNAs, and their role in various autoimmune diseases, including MS, have been investigated. The role of microRNA-146a (miRNA-146a) as a negative regulator of immune activation is well established. This molecule is involved in a negative feedback loop: it is induced by NF-kB, but also inhibits its activation.

Objectives: To evaluate the expression of circulating miRNA-146a in the serum of Portuguese MS patients.

Methods: The study included 76 MS patients (Mean age: 45±12 years; 59.2% female; Mean disease duration: 13±8 years; 59 Relapse Remitting MS; 17 Progressive MS) and 78 matched healthy controls (HC) (Mean age: 44±10 years; 60.3% female). RNA extraction from serum was performed using the miRNeasy Serum/Plasma Kit. Relative expression values were calculated using the $2^{-\Delta\Delta Ct}$ method. Differences in ΔCt were evaluated using a two-tailed Student's t-test.

Results: Significantly increased expression of miRNA-146a was found in the serum of MS patients compared with HC (fold change 5.86; $p< 0.0001$). The RRMS group had higher serum levels of miRNA-146a compared with the Progressive MS group (26.8 vs. 25.4, $p=0.036$).

Conclusions: Circulating miRNAs have emerged as potential biomarkers for several human diseases including MS. One of the miRNAs that seems to be differentially regulated in MS, in different tissues and cells, is miR-146a: it has been found to be increased in brain lesions, serum and blood-derived immune cells. In this study we also found higher serum levels of miRNA-146a in MS patients. Relapse remitting patients presented the highest values, which agrees with the notion that inflammatory mechanisms are predominant in this stage of the disease.

These are preliminary results of a country-wide multicentric project that will study several immunologically relevant microRNAs in a large cohort of MS patients.

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Immunology

P434
Innate signaling in central nervous system recruits myeloid suppressor cells

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Introduction: Regulation of neuroinflammation is necessary to maintain central nervous system (CNS) homeostasis and has therapeutic potential in diseases such as multiple sclerosis. The CNS contains parenchymal and extraparenchymal myeloid cells that can play a regulatory role. We have examined the capacity of innate-signaled myeloid cells to regulate experimental autoimmune encephalomyelitis (EAE) in mice.
Methods: Mice received a fluorescent-conjugated bispecific NOD2- and TLR9-agonist microparticle MIS416 either intravenously or by intrathecal injection to extraparenchymal leptomeningeal, ventricular and subarachnoid space. MIS416 has previously been shown to suppress EAE when given peripherally.
Results: Intravenous MIS416 induced significant extraparenchymal infiltration from blood of monocytic myeloid cells ($CD45^{high}$, $Ly6C^{+}$, $F4/80^{+}$, $CD11b^{+}$, $CD11c^{+}$) that had phagocytosed MIS416. Intrathecal MIS416 induced infiltration of similar magnitude but in contrast to peripheral injection, over 30% of the MIS416-phagocytosing cells were granulocytic ($Ly6G^{high}$, $Ly\text{-}6C^{low}$, $Gr1^{high}$, $CD11b^{+}$, $CD11c^{-}$). Both populations were also $PDL1^{+}$. mRNA for the neutrophil-recruiting chemokines CXCL1 and CXCL2 were upregulated in CNS. When given to mice showing first symptoms of EAE, intrathecal MIS416 suppressed disease - this did not occur in mice lacking the Type I IFN receptor. Extraparenchymal MIS416-phagocytosing cells, including polymorphonuclear neutrophils, were shown to produce IFNβ in reporter mice, and sorted monocytic and granulocytic cells expressed IRF7, indicating IFN response.
Conclusions: CNS-innate signaling uniquely recruits granulocytic myeloid-derived phagocytes from blood. These and co-infiltrating phagocytic monocytic myeloid cells produce IFNβ and suppress EAE by a Type I IFN-dependent mechanism. This endogenously-triggered pathway likely contributes to CNS homeostasis and may have therapeutic potential.

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P435

Defining the cellular and molecular mechanisms mediating the migration of human $CD4^{+}$effector T-cell subsets across the human BBB *in vitro*: the role of PECAM-1 and CD99

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Introduction: The blood-brain barrier (BBB) strictly controls lymphocyte entry into the central nervous system (CNS). The BBB breakdown, with a subsequent infiltration of inflammatory cells into the CNS, is an early key step in the pathogenesis of multiple sclerosis (MS). Although recent MS drugs targeting immune cell trafficking (e.g. Natalizumab and fingolimod) are highly effective, these treatments are associated with rare but severe side effects like progressive multifocal leukoencephalopathy (PML), suggesting that the current therapies also target immune cells mediating immunosurveillance of the CNS. It is thus essential to differentiate disease relevant pathogenic T cell subsets from non-pathogenic subsets and to explore differences in the molecular mechanisms for entering the CNS. To this end molecular mechanisms has largely been studied in experimental autoimmune encephalomyelitis (EAE), but EAE does not mimic the full picture of MS neuropathology. This underscores the need of meaningful studies with human tissues and cells. We have recently established a novel *in vitro*human BBB model by co-culturing human $CD34^{+}$cord blood cells derived endothelial cells with bovine pericytes. Here we have adapted this model for use in T-cell migration research.
Objective and Aims: To study if human $CD4^{+}$effector T cells cross the BBB through the endothelial junction (paracellular) or through a pore in the endothelial cells (transcellular) we have started to investigate the role of the junctional adhesion molecules PECAM-1 and CD99 in this process. PECAM-1 and CD99 have been shown mediate diapedesis of neutrophils across peripheral vascular beds. Their role in mediating the migration of $CD4^{+}$T cell subsets across the BBB remains to be explored.
Methods and Results: Applying blocking antibodies, we observed anti-CD99 blocking antibodies reduce $CD4^{+}$T cell migration across the BBB *in vitro*, while anti-PECAM-1 blocking antibodies did not interfere with this process.
Conclusions: These data shows that human effector $CD4^{+}$T cell have different molecular mechanisms employed for crossing the BBB compare to innate immune cells.

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Characterisation of pro- and antiinflammatory mechanisms in the gut mucosa of patients with multiple sclerosis

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Introduction: The gut microbiota and their effects on the intestinal immune system are thought to play a fundamental role in initiating autoimmune diseases such as multiple sclerosis (MS) by inducing inflammatory cascades in the intestinal mucosa and driving T cell differentiation toward proinflammatory phenotypes.
Objective: Little is known about T cell differentiation and the transforming growth factor-beta (TGF-ß) signalling pathway in the intestinal mucosa of MS patients.
Aims: To elucidate if the TGF-ß signalling pathway, its inhibitor Smad7 and pro- and anti-inflammatory T cell differentiation markers are altered in the intestinal mucosa of MS patients.
Methods: We retrospectively analysed 103 intestinal samples of 27 MS and 27 control patients by immunohistochemistry for Smad7, the downstream signalling molecule pSmad2/3 and the T cell differentiation markers IFN-γ, FoxP3 and IL-17. Positive cells were counted per 0.1 mm^2 in the lamina propria of colonic tissue and compared by student´s t test or Mann-Whitney U test. Using binomial logistic regression, we tested the predictive capacity of different stainings for the diagnosis of MS.
Results: We found an increased expression of Smad7 (p=0.0966) and IFN-γ (p=0.0108) in the lamina propria of intestinal specimens from MS patients, consistent with a significant decrease in the expression of pSmad2/3 (p=0.0131), FoxP3 (p=0.0389), and IL-17 (p=0.0155). No differences in expression of these markers in our MS cohort were found when samples were subdivided according to blood supply (superior mesenteric and inferior mesenteric artery/internal iliac artery). Disease-related clinical characteristics (age at onset, subtype, EDSS, occurrence of relapses, MS medication) were not correlated with the expression of Smad7 and T cell differentiation markers, except for a trend toward decreased CD4 expression (p=0.0755, r=-0.3477) in the lamina propria of MS patients with duration of disease. In a binomial logistic regression model the expression levels of Smad7 and IL-17 had a significant predictive capacity on the presence of disease (Chi-square(2)=9.700, p=0.008).
Conclusions: The TGF-ß signalling pathway was suppressed and an imbalance of pro- and anti-inflammatory T cell subsets found in the intestinal mucosa of MS patients. Further research is required to determine if an altered intestinal microenvironment in MS patients affects T cell differentiation and if its modulation has an impact on MS disease activity.

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P437

Mesenchymal stem cells from patients with MS in interaction with autologous immune cells have defective immunomodulatory activity and enhance production of inflammatory cytokines

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Introduction: Mesenchymal Stem Cells (MSCs) have dual effects: immunomodulatory and tissue protective and possible regenerative. Thus they have potential for cell-based therapies in MS. Previous studies show a differential ability of MSC to regulate Th17 and Th1 cells, but few studies have compared directly the immunomodulatory effects of MSC from MS patients and healthy volunteers towards autologous immune cells such as peripheral blood mononuclear cells (PBMC). In addition, MSC effects on T cells expressing GM-CSF are not known. In this study, we compared the immunomodulatory activity of MSC from patients with MS and those from healthy volunteers against autologous immune cells.
Objective: To compare the immunomodulatory activity of mesenchymal stem cells from patients with MS and healthy volunteers against autologous immune cells.
Aims: To gain insight into MSC in MS.
Methods: PBMC from 5 SPMS patients and 6 healthy controls (HC) were stimulated with anti-CD3/CD28 in monoculture or coculture with autologous bone marrow MSC (>95% MSC phenotype panel positive, passage 5 or 6) for 72h and 5h restimulation with PMA/ionomycin, followed by intracellular staining for IL-17, IFN-γ and GM-CSF. Cytokine expression was then quantified using flow cytometry. Supernatants of unstimulated MSC prior to co-culture were tested for a panel of cytokines and chemokines using a multiplex array and individual cytokine ELISA for some cytokines. Gene expression profiling was performed to explore differences between the MSC from MS and controls. For this, Lexogen QuantSeq library prep, which produces mostly 3' end near poly-A reads from mRNAs, was employed.
Results: Unstimulated MSC from MS patients produced less IL-10 (p=0.03) and more osteopontin (OPN) (p=0.002) than those from HC. MSC from HC reduced the proportion of autologous T cells expressing IL-17 (Th17), IFN-g (Th1), and GM-CSF by

~40%, whereas those from MS patients had the opposite effect by increasing autologous Th17 cells, GM-CSF-expressing T cells by ~100%, and did not suppress Th1 cells. Gene expression profiling shows down-regulation of pathways and regulators of TGF-β1.
MSC from SPMS patients have deficient immunomodulatory ability towards immune cells from the same patients, compared to MSC from HC in interaction with autologous immune cells. MSC trials are feasible but immunological monitoring is necessary. Restoration of immunomodulatory function (e.g. transplanting MSC with exogenous IL-10) may be helpful.

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P438

Cytotoxic and regulatory roles of mucosal invariant T (MAIT) cells in multiple sclerosis (MS)

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Background: MAIT cells are a subset of innate T lymphocytes characterized by the expression of an invariant TCR α-chain (Vα7.2-Jα33) paired with a limited number of Vβ chains. These cells recognize Riboflavin metabolites from a range of microbes presented by MHC Class-I MR1. We recently demonstrated that MAIT cell clones isolated from both peripheral blood and CSF presented similar oligoclonality, suggesting that peripheral blood may reflect CNS inflammatory events. Furthermore, MAIT cells correlated with disease activity. In this study we characterized the cytotoxic activity of MAIT cells and investigated possible ways of inhibiting their activity
Methods: Thirty-four MAIT cell clones (TCCs) isolated from peripheral blood and 23 TCCs isolated from CSF in 7 relapsing remitting MS patients were studied. TCRα and -β chains were characterized using high -throughput deep RNA sequencing. TCCs were stimulated with the Riboflavin derivatives 5-OE-RU and 5-OP-RU. Cytotoxicity was measured by FATAL assay, using EBV transformed B cell lines (BCLs) as target. Granzyme (Grz) B and perforin were assessed by ELISA. Activation markers CD25 and CD69 and the degranulation marker CD107a were measured by flow cytometry.
Results: MAIT TCCs from both blood and CSF in response to 5-OE-RU and 5-OP-RU showed marked activation demonstrated by increased expression of CD25 and CD69. They also induce lysis of BCLs, associated with cellular degranulation measured by the expression of CD107a, and elevation of GrzB and perforin levels. These effects were inhibited by anti-MR1 blocking antibody. Pre-activation of MAIT cells with *E.Coli* infected HeLa cells or IL-7 enhanced significantly their cytotoxic capacity. MAIT cells activity was inhibited by the folic acid derivatives 6-formylpterin (6-FP) and acetyl-6 formylpterin.
Conclusions: MAIT cells play potential roles in autoimmune diseases including MS. Given that MAIT cells have shown important correlation with the course of the disease, understand their mechanisms of action and evaluate their inhibitors might open new therapeutic strategies.

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P439

Impaired neutrophil death in AQP4-IgG-seropositive NMO patients

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Introduction: In contrast to multiple sclerosis (MS), neutrophils accumulate in neuromyelitis optica (NMO) lesions. Our group has recently shown that whilst peripheral blood neutrophils of patients with NMO and MS display an activated phenotype compared to healthy controls (HC), NMO neutrophils have deficient functionalities in comparison to MS. Thus, we hypothesised that an impaired cell death of NMO neutrophils might support their accumulation in inflammatory lesions.
Our **aim** was to evaluate susceptibility to Phorbol Myristate Acetate (PMA) induced cell death in circulating neutrophils of AQP4-IgG-seropositive NMO patients.

Patients and methods: Fresh blood from nine AQP4-IgG-seropositive patients (eight female, mean age 48.7 years, SD=13.2) diagnosed with NMOSD according to the 2015 IPND criteria was collected; median EDSS was 4.0 (1.5-6.5), mean disease duration 5.4 years (SD=4.1). Six patients were treated with rituximab, two with azathioprine, and one with tocilizumab. Matched age/gender healthy donors were used as controls. Neutrophilic apoptosis was induced by incubating granulocytes with PMA for 30 min at 37 °C. The mean percentage of NMO neutrophils after PMA treatment was 82.85% (SD=21.9; N=9). Afterwards cell death was analysed by flow cytometry in $CD16b^+$ neutrophils, using 7- AAD and Annexin V staining.
Preliminary Results: The percentage of dying neutrophils (CD16b+, Annexin V+, and 7-AAD+) was higher within the HC samples, 52.56% (SD=15.02; N=9), than NMO samples, 44.03% (SD=18.26; N=9, **p=0.0128**). Neutrophil death in NMO patients show reduced susceptibility compared to HC in our *in vitro* set-up.
Conclusions: Defective neutrophil death accompanied by neutrophil accumulation promoting a pro-inflammatory environment has been already shown for other chronic inflammatory diseases. Thus, the observed impaired cell death of neutrophils from NMO patients may contribute to neutrophil accumulation and to maintain chronic inflammation in NMO lesions. However, since the NMO patients included in this study were under immunomodulatory treatments, further evidence from untreated patients is needed to support this conclusion.

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MS holds a patent for manufacturing of phantoms for computed tomography imaging with 3D printing technology and received research support from Federal Ministry of Economics and Technology.
FP serves on the scientific advisory board for Novartis; received speaker honoraria and travel funding from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, and Shire; consulted for SanofiGenzyme, Biogen Idec, MedImmune, Shire, and Alexion; and received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, Arthur Arnstein Stiftung Berlin, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis of the USA.
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Chitinase-3-like protein 1 could be a predictor of disability progression in patients with primary progressive multiple sclerosis

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Introduction: Potential cerebrospinal fluid (CSF) and serum candidate biomarkers, reflecting the inflammatory and/or the neurodegenerative processes associated with multiple sclerosis (MS) have been identified, but have not been well characterized in patients with primary progressive multiple sclerosis (PPMS)
Objective: To assess the correlation between CSF biomarkers and disease activity (physical and cognitive) in PPMS.
Methods: A multicentre, cross-sectional study was conducted in a sample of adult patients with PPMS (McDonald 2010 criteria). Chitinase-3-like protein 1 and 2 (CHI3L1 and CHI3L2) and neurofilament light chain (NfL) were analysed in stored CSF samples obtained at the time of diagnosis and correlated to disability progression measured by Expanded Disability Status Scale (EDSS), 9-Hole-peg test (9HPT) and timed 25-foot walk test (T25-FW) and cognitive evaluation measured by brief repeatable neurophyscological battery (BRNB.)
Results: Twenty-five out of 55 subjects had availability of CSF samples for study (mean age 57 ± 9.4 years, 52% female). The median time from diagnosis to baseline EDSS was 3.5 years (IQR 1.2-6.4), and the median Expanded Disability Status Scale (EDSS) score at diagnosis was 3.5 (interquartile range 2.5-4.5). CHI3L1 levels were associated to a greater EDSS at baseline (*correlation coefficient* 0.490, *p=0.013*). Furthermore, a trend to a negative correlation was observed with CHI3L2 and EDSS (*correlation coefficient* -0.366, *P= 0.086*). No other correlations, including NfL, were observed.
Conclusion: CHI3L1 in CSF could be a good biomarker for disability progression in PPMS patients. NfL levels in CSF were not related with the evolution of disability in our series of PPMS patients.

Disclosure

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Preferential usage of the G1m1 allotype in intrathecal virus-specific antibodies in multiple sclerosis

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Introduction: Intrathecal synthesis of immunoglobulin G (IgG) is a hallmark of multiple sclerosis (MS), with IgG1 being the dominant isotype. However, the mechanisms driving the IgG production remain enigmatic. We have recently shown that IgG1-secreting B cells of the G1m1 allotype are exclusively recruited to the cerebrospinal fluid (CSF) in G1m1/G1m3 heterozygous MS patients, whereas B cells of the G1m1 and G1m3 allotypes of IgG1 are evenly distributed in blood, as expected from random allelic exclusion.

Objectives: The selection of G1m1 positive B cells to the CSF could be driven by the target antigen of the B cells. To explore this possibility, we set out to determine the IgG1 allotypes of intrathecally synthesized antibodies against measles, rubella, and varicella zoster virus (VZV), which are believed to be the result of non-specific bystander activation of B cells in MS.

Methods: Paired CSF and serum samples from oligoclonal band (OCB) positive relapsing-remitting MS patients (n = 30) were screened for intrathecal IgG1 production against measles, rubella and VZV through isoelectric focusing and affinity blotting against nitrocellulose membranes coated with viral antigens. The G1m1 and G1m3 allotypes of the virus-specific antibodies were determined using affinity blotting and ELISA.

Results: We found intrathecal IgG1 synthesis against measles in 16/30 (53%), rubella in 16/30 (53%), and VZV in 15/30 (50%) patients. Collectively, we observed antibody production against either virus in 25/30 (83%) cases. The G1m1 skewing was maintained for all viral antigens, with 12/15 (80%; $p = 0.013$) cases of IgG1 against measles being exclusively of the G1m1 allotype, and similarly 14/16 (87.5%; $p = 0.001$) in the case of rubella and 14/14 (100%; $p < 0.001$) in the case of VZV. Similarly, ELISA results showed increased CSF/serum ratios for G1m1 as opposed to G1m3 directed against measles (2.05 vs. 1.46; $p = 0.041$), rubella (2.00 vs. 1.15; $p < 0.001$), and VZV (2.28 vs. 1.00; $p < 0.001$).

Conclusion: There is a strong G1m1 predominance of intrathecally synthesized antibodies against measles, rubella and VZV in G1m1/G1m3 heterozygous MS patients. This suggests that the selection of IgG1-secreting G1m1 B cells to the CSF of MS patients, and the perpetual intrathecal immunoglobulin synthesis, is driven by antigen-independent mechanisms.

Disclosure

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Personalizing health care in multiple sclerosis using systems medicine tools: presentation of the cytomics data from the Sys4MS project

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Background: Development of personalized health care for multiple sclerosis (MS) is hindered by a poor understanding of the biological processes underlying the disease, their interactions, and the heterogeneity between patients. Further progresses in the development of MS disease modifying treatments (DMT) largely depend on a greater knowledge of the immunological asset. Analysis of circulating immune cells by flow cytometry has revealed MS-associated alterations in the composition and function of T and B cell subsets, including temporal changes associated with disease activity and response to treatment.

Aim: By combining integrative omics, imaging and clinical data, we aim at developing algorithms that can be used in clinical practice to define the prognosis and select the best therapeutic approach.

Methods: We present cytomics data obtained in four European centers by flow cytometry of immune cell subsets in PBMC samples from 246 MS patients (age 42.5 ± 10 years; sex: 67.5% female; disease duration: 10.6 ± 8 years; subtype: 73.5% RRMS; 20% PMS; 6.5% CIS; mean EDSS: 2.4 ± 1.7) and 77 healthy controls (HC). Assays were strictly standardized using specifically prepared antibody-cocktail lyotubes. Differences between groups were assessed by analysis of covariance (ANCOVA) adjusting for sex and age.

Results: Comparison with HC indicated that the global MS population had significantly lower frequencies of naïve-Treg ($p=0.007$) and Th1/17 ($p=0.04$) and higher total Treg ($p=0.004$) and Breg ($p=0.02$). No differences in the same cell populations were found when focusing on untreated MS patients versus HC. Regarding the use of DMT, we found that patients receiving high-efficacy drugs had less naïve-Treg compared with the other groups separately (HC, untreated patients and patients receiving low efficacy drugs; $p< 0.0001$) and more total Treg and Breg compared to untreated patients (Treg $p=0.02$; Breg $p=0.01$) and HC (Treg $p=0.0002$; Breg $p=0.007$); such difference did not reach the

statistical significance comparing patients receiving high-efficacy to those receiving low-efficacy drugs.
Conclusion: Our results show significant differences in specific immune cells populations between patients and controls. An increase in Treg and Breg frequencies was evident in treated patients, in particular in those receiving high-efficacy drugs. Such cytomics markers will be used in the development of clinical decision support systems for improving disease management.

Disclosure
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P443
Soluble CD40 ligand contributes to blood-brain barrier breakdown in patients with multiple sclerosis and mice with experimental autoimmune encephalomyelitis

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Objective: To elucidate the potential role of soluble CD40 ligand (sCD40L) in blood-brain barrier (BBB) disruption in patients with multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) mice.
Methods: Serum and cerebrospinal fluid (CSF) sCD40L levels in 29 patients with MS and 27 disease controls (DCs) were measured using multiplex immunoassay. Samples from patients with MS were obtained within 50 days after the onset of an attack. Clinical and laboratory profiles including CSF/serum albumin ratio (Qalb), a marker of BBB breakdown, were also investigated. In addition, recombinant mouse sCD40L was used in mice with EAE *in vivo* and the human brain microvascular endothelial cell (HBMEC)-based BBB *in vitro* model. Permeability coefficient (Pe, cm/min) was calculated by the sodium fluorescein permeability assay in the HBMEC/ci18-based *in vitro* BBB method.
Results: Serum sCD40L levels, which was higher in patients with MS than in DCs [median, 2480 versus 786 pg/mL; interquartile range (IQR), 2590 vs 1379; P = 0.046], was positively correlated with Qalb (Kendall's tau-b = 0.29, P = 0.044). Although CSF sCD40L levels were higher in patients with MS than in DCs (median 38.5 vs 4.8 pg/mL, IQR 45.7 vs 23.6, P = 0.002), no correlation was found between CSF sCD40L and Qalb. EAE scores of mice receiving high-dose sCD40L were worse than those receiving low-dose sCD40L and controls. Pe was increased by sCD40L treatment in the HBMEC-based BBB model (median, 2.43 vs 1.78 10^{-3} cm/min; IQR, 0.85 vs 0.64; P = 0.032).
Conclusions: Soluble CD40L may facilitate inflammation in MS and EAE by BBB disruption.

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P444
Dissecting the antigen specificity of cerebrospinal fluid-infiltrating CD4+ T cells in multiple sclerosis

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Extensive effort has been made to identify the target antigen/s in multiple sclerosis (MS), and the greatest attention has been directed to myelin proteins. The identification of $CD4^+$ T cells reactive to epitopes of several myelin proteins has been a consistent finding. Among the myelin proteins, myelin basic protein (MBP) is the best studied. Interestingly, reactivity of autoimmune T cells against post-translational modifications of autoantigens, specifically against citrullinated peptides, has been observed in MS. It has been shown in this laboratory that T cell reactivity against citrullinated MBP is elevated in peripheral blood of MS patients, suggesting that T cells specific for citrullinated epitopes escape central immune tolerance.
It is suggested that citrullination/deimination of MBP induces the generation of new epitopes triggering as a consequence autoreactivity. We aimed to investigate the specificity of cerebrospinal fluid(CSF)-infiltrating $CD4^+$ T cells against immunodominant myelin- and citrullinated versus non-citrullinated peptides.
Snap frozen brain tissue from MS and control brains was used in a bottom-up proteomics study using pressure cycling technology. The newly identified citrullinated peptides together with myelin peptides will be used to address the recognition of brain- and CSF-infiltrating CD4+ T cells from MS patients, measuring proliferation (3H-thymidine incorporation), cytokine production and functional phenotype.
The proteomics study identified 8 new sites of citrullination in the MBP molecule that were expressed at high levels in the white matter of MS cases compared to healthy controls. Also, citrullination of glial fibrillary acidic protein (GFAP) is found more abundantly in the white matter of MS brains. Current experiments are assessing the CSF T cell reactivity against myelin, newly defined citrullinated and the corresponding unmodified brain epitopes. Preliminary results indicate that specific citrullinated epitopes are recognized.
Further investigation is needed to support the idea that citrullination is linked with autoimmunity in MS and that T cells specific for citrullinated epitopes escape central tolerance. Knowledge about the target antigens of CSF-infiltrating T cells is not only important for understanding the disease pathogenesis, but also for improving treatment.

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P445

The role of lipid-regulated LXR-mediated networks in driving pathogenic T-cells in people with multiple sclerosis

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Autoreactive $CD4^+$ T-cells, abnormal regulatory T-cells (Tregs) and defects in lipid metabolism that influence T-cell responses are crucial in the pathogenesis of multiple sclerosis (MS). Liver-X-receptors (LXRs) are key transcriptional regulators of cholesterol metabolism with anti-inflammatory effects in immune cells. We hypothesise that LXR activation influences immune cell behavior by altering the lipid content of plasma membrane (PM) microdomains, enriched for cholesterol and glycosphingolipids (GSLs) that regulate immune-cell signaling and that this transcriptional regulatory network is defective in patients with MS.T-cell subsets from healthy donors had distinct PM lipid profiles with Tregs having increased GSL ($p =< 0.001$) and reduced cholesterol compared to Tresp resulting in reduced Treg membrane fluidity. These changes were mirrored by increased Treg expression of GSL biosynthesis enzyme (UDP-Glucose Ceramide Glucosyltransferase, UGCG, $p=0.0001$), the cholesterol metabolism regulator LXRβ, and LXR-target genes (ATP binding cassette sterol transporter, ABCG1 ($p=0.001$); the fatty acid regulator, fatty acid synthase, FASN; and lipid trafficking enzyme, Niemann Pick type C1-NPC1, ($p=0.0001$)) thus supporting a role for lipid metabolism in maintaining Treg/Tresp homeostasis and function. Stimulation of LXR by LXR-ligands (both endogenous, 24,25-epoxycholesterol and synthetic, GW3965) modulated PM cholesterol and GSL levels by regulating the expression of GSL biosynthesis enzyme (UGCG) and sterol transporter (ABCG1). This resulted in reduced membrane fluidity and was associated with reduced Tresp proliferation and increased production of interleukin-2.Interestingly, PM-lipids and lipid metabolism genes were dysregulated in ex vivo Tresp and Tregs from people with MS. PM cholesterol and GSL were increased in Tregs and Tresp ($p =< 0.05$) compared to healthy donors. Furthermore, $CD4^+$ T-cells isolated from people with MS had reduced LXRβ expression and significantly reduced expression of LXR target genes including ABCG1 (regulating cholesterol efflux), FASN (regulating fatty acid biosynthesis) and NPC1 (cholesterol trafficking) compared to healthy donors ($p =< 0.001$) suggesting lipid metabolism is altered in MS $CD4^+$ T cells. Initial genome-wide gene expression analysis identified that some of these pathways were significantly modulated by 12 month interferon-β therapy in T-cells from people with MS.Thus altered lipid metabolism could influence MS pathogenesis.

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Microbiology and Virology

P446

Intestinal colonization by epsilon toxin-producing *Clostridium perfringens* strains is associated with multiple sclerosis

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Introduction: The microbiome and metagenome are essential to human health and homeostasis. While alterations in the microbiome have been described in MS, there is no demonstrated link between the gut microbiome and MS lesion formation. *Clostridium perfringens* epsilon toxin is an attractive candidate for new lesion formation as it selectively targets both CNS endothelial cells and oligodendrocytes/myelin.
Objectives: To determine whether MS patients are more likely than healthy controls to be colonized by epsilon toxin-producing strains of *C. perfringens.*

Aims: 1. Screen for epsilon toxin production in fecal samples from people with MS and healthy controls. 2. Determine the *C. perfringens* toxinotype in fecal cultures by PCR-based genotyping. 3. Isolation of a pure epsilon toxin-producing strain from MS subjects. 4. Verify that epsilon toxin-producing *C. perfringens* strains isolated from MS subjects are not laboratory strain contaminants. 5. Preliminary analysis of the genetic composition of the MS-related epsilon toxin plasmid.
Methods: We developed a highly sensitive ELISA for detection of epsilon toxin from clinical samples. Fecal samples from consented subjects were placed in Rapid *Perfringens* Media for anaerobic culture in a microtitre plate. Supernatants from the microtiter plate were probed by ELISA. Wells corresponding to positive hits by ELISA were then used for PCR based genotyping and multiple rounds of subculture.
Results: 21% of tested MS subjects are colonized by *C. perfringens* type B in their gut compared to 0% of healthy controls. Sequence analysis confirmed that patient derived type B strains were not due to contamination by the laboratory strain.
Conclusions: Colonization of the gut by *C. perfringens* type B is statistically associated with MS. While two epsilon toxin-producing *C. perfringens* strains (type B and type D) exist in nature, thus far we have identified only type B strains from MS subjects.

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P447

Clostridium perfringens induced blood-brain barrier permeability: specificity and temporal dynamics in a humanized zebrafish model

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Background: *Clostridium perfringens* Epsilon toxin (ETX) is widely known as the causative agent of multifocal CNS white matter disease in ruminants. Recently, ETX has been implicated as a potential actor in Multiple Sclerosis (MS) pathogenesis. The toxin appears to enter the CNS by targeting the blood-brain barrier (BBB), reducing its integrity, before entering into brain parenchyma and targeting oligodendrocytes. However, the mechanism by which the toxin opens the BBB, the kinetics of its action, and its effects in a live organism are still unknown.
Objective: To generate a humanized zebrafish BBB model expressing the Myelin and Lymphocyte Receptor Protein (hMAL) in order to: 1) establish the kinetics of real-time, *in vivo* ETX-MAL binding, 2) determine if ETX requires MAL to induce neurovascular pathology, 3) assess whether ETX can be neutralized using an antibody.
Methods: Zebrafish cerebellar sections were examined for ETX vascular binding via immunohistochemistry and were compared to mouse WT controls. Zebrafish zygotes were injected with hMAL-GFP or tetraspanin receptor control, hBENE-GFP, under an endothelial promoter. GFP Positive fish were injected intravenously 3-4 days post fertilization (DPF) with Alexa-tagged pro-ETX (pETX). GFP vessels were live imaged and evaluated for toxin-receptor colocalization using confocal microscopy. At 6-7 DPF other hMAL or hBENE fish were co-injected with active ETX or H149A mutant ETX plus dextran dye to look for BBB disruption and vascular pathology using confocal full-brain z-stacks. Experiments were repeated after ETX neutralization with JL008 antibody. Images were quantified using Imaris.
Results: WT zebrafish showed no affinity for ETX, but fish which expressed hMAL exhibited pETX binding in a time dependent manner. Activated toxin in hMAL endothelial-expressing fish initiated dramatic BBB disruption demonstrated by causal leakage of a 2,000 kDa dextran, hMAL receptor recycling, vessel narrowing, and focal perivascular edema when compared to receptor or toxin controls. Incubation of active ETX with JL008 antibody abrogated all assessed vascular pathology.
Conclusion: ETX requires endothelial expressed MAL protein to elicit BBB pathology and can be blocked by neutralizing antibody. This finding adds to the body of evidence implicating the ETX paradigm in MS by providing the first visualization of the toxin's action in a live organism and strengthens the proposal that MAL is the ETX receptor with a new BBB model.

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Environmental factors

P448

Investigating the gene-environment interaction in multiple sclerosis through a "candidate-interactome" approach

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Introduction: We evaluated genetic information to assess the causative role of environmental factors in multifactorial diseases. In our previous work on MS, Epstein Barr virus (EBV) had emerged as potentially relevant for disease etiology

Methods: We analyzed nominal statistical evidence of association, at thegenome-wide level, in multiple sclerosis (MS) and in other diseases, looking for statistical enrichment of associations among "candidate interactomes" (groups of genes whose products are known to physically interact with environmental factors that may be relevant for disease pathogenesis).

We obtained 20 candidate interactomes from the literature: 9 viruses, 1 bacterium, 10 cellular factors (9 proteins and 1 noncoding RNAs target repository). We obtained the MS GWAS (GWAS 2011 and Immunochip), type 1 and type 2 diabetes, rheumatoid arthritis, inflammatory bowel disease, bipolar disorder, hypertension, coronary artery disease and related healthy controls from Wellcome Trust Case Control Consortium,2 (WTCCC2). To evaluate globally the contribution of all the SNPs analyzed in both the datasets of MS GWAS, we constructed METACHIP1: a combination of the former two where GWAS 2011 data was given preference in case of overlap (e.g., if both chips had a SNP in the same position, the GWAS-2011 p-value was preferred) and METACHIP2 where Immunochip data was given preference. We used Association LIst Go AnnoTatOR (ALIGATOR) program to search for statistical enrichment of associations between interactomes and genome-wide association data (considering all the SNPs with a p-value< 0.05).

Results: We show that the contribution to disease etiology of EBV, and possibly other herpesviruses, is specific for MS and not for other EBV- related conditions such as rheumatoid arthritis. To assess the functional correlates of this finding, we analyzed gene expression lists from the peripheral blood of persons with MS and from cortical areas of post-mortem MS brains. In these datasets, we found that the frequency of MS-associated genes, that are part of the EBV interactome, was higher in the dysregulated gene lists than expected by chance.

Conclusions: This study shows that the interaction between viruses and disease predisposing genes is relevant and, to some extent, specific for the etiology of MS.

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Altered EBV transcriptional profile in the peripheral blood of CIS and MS patients

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EBV infection is strongly associated with MS and increasing evidence indicates that EBV deregulation might be implicated in the dysimmune process that targets the brain and spinal cord. Some studies reported that EBV DNA load is higher in peripheral blood mononuclear cells (PBMC) of patients with MS compared to control subjects. To investigate this issue further, droplet digital PCR and pre-amplification real time RT-PCR were used to quantify EBV DNA and RNA, respectively, in PBMC from healthy donors (HD; n = 28), therapy-free patients with relapsing-remitting MS (RRMS; n = 61), and CIS patients (n = 25). Patients included in the study were enrolled at the MS centers of San Luigi Gonzaga Hospital/Orbassano, Florence University and Cagliari University; PBMC samples from HD were obtained from CRESM/San Luigi Gonzaga Hospital.

EBV DNA was detected in PBMC from 46% of therapy-free RRMS patients, 36% of CIS patients and 39% of HD, without significant differences in EBV DNA frequency or amount between patients and controls. EBV transcripts were detected in PBMC from 22/61 RRMS patients (36%), 6/25 CIS patients (24%), and 7/28 (25%) HD. However, the EBV transcriptional profile markedly differed between patients and HD. Six out of 7 EBV+ samples from the 28 HD contained only EBER1 (latency 0) and only one sample displayed very low amounts of both EBER1 and LMP1 (latency II program). Interestingly, EBV transcripts associated with EBV latency activation (EBNA3A, EBNA1, LMP1, LMP2A: latency III and latency II programs) and lytic cycle (BZLF1, gp350/220) were detected in 18/22 (82%) and in 3/6 (50%) EBV+ RNA PBMC samples from RRMS and CIS patients, respectively. EBV transcripts were also quantified in CSF cell samples (n=76) matched to PBMC from CIS and RRMS patients. Despite the percentage of patient CSF samples with detectable EBV RNA was very low (7%, 5/76 samples), transcripts associated with EBV latency disruption and/or entry into the lytic cycle were present in all 5 EBV RNA+ CSF cell samples.

This is the first study to show EBV RNA alterations in peripheral blood of CIS/MS patients compared to HD, strengthening the idea that altered control of EBV infection is associated with the disease. These data also suggest that RNA markers of EBV deregulation

can be monitored in the peripheral blood during therapy and could provide useful information on the relationship between drug efficacy and changes in EBV-immune system interaction.

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P450

Link between intake of monounsaturated fatty acids and cerebral gray matter atrophy in early MS

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Introduction: Important associations between fatty acid (FA) intake and disease-related outcomes have been suggested by limited pre-clinical and clinical studies in MS. Relevant to the concept of MS as a neurodegenerative disease, this line of research is already well developed in the aging literature, where FA intake and adherence to Mediterranean-style diet are associated with imaging and clinical outcomes of cognition. In particular, it has been suggested that intake of monounsaturated fatty acids (MUFAs), found in foods such as olive oil, avocados, and nuts, may be a driving factor behind links observed in aging, possibly due to reduction in oxidative stress. We therefore evaluated the relationship between the FA (monounsaturated, polyunsaturated, saturated) intake and cerebral gray matter in our early MS cohort.
Objective: Evaluate associations between FA intake and cerebral gray matter in early MS
Methods: We utilized baseline data from the NYC RESERVE cohort, an ongoing prospective longitudinal study evaluating risk and protective factors for disability in early MS (< 5 years diagnosed). Here we report on the first 140 participants (age 34.1±7.6; 90 women, 2.2±1.5 years since diagnosis). Participants were placed into tertiles of FA intake (low, medium, high, based on food frequency questionnaire). Cortical thickness (CT) and normalized grey matter (nGM) were derived from 3D T1 3T MRIs (FreeSurfer).
Results: CT was lower among patients with low MUFA intake (2.45, 95CI: 2.42-2.48) than patients with medium (2.48, 95CI: 2.46-2.51, p=.059) or high (2.50, 95CI:2.47-2.52, p=.017) intake, after adjusting for age, sex, socioeconomic status (patient/maternal education) and T2 lesion volume (T2LV). Suggesting a disease-specific association, MUFA intake attenuated the expected negative relationship between T2LV and CT in our cohort (p for interaction=0.046). Results were similar for nGM. We did not note significant links between saturated or polyunsaturated FA intake and CT or nGM.
Conclusions: In our cohort of patients with early MS, we detect a link between MUFA intake and measures of cerebral gray matter atrophy highly associated with disability in MS (CT and nGM). Further, MUFA intake's attenuation of the negative relationship between T2LV and CT and nGM suggests that MUFA intake may serve a protective role in MS patients, limiting the impact of MS-related lesions on cerebral gray matter, which may have important implications later in the disease.

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P451

The bio-psycho-social associations of smoking in multiple sclerosis

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Background: Smoking is thought to be a risk factor for developing multiple sclerosis (MS) as well as converting from clinically isolated syndrome to definite MS. In addition, smokers have a higher relapse rate, greater brain atrophy and higher disability than non-smokers though a recent meta analysis of 11 studies on disability and smoking had found methodological inconsitencies. There has been little examination of the effects of smoking on MS symptomatology and quality of life (QoL).
Objective: To determine differences across a wide range of MS symptoms, disability measures and QoL, by smoking history.
Method: Multiple self-report instruments describing a bio-psycho-social model of MS, and detailed smoking history, were administered concurrently to patients with definite MS as part of the TONiC study, a multicentre, UK study of factors affecting QoL in MS. Subject characteristics including disease type and

EDSS band were determined by a physician at study enrolment. Summed raw scale scores were converted to interval level data by application of the Rasch measurement model. Differences in mean scale measurements were determined by one-way ANOVA (alpha 0.05).

Results: 2397 records were available for analysis. There were 49% who had never smoked, 37% ex-smokers, 14% current smokers. 74% were female, 65% had relapsing, 12% primary progressive and 23% secondary progressive disease. 50% were fully ambulatory (EDSS 0-4), 38% EDSS 4.5-6.5, 7% EDSS 7.0-7.5, 5% 8.0-9.5. There were significant differences in nearly all domains measured; in general there was a gradient from never-smokers to ex-smokers to current smokers (never-smokers consistently the best). This was seen for QoL (WHOQOL, LMSQOL, EQ-5D), disability/impact (WHODAS2, London Handicap, MSIS-29), fatigue, spasticity, pain, sleep, vision, sexual functioning, self-efficacy & depression (all $p< 0.001$). Anxiety was equally greater in both ex-smokers and current smokers. No differences were seen in worry, multidimensional health locus of control, coping or bladder function. There was no difference in age at disease onset. Subgroup analysis revealed that many of the differences were less or lost in primary progressive disease.

Conclusion: A history of smoking is associated with poorer outcomes across nearly all aspects of relapsing MS but these associations are weaker in primary progressive disease. Association does not imply causation and a dedicated smoking cessation study is required.

Disclosure

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The association between smoking status and comorbidities and other symptoms in patients with multiple sclerosis

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Introduction: Smoking is a risk factor for multiple sclerosis (MS) development and it could be related with a faster disability progression rate measured by Expanded Disability Status Scale (EDSS).

Objectives: Our objective is to evaluate if smoking increases symptoms and comorbidites associated with multiple sclerosis and therefore is related with a low quality of life.

Methods: We randomly recruited a sample of 177 adults with definite MS who accepted to complete a self-administered questionnaire (98%) about their exposure to tobacco. We then divide them into three groups: smokers, former smokers or unexposed. We also collected clinical and demographic variables from our database such as the presence of vascular risk factors and autoimmune diseases and the prevalence of symptoms related to MS like depression, anxiety, cognitive decline, visual problems, sphincters disorders, fatigue, spasticity, pain and headache in our sample. We describe the associations between smoking and these clinical variables.

Results: There were 177 patients, 119 women and 58 men with a mean age of 42 years (20-82). The mean duration of disease was 12 years (1-42). 31% were smokers, 41% never smoked and 28% were former smokers. Depression, anxiety, cognitive decline, visual problems and spasticity were more prevalent in patients exposed (smokers and former smokers) than in unexposed patients with significant differences ($p< 0.05$) in depression and spasticity. A positive correlation ($p< 0,05$) was found between the number of years of smoking exposure, pack-year index and accumulated EDSS at the moment of the study and depression, cognitive decline complaints, sphincters dysfunction and spasticity. The prevalence of other vascular risk factors such as high blood pressure, hyperlipidemia and diabetes, and other autoimmune diseases was low in our sample and we did not find significant differences between groups.

Conclusions: Depression, visual problems and spasticity were more common in patients exposed and were also significantly correlated with time and dose of tobacco exposure. Smokers and former smokers had a higher EDSS score, perhaps this may interfere with these results.

Our conclusions provide additional reasons to incentive smokers to quit.

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Neurobiology

P453

Identification of oligodendroglial secreted factors inducing nodal protein clustering in the central nervous system

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The fast and reliable propagation of action potentials along myelinated fibers relies on the clustering of voltage-gated sodium channels (Na_v) at the nodes of Ranvier. Our recent study uncovered the influence of oligodendroglial secreted factors for nodal protein clustering before myelination (i.e. prenodes) on hippocampal interneurons and extended to electrophysiological characterization and *in vivo* relevance (Freeman et al., 2015). We further characterized the oligodendrocyte-conditioned medium (OCM) activity and found that addition of a combination of recombinant cell adhesion molecule and extracellular matrix proteins on purified neuron culture is sufficient to induce Na_v clustering in the absence of oligodendrocytes. Furthermore, inhibition of the protein activity in the OCM, using an immunodepletion approach and knock out models, reduces its clustering activity. Altogether this suggests that early events of nodal protein clustering result in a complex interplay of cell adhesion molecules and extracellular matrix proteins. Moreover, to further characterize the intrinsic neuronal properties within the cells that develops nodes prior to myelination, we analyzed their electrophysiological properties. We also use a gene expression analysis approach to compare gene expression in hippocampal neurons with and without prenodes. This could allow for identification of specific roles for oligodendrocytes or their precursors in the developing nervous system and interactions that mediate myelination of interneurons.

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Molecular mechanisms underlying T cell-oligodendrocytes interactions in neuroinflammation

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Background: The mechanisms driving oligodendrocyte (OL)/myelin sheath injury in MS are poorly understood and no neuroprotective therapeutic strategy is available. Pro-inflammatory CD4 T cells are pivotal immune mediators in MS and its animal model experimental autoimmune encephalomyelitis (EAE). Activated CD4 T cells can exert cytotoxicity towards OLs in vitro and their presence worsens OLs injury and impairs remyelination in vivo. Using two-photon live imaging in EAE, we observed direct interactions between activated CD4 T cells and OLs in vivo. As OLs do not express MHCII, the molecular mechanisms underlying these interactions are unknown. CD4 T cells found in MS brains express high levels of specific cell adhesion molecules (CAMs) and CAM ligands (CAMLs). We hypothesize that OLs express the cognate ligands of these CAMs/CAMLs in inflammatory conditions such as MS and EAE.
Aim: To characterize CAMs expression by human and mouse OLs in resting vs. inflamed conditions.
Methods: CAMs expression was measured by flow cytometry (FACS) on human (MS vs control) and mouse (EAE vs control) OLs ex vivo. Adult human and murine OLs in primary culture were exposed to anti- or pro-inflammatory cytokines or activated T cells before assessment of CAMs expression in vitro by FACS and qRT-PCR. Immunofluorescence (IF) on MS vs control human brain frozen sections and on EAE vs control CNS slices was used to determine expression of CAMs in situ.
Results: Adult human and murine OLs express MCAM, ALCAM and ICAM-1. Expression of CAMs, especially ICAM-1, increases on human and murine OLs in inflammatory conditions ex vivo (MS lesion vs. control, EAE vs. controls). Exposure to TNF and IFN-gamma or co-culture with activated T cells increases CAMs expression by human OLs in vitro. Co-expression of CAMs by OLs (Nogo-A) is observed in MS, EAE and control CNS sections in situ.
Conclusions: OLs express higher CAMs levels in inflammatory conditions, suggesting that CAMs/CAMLs interactions could play a role in CD4 T cell-mediated OLs injury in MS and EAE. Functional studies will evaluate the impact of blocking/depleting CAMs on OLs in neuroinflammation.
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Comparison of glia cell damage in exemplary hereditary leukodystrophies

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X-linked adrenoleukodystrophy (X-ALD), metachromatic leukodystrophy (MLD) and globoid cell leukodystrophy or Krabbe's disease (GLD) are three relatively common examples of hereditary demyelinating diseases caused by a dysfunction of peroxisomal or lysosomal lipid degradation. In all three conditions, accumulation of non-degraded lipids leads to the destruction of cerebral white matter. Because of their relatively high lipid content, oligodendrocytes are generally considered key to the pathophysiology of leukodystrophies. However, the variable response to allogeneic stem cell transplantation points to the importance of cells related to the hematopoietic lineage in the pathogenesis of these diseases. In the present study, we aimed to better characterize the pathogenetic role of microglia in the above mentioned leukodystrophies. We applied recently established microglia markers to human autopsy cases of X-ALD, MLD and GLD, an approach that enabled the delineation of distinct lesion areas in acutely evolving demyelinating lesions. Comparing different glia cell types, we found that microglia were affected early and severely. In all three diseases, we saw signs of microglia cell death in different lesion stages. However, the morphology and dynamics of microglia decay were distinct in the diseases examined here. In summary, the use of new microglia markers showed early and severe damage to microglia in the pathogenesis of the here examined leukodystrophies. This hints at a more sophisticated role of microglia in these diseases than the mere removal of cell and myelin debris, and provides a further example of the complex interplay of different glia cell types in central nervous system diseases.

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Neurodegeneration

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Retinal ganglion cell layer and cervical spinal cord gray matter atrophy are present and underlie pathway specific disability in very early stage multiple sclerosis

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Introduction: Cortical and subcortical brain gray matter (GM) atrophy occur early in the course of MS, but whether this underlies any early clinical dysfunction is unclear. Cervical spinal cord (SC) GM area and retinal ganglion cell layer (GCL) thickness are relatively easy to obtain, easy to quantitate and are promising means for assessing GM injury in MS. However, detailed assessments of these metrics and associations with disability metrics at the earliest disease stages have not been performed.
Objectives / aims: To investigate whether in early MS, GM atrophy can be detected in the retina and cervical SC, and whether it is associated with prior relapse and pathway specific or total disease related disability.
Methods: Sixty-four patients with median disease duration of 6 months (mean age 36.9 years, 20 men, median EDSS 2.0) and 42 matched healthy controls (HC) (mean age 36.9 years, 12 men) were investigated. SC GM and WM areas at C2/C3 (by PSIR imaging), GCL and retinal fiber nerve layer (RFNL) thickness (by SD-optic coherence tomography) were measured. Area and thickness differences betw. groups, and the associations between GM metrics and both focal (9-Hole Peg Test (9-HPT), 2.5% low contrast letter acuity (LCLA)) and global (Expanded Disability Status Score (EDSS), Symbol Digit Modalities Test (SDMT)) disability metrics were assessed using multivariable regression.
Results: SC GM areas and GCL were both sig. reduced in relapsing ($p=0.0252$, $p=0.0030$) and progressive patients (both $p< 0.0001$) compared to HC in the absence of sig. SC WM and RFNL reductions. SC GM and GCL atrophy were each also detected in subgroups of patients without prior SC relapse ($p=0.0086$) or optic neuritis ($p=0.0095$), respectively. Adjusting for age and sex, both SC and retinal GM metrics showed sig. associations with their corresponding focal disability metric (9-HPT: adj. $R^2=0.29$, LCLA: adj. $R^2=0.30$); associations with global disability metrics (EDSS: adj. $R^2=0.12$, SDMT: adj. $R^2=0.07$) were weak/non-sig.
Conclusions: At an early stage of MS, GM atrophy can be detected in the SC and retina in the absence of WM atrophy, even in patients without prior relapses in the corresponding functional system. Retinal and cervical SC GM atrophy correlate with focal disability metrics. This suggests that although GM is widespread at the earliest disease stages, it is not evenly distributed and provides evidence that GM injury underlies disability even very early in the disease.

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Effect of delayed-release dimethyl fumarate on cognition in Italian patients with relapsing remitting multiple sclerosis: the phase 4 StarTec study

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Introduction: Delayed-release dimethyl fumarate (DMF) has demonstrated good efficacy and a favourable benefit-risk profile in patients with relapsing-remitting multiple sclerosis (RRMS) in Phase 3 studies (DEFINE/ CONFIRM).
Objectives: To evaluate the effectiveness of DMF in RRMS patients treated in real-world clinical practice over 2 years, with a focus on cognition, as well as other functional outcomes function.
Methods: This multicentre (24 Italian sites), single arm, open-label study, enrolled 232 patients. Of the 232 patients, 217 were eligible for analysis; 156 patients completed the study. All patients were assessed at baseline and every 12 months thereafter using the Rao's Brief Repeatable Battery (BRB), Stroop test and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Cognitive impairment (CI) was defined as failure in ≥2 out of 10 batteries among the BRB and Stroop test.
Results: Of 167 patients with cognitive data over 2 years, 83 (49.7%) did not develop CI. However, 29% (49/167) patients in the intent-to-treat population exhibited CI at baseline. Of these, 34 patients had cognitive data available at Year 2: among these, 19 (55.9%) did not experience deteriorating CI over 2 years compared to baseline. The unadjusted ARR at Year 1 and Year 2 was 0.265 and 0.19, respectively. The majority of patients were relapse-free (n=175; 80.6%) and had no evidence of disability progression (n=177, 94.1%), as per 6-month sustained EDSS at 2 years Overall, there were significant decreases in total scores on the Modified Fatigue Impact scale, Montgomery and Asberg Depression Rating Scale and Environmental Status Scale over 2 years. There was a significant increase in EQ-5D Health Survey VAS from baseline to each post-baseline visit and over the study period ($P< 0.0001$). One-hundred-fifty-five (71.4%) out of 217 patients experienced mostly mild to moderate treatment-emergent adverse events, most commonly flushing (41.9%).
Conclusions: These findings suggest that DMF can delay cognitive worsening in RRMS patients. A positive effect on patient reported outcomes, including fatigue, depression, activities of daily living and quality of life was reported.

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Serum Neurofilament light chain concentration correlates with cognitive impairment and brain atrophy in relapsing remitting MS

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Background: Neurofilaments are structural proteins of neurons, axons and dendrites and increased levels of neurofilament light chain (NfL) have been reported in serum of Multiple Sclerosis patients, correlating with CSF levels, disease severity, worse clinical outcome and MRI lesions. Current NfL observations do not include correlations with cognitive deficits and brain atrophy, which mostly have axonal loss as pathological substrate.
Objective: to evaluate in a sample of homogeneous MS patients with relapsing remitting course and same therapy, the correlation between serum NfL levels and cognitive impairment as well as brain atrophy.
Methods: 18 right handed relapsing remitting MS patients (mean age 45 years, mean EDSS 2), prescribed with interferon beta 1a from no more than a semester, were submitted to neuropsychological evaluation with Brief Repeatable Battery (BRB) and Delis Kaplan Executive Function Sorting (DKEFS) tests, MRI to assess gray matter volume and density and NfL serum concentration by using SR-X immunoassay analyzed, Simoa TM, which runs ultrasensitive paramagnetic bead-based enzyme-linked immunosorbent assays (Quanterix Corp, Boston, MA).
Results: a significantly increased serum NfL level was found in MS cases compared to age matched controls (p=.03). Serum NfL correlated with age (Pearson r=.58; p=.001). A positive correlation was found between serum NfL and Cognitive Impairment Index (CII, calculated by summing -z scores in each cognitive test, Spearman p=.04), memory (Selective reminding test, Spearman p< .05) and executive function (DKEFS Sorting test description p=.03) tests. More severely impaired patients in cognition (CII>8) had significantly higher serum NfL (9.04 pg/ml) than less severely impaired ones (6,31 pg/ml; Mann Whitney p=.003). A significant correlation was found between NfL and GM density in the right parahippocampus and between CII and GM density in the right prefrontal region.
Conclusions: serum NfL values are related to cognitive deficits and to measures of brain atrophy. These data, though obtained in a small sample, support the future use of serum NfL as a surrogate marker of disability in MS patients, with particular regard to axonal injury.

Disclosure

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P459

Leptomeningeal contrast enhancement correlates with neurodegeneration in multiple sclerosis

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Background: Leptomeningeal contrast enhancement (LMCE) on magnetic resonance imaging (MRI) is associated with disease progression and neurodegeneration in multiple sclerosis (MS). Studies show that both cortical grey matter (GM) and white matter (WM) lesions correlate with neurodegeneration. It is unknown if LMCE correlate with WM or GM lesions.
Aim: The aim of this study was to assess the relationship between LMCE and lesion burden of the brain white and grey matter in patients with MS.
Objectives: To measure the volume of white and grey matter lesions in patients with and without LMCE and to assess the correlation of lesion load and volumes of brain structures.
Materials and methods: LMCE were detected on 3 Tesla MRI with post-contrast fluid attenuated inversion-recovery (FLAIR) sequence, 10-12 minutes after gadolinium administration. WM and intracortical GM lesion load on FLAIR/T2 and double inversion-recovery (DIR) sequences respectively was manually counted using 3D Slicer. Normalized brain volume (NBV), WM and GM volume were counted using SIENAX software. Cortical thickness, total ventricles, thalamus and hippocampal volumes were assessed with FreeSurfer.

Results: 54 MS patients (20 male and 34 female) were included. LMCE was detected in 23/54 (43%) patients. The median (IQR) age was 36 (25) years in LMCE(-) patients and 43 (22) years in LMCE(+) patients, p=0.0613. The disease duration was significantly lower in LMCE(-) vs LMCE(+) patients - 64 (104) months and 121 (142) months respectively, p=0.0094. LMCE(+) patients revealed some higher WM and GM lesions load, but the difference was not statistically significant. In LMCE(+) patients, volume of WM lesions, but not GM lesions, revealed significant negative correlation with NBV (r=-0.4792, p=0.0207), whole WM volume (r=-0.5158, p=0.0118), cortical WM volume (r=-0.5632, p=0.0051) and significant positive correlation with total ventricles volume (r=0.6423, p=0.001). In LMCE(-) patients, volume of WM and GM lesions showed significant positive correlation only with total ventricles volume (FLAIR: r=0.723, p< 0.0001; DIR: r=0.5458, p=0.0015). WM and GM lesion load didn't correlate with disease duration or age in both groups. In LMCE(-) group GM lesions volume correlated with WM lesions volume (r=0.5543, p=0.0012), but not in LMCE(+) group.
Conclusion: WM lesions in LMCE(+) MS patients are associated with more profound neurodegeneration that is independent from age, disease duration and GM lesions.

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Unilateral motor progression in multiple sclerosis: the impact of single critical corticospinal tract lesions

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Introduction: Progressive motor impairment anatomically attributable to a single demyelinating lesion is seen in patients with "progressive solitary sclerosis". These "critical lesions" are generally prominent lesions located in the spinal cord along corticospinal tracts and associated with focal atrophy. Rare multiple sclerosis (MS) patients with exclusively unilateral motor progression may offer insight into the role of such critical lesions in the development of progression.
Objective: To determine if progressive exclusively unilateral motor impairment in MS can be attributable to a single critical lesion.
Methods: We included Mayo Clinic patients (1996-2017) who had: (1) ≥1 year of unilateral motor progression; (2) no contralateral pyramidal symptoms/signs; (3) >5 central nervous system demyelinating lesions; (4) fulfilled 2017 McDonald MS criteria. A blinded neuroradiologist evaluated MRI's and determined whether a single potential critical lesion could be identified based on MRI characteristics .
Results: Thirty-eight patients were included: primary progressive MS, 20 (53%); secondary progressive MS, 18 (47%). Median age at progression onset was 55 years (range, 39-73). Median EDSS was 5 (range, 2.5-7.5) at last follow-up (median, 119.5 months from symptom onset; range, 22-418). Progressive unilateral motor impairment was characterized by (face-sparing) hemiparesis or monoparesis. The likelihood of detecting at least one demyelinating lesion along the corticospinal tract to which the deficit could be attributed was higher (100%) than on the contralateral side (39%) (p< 0.0001). The neuroradiologist identified a single potential critical lesion in 26 cases (68%): cervical cord, 20; thoracic cord, 6. In all 26 the progressive motor deficits were attributable to the identified critical lesion. Of the remaining 12 patients, eight had two potential critical lesions along the same corticospinal tract to which the deficit localized.
Conclusion: In MS patients with unilateral motor progression, a single, recognizable critical lesion along corticospinal tracts may be responsible.

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P461
Deletion of the activity-dependent transcription factor neuronal PAS domain protein 4 protects against clinical disease in models of multiple sclerosis

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Introduction: Several processes involving inflammatory cells and their mediators contribute to neurodegeneration in MS. Neuronal

PAS Domain Protein 4 (Npas4) is a basic-helix-loop-helix transcription factor implicated in neuronal health, plasticity, and protection. Npas4 regulates genes that control inhibitory synapse development, a "master switch" to calm over-excited cells that also binds aryl-hydrocarbon receptor nuclear translocator 2 (ARNT2) to regulate brain-derived neurotrophic factor (BDNF) transcription.
Objectives/Aims: In experimental autoimmune encephalomyelitis (EAE), we showed that Npas4 message rises pre-clinically in the CNS yet Npas4, ARNT2 and BDNF all drop at onset and are lowest at peak disability. We hypothesized Npas4 is required for neuronal survival in inflammatory settings and would be protective in EAE.
Methods: Npas4 expression was examined in enriched neuronal cultures in response to immune cells, oxidative stress, glutamate and KCl. The functional relevance of Npas4 was examined following knockdown (KD) with siRNA and chronic-progressive EAE induced in Npas4-deficient (KO) mice.
Results: Npas4 expression is negligible compared to constitutive ARNT2 in cortical neurons *in vitro*. Oxidative stress, co-culture with activated immune cells and glutamate each drive *de novo* Npas4 expression accompanied by enhanced BDNF expression. Npas4 induction is Ca^{2+} dependent and secondary to *de novo* RNA and protein synthesis. Notably the cytotoxicity following H_2O_2 exposure is significantly reduced by Ca^{2+} chelation with EGTA. *In vitro*, Npas4 KD limits increases in BDNF with minimal effects on viability. Notably, ARNT2 KD has no influence on neuron viability or BDNF expression; we attributed this to an uncoupling of Npas4 and ARNT2 to BDNF expression. In contrast, sustained increases in Npas4 after H_2O_2 or glutamate exposure are associated with morphological changes and losses in viability. Npas4 KO mice are protected against severe disability in EAE, where cumulative and peak disease scores are reduced by 50-60% in KO mice.
Conclusions: Our findings of Npas4 expression in response to inflammatory stressors lead us to question a neuroprotective role for Npas4 in chronic inflammatory settings. Instead, we propose that Npas4 signaling in response to Ca^{2+} increases the susceptibility of neurons to damage, and warrants further investigation as a potential target to limit neurodegeneration during processes involved in MS onset and progression.

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Repairing mechanisms

P462
miR-27a inhibits oligodendrocyte precursor cells maturation to oligodendrocytes in during remyelination

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Introduction: Micro RNAs (miRNAs) are single stranded, 19-23 nucleotide long, non-coding RNAs that regulate gene expression at posttranscriptional level by complementary binding to 3' untranslated region (UTR) regions of target genes. Modulation of gene expression by miRNAs plays central role in several neurodegenerative diseases including multiple sclerosis (MS), a chronic inflammatory demyelinating disease. Failure in remyelination is considered one of the main reasons for MS disease progression. This failure in remyelination is however commonly associated with presence of immature oligodendrocytes (OLs) within lesions of MS brains.
Objective: To evaluate functional role of miR-27a during oligodendrocyte lineage development**.**
Methods: Global genome expression analysis and RT-qPCR was applied to analyze and validate miRNA expression level in chronic demyelinated postmortem human brain. Further, role of miR-27a in myelination was investigate using in vitro primary oligodendrocyte progenitor cell (OPCs) culture system.
Results: miR-27a expression was significantly downregulated in demyelinated MS lesion. Our in vitro functional assay showed that transient transfection of chemically synthesized miR-27a (mimic) in OPCs inhibited differentiation of OPCs into mature OLs. We also found that miR-27a overexpression cause significant increase in levels of Chondroitin sulfate proteoglycan 4 (Cspg4/Ng2) protein without increase in proliferation of the OPCs. At mRNA transcripts and protein level, expression of miR-27a showed dysregulation of genes involved in Wnt-β-catenin signaling pathways which have been reported to negatively regulate OLs differentiation.
Conclusions: Taken together, our results indicate that miR-27a may play a major role in arresting OPCs in the immature state leading to remyelination failure in MS.

Disclosure

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Oncostatin M-induced astrocytic TIMP-1 enables remyelination

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Introduction: Multiple sclerosis (MS) is a chronic disabling disease of the central nervous system (CNS), characterized by focal areas of inflammation in which myelin, oligodendrocytes (OLGs) and neurons are damaged. Oncostatin M (OSM), a member of the interleukin (IL)-6 cytokine family, is produced in lesions of MS patients and we demonstrated in previous research that OSM protects against demyelination in the cuprizone mouse model and enhances neurite outgrowth during spinal cord injury.

Objectives: In this study, we investigate the role of OSM in remyelination in the cuprizone model, and its underlying mechanism.
Methods: Using cuprizone-induced demyelination in mice, we investigated the effect of OSM receptor deficiency in OSMR KO mice on one hand and the effect of local OSM overexpression (using stereotactical injection of lentiviral vectors) on the other hand. Tissue analysis by means of qPCR and immunohistochemistry was done to reveal differences in genotypes or treatment groups. In vitro cell cultures were used to determine mechanistic processes.
Results: Here, we show that OSMR-deficient mice have an impaired remyelinative capacity after cuprizone-induced demyelination. In parallel, local OSM overexpression enhanced remyelination. Interestingly, we found that local OSM overexpression induced activation of astrocytes, and that these astrocytes produced TIMP-1, a matrix metalloproteinase inhibitor. To assess whether TIMP-1 is the downstream mediator of OSM in enhancing remyelination, TIMP-1 KO mice were fed a cuprizone diet. TIMP-1 KO mice phenocopied OSMR KO mice and showed reduced remyelination. Currently, the mechanism of TIMP-1 mediated remyelination is being investigated.
Conclusions: Local expression of OSM in demyelinated lesions activates astrocytes to produce TIMP-1, which enables remyelination. Exploring this further will result in important fundamental and therapeutically applicable knowledge for MS patients.

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Chondroitin sulfate proteoglycans impede oligodendrocyte differentiation through rho-kinase and myosin II

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Introduction: Oligodendrocyte precursor cells migrate to lesion sites to repair myelin. Throughout MS progression, this ability to repair diminishes considerably and is thought to be a consequence of lesion-associated inhibitory factors, including chondroitin sulfate proteoglycans (CSPGs), which perturb OPC maturation into myelinating oligodendrocytes. These factors are known to inhibit the differentiation process, yet the mechanism driving this signal remains unclear.
Objectives: The current study aims to characterize the oligodendrocyte response to CSPGs, as well as explore the molecular pathways involved in CSPG-mediated inhibition of oligodendrocyte differentiation.
Aims: We hope to investigate signaling proteins in oligodendrocytes that have been previously implicated in CSPG-mediated inhibition of neuronal morphology. We will first explore the involvement of GSK3ß, followed by rho kinase and non-muscle myosin II (NMII).
Methods: A primary oligodendrocyte cell culture system was used. Characterization of morphological and molecular differentiation was performed following manipulation of the signaling pathways of interest.
Results: We have validated the negative impact of CSPGs on oligodendrocyte morphology in our system. Interestingly, CSPG-mediated inhibition of neuron development depends greatly on both GSK-3ß and RhoA activity. Here we show that GSK-3ß signaling is likely not crucial in mediating the effects of CSPGs in oligodendrocytes. Contrastingly, inhibition of Rho kinase improved the morphological perturbations of oligodendrocyte differentiation in the presence of CSPGs, as did inhibition of downsteam NMII. It has become clear that oligodendrocytes are mechanosensitive, and that differentiation relies on a permissive mechanical substrate. Interestingly, the transmission of mechanical cues relies on rho kinase/NMII signaling. Ongoing studies will explore the possibility that CSPG-mediated inhibition of oligodendrocyte differentiation occurs as a result of an altered mechanical environment.
Conclusion: This study reveals specific targets involved in CSPG-mediated inhibition of oligodendrocyte growth. It also highlights previously unappreciated differences between oligodendrocyte and neuronal responses to the same inhibitory cue. Further investigation of these mechanisms will provide a better understanding of the lesion microenvironment contribution to pathophysiology in multiple sclerosis.

Disclosure

Sarah Cummings: nothing to disclose

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Impact of cerebrospinal fluid on human Wharton jelly mesenchymal stem cells *in vitro* - therapeutic implications to multiple sclerosis

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Objective: Wharton´s jelly (WJ-MSC) mesenchymal stem cells are attractive therapeutic option in multiple sclerosis (MS), related to their proliferation, capacity in culture and prospective immunoregulatory and regenerative potential. Clinical trials with mesenchymal stem cells in patients with multiple sclerosis (MS) are currently conducted, one of proposed and tested route of cell delivery is intrathecal. WJ-MSC and cerebrospinal fluid (CSF) interactions are interesting question and require further explanation.
Methods: WJ-MSC obtained from The Polish Stem Cells Bank were cultured with condition of proinflammatory cytokine interferon gamma (IFNg), 5% CSF from multiple sclerosis patients (n=5) and control CSF (n=5). After 24 hours incubation the next step was 24 hours culturing free of serum, at the end supernatants were collected. Quantitative analysis of the 27 cytokines and

growth factors in the WJ-MSCs culture supernatants were performed using Bio-Plex Multiplex Immunoassays (Biorad) in two independent experiments.

Results: Addition of proinflammatory cytokine INF-gamma to WJ-MSC culture showed increased expression of Il-4, Il-6, Il-9, Il-15, Il-17, IP-10, RANTES and VEGF, FGF, PDGF. Whereas incubation with control CSF resulted in increased level of Il-1, Il-5, Il-6, IP-10, RANTES, FGF, G-CSF, GM-CSF, VEGF compare to medium condition. In WJ-MSC treated in culture with 5% MS CSF we observed significant higher level of Il-5, Il-6, RANTES, FGF, GM-CSF, VEGF compare to control CSF ($p< 0.05$). Both control and MS CSF culture conditioning resulted in significant reduction of eotaxin compare to medium condition culture.

Conclusions: WJ-MSC are promising therapeutic strategy for patients with multiple sclerosis. WJ-MSC immunosuppressive and regenerative potential depends on the surrounding environment, those dependencies require further research in cell therapy for MS.

Disclosure

nothing to disclose

MRI and PET

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Infratentorial and spinal cord lesions, cumulative predictors of disability?

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Introduction: Infratentorial and spinal cord lesions are frequently present in multiple sclerosis. Their location suggests an important role in motor function and consequently lesions in these areas often contribute to disability. The aim of this study was to determine whether infratentorial and spinal cord lesions cumulatively predict disability progression better than these locations separately.

Methods: We included 156 patients from the Amsterdam MS cohort shortly after their first clinical event. Patients were followed for 6 (n=156) and a subset for 11 years (n=95). Baseline (BL) brain and spinal cord MRI were performed and lesions were counted per region (supratentorial, infratentorial and spinal cord). Expanded Disability Status Scale (EDSS) was obtained, and in order to determine EDSS-plus progression also the 25-foot walk test and 9-hole peg test were measured at BL and after 6 and 11 years. Patients were divided into 4 groups according to MRI lesion location at BL: 1. Patients with both spinal cord and infratentorial lesions (n=54, 34.6%); 2. Patients with spinal cord lesions but no infratentorial lesions (n=58, 37.2%); 3. Patients with infratentorial but no spinal cord lesions (n=15, 9.6%); 4. Patients without spinal cord and infratentorial lesions (n=29, 18.6%). Logistic regression was performed to determine the risk for EDSS- and EDSS-plus progression after 6 and 11 years.

Results: Median EDSS was 2.0 (IQR 1.5-3.0) at BL, 2.5 (IQR 1.5-3.5) after 6 years and 3.0 (IQR 2.0-4.0) after 11 years. Fifty-one patients (32.7%) showed EDSS-progression after 6 years and 48 (50.5%) after 11 years. EDSS-plus progression after 6 years was seen in 66 patients (50.0%) and in 55 patients (66.3%) after 11 years. Odds ratios showed trends towards spinal cord lesions alone having more impact than infratentorial and spinal cord lesions together. Sub-analyses comparing patients with and without spinal cord lesions showed a higher risk for EDSS progression after 6 years (OR 2.8; p=0.027) and after 11 years (OR 4.1; p=0.009). For patients with infratentorial lesions versus patients without infratentorial lesions no difference was found.

Conclusions: Our results suggest that the presence of spinal cord lesions tends to be more important for predicting EDSS progression than infratentorial lesions. Adding up both spinal cord lesions and infratentorial lesions did not result in a better prediction of disability.

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L.J. Balk has nothing to disclose

J.J.G. Geurts is an editor of MS journal and serves on the editorial boards of Neurology and Frontiers of Neurology and is president of the Netherlands organization for health research and innovation and has served as a consultant for Merck-Serono, Biogen, Novartis, Genzyme and Teva Pharmaceuticals.

F. Barkhof serves as editorial board member of Brain, European Radiology, Neurology, Multiple Sclerosis Journal and Radiology. He has accepted consulting fees from Bayer-Schering Pharma, Biogen-IDEC, TEVA, Merck-Serono, Novartis, Roche, Jansen Research, Genzyme-Sanofi, IXICO Ltd, GeNeuro, Apitope Ltd and speaker fees from Biogen-IDEC and IXICO. Has received grants from AMYPAD(IMI), EuroPOND (H2020), UK MS Society, Dutch MS Society, PICTURE (IMDI-NWO), NIHR UCLH Biomedical Research Centre (BRC), ECTRIMS-MAGNIMS.

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Rapid and reliable, fully-automated brainstem segmentation for application in multiple sclerosis

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Introduction: Atrophy is a hallmark of neurodegeneration in Multiple Sclerosis (MS) that can be quantified by MRI. Brainstem (BS) atrophy is under-investigated in MS.

Objective and aims: To assess accuracy and reproducibility of a fully-automated deep learning-based segmentation method for BS volumetry in 3D high-resolution T1w MRI data of healthy controls (HC) and MS patients.

Methods: Segmentation was done using multi-dimensional gated recurrent units (MD-GRU; Andermatt et al., 2016 (DOI 10.1007/978-3-319-46976-8_15), Andermatt et al., 2017 (DOI 10.1007/978-3-319-75238-9_3)) a deep learning-based, fully-automated semantic segmentation approach employing a convolutional adaptation of gated recurrent units (GRU; Cho et al., 2014 (http://arxiv.org/abs/1409.1259)). In brief, MD-GRU traverses an image forward and backward along each of its spatial dimensions to infer the current segmentation class label from the local appearance and its surrounding context. The respective neural network was trained for 100'000 iterations on 67 scans (17 HC, 50 patients). Mean Dice score wrt. an expert-labeled manual ground truth was used to select the final training state for evaluation:the state producing the highest score on the 3 labeled sub-regions of the BS (midbrain (M), pons (P) and medulla oblongata (MO)) in a separate set of 20 patients' scans was chosen for further analyses. Expert-labeled manual BS segmentations were then used to validate the accuracy of the automated segmentation in another independent set of 20 patients' scans using Dice scores. The reproducibility of the segmentations was assessed in 11 HC that underwent a MR test-retest experiment with repositioning in-between. The mean %-change betw. test and retest and the respective intra-class correlation coefficients (ICC) were calculated.

Results: Accuracy: In the validation set, the mean Dice scores comparing automated to the manual segmentations were (mean/SD):0.97/0.006 (total BS); 0.95/0.015 (M);0.97/0.008 (P); 0.96/0.014 (MO). Reproducibility: The mean %-change/SD between test-retest scans was 0.47%/0.004 for the automated and 0.82%/0.005 for the manual segmentation of the total BS. The ICC of the automated test-retest segmentations of the total BS, M and P were all >0.99, of MO 0.97.

Conclusions: This fully-automated BS segmentation provides accurate, reproducible segmentations in HC and MS patients in 200sec/scan on a Nvidia GeForce GTX 1080 GPU and has potential for use in longitudinal studies.

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Presence of CSF oligoclonal bands is associated with periventricular NAWM damage gradient severity in clinically isolated syndrome

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Introduction: Normal appearing white matter (NAWM) damage is not randomly distributed though the brain in multiple sclerosis (MS), but it is more severe around the lateral ventricles. Indeed, an outside-in gradient in NAWM damage from periventricular NAWM toward deep grey matter has been observed across all the MS spectrum, possibly due to a proximity effect to CSF.

Objectives: To evaluate if in subjects with clinically isolated syndrome (CIS) the periventricular distribution of NAWM damage was associated with the presence of cerebrospinal fluid (CSF) oligoclonal bands (OCB).

Methods: Thirty subjects with a diagnosis of CIS (18 females, 12 males; mean age, 39 ± 11.8 years; EDSS range 0-2) were included in this study and underwent a brain MRI scan and CSF examination within 75 days from their first clinical event. The presence of CSF and serum oligoclonal bands was assessed for all CIS subjects. Twenty-four healthy volunteers (11 females, 13 males; mean age, 37.71 ± 19.5 years) were also recruited as MRI controls. Diffusion weighted MR was acquired for all subjects and used to compute skeletonized mean diffusivity (MD) NAWM maps. The supra-tentorial voxels between 2 and 6 mm of distance from the lateral ventricles were included in the periventricular NAWM mask while the voxels between 6 and 10 mm from the lateral ventricles were included in the deep NAWM mask; mean MD values were then computed separately for these two masks. Using healthy controls data to convert NAWM MD values in z scores, the NAWM damage gradient was calculated as (periventricular NAWM z score - deep NAWM z score) / (periventricular NAWM z score) and then compared between subjects with and without CSF OCB.

Results: Twenty CIS subjects presented with CSF-only OCB (CSF-OCB+), nine CIS with no OCB in CSF (CSF-OCB-) or serum and one with OCB in both serum and CSF. There was a significant steeper gradient of periventricular NAWM damage in with CSF-OCB+ CIS than in CSF-OCB- CIS subjects (0.35 ±0.05 vs. 0.26±0.05, t=4.45, p< 0.001). This difference in the NAMW

periventricular gradient remained significant correcting for total WM lesion load and for brain parenchymal fraction (p=0.008). There was no difference in the two groups in total skeletonized MD (p=0.35).

Discussion: The association between presence of CSF-OCB and of a steeper outside-in gradient in NAWM periventricular damage supports a role for CSF soluble factors in mediating the distribution of NAWM damage in MS.

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A.Uccelli: has received consulting honoraria and/or speaker fees and basic science study grants from Biogen Idec; consulting honoraria and/or speaker fees from Genzyme, Roche, Sanofi Aventis, and Teva; consulting honoraria and/or speaker fees and a basic science study grant from Novartis; consulting honoraria and/or speaker fees and a basic science study grant from Merck Serono
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Lesion patterns topology is associated with regional cortical atrophy and predicts disease-related disability

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Background: Grey (GM) and whiter matter (WM) microstructural alterations are important hallmarks of neuroinflammation in multiple sclerosis (MS). Both processes contribute differently to disease progression and disability. It is however, not clear how the distribution of WM lesions influences GM atrophy and long-term clinical outcome. In this study, we investigated the interrelation of lesion topology and GM atrophy and its impact on emerging functional disability.

Methods: We included 119 patients (mean age ± standard deviation: 34.6 ± 9.8 years, 38 males) with early (disease duration: 37.2 ± 1.5 months) relapsing-remitting MS (RRMS) and performed 3T magnetic resonance imaging (MRI) at baseline and one year later. We applied independent component analyses (ICA) on MRI data to discover distinct patterns from two inputs, first: WM lesion distribution derived from the T2-images and delineation with Lesion Segmentation Tool (LST under VBM8 and SPM12) and second: the rate of cortical atrophy (as derived from Freesurfer) from each voxel of the brain of the same patient. We then calculated the eigenvalue association of WM lesion patterns and the spatial extent of cortical atrophy. The predictive value of patient-specific lesion burden for each pattern has been used to predict emerging clinical disability (EDSS worsening) at the second time point by receiver operating characteristic analysis.

Results: We identified three significant associated patterns (bilateral, lateralized and cerebellar) of white matter lesions and corresponding cortical atrophy. The cerebellar lesion pattern was associated with the largest extent of cortical atrophy, mainly in the temporal and frontal regions. Each of the patterns discriminated progression of disability over one year as quantified by EDSS worsening. However, the lesion burden as determined by the cerebellar pattern was associated with the worst clinical outcome.

Conclusions: Our findings indicate that a distinct spatial distribution of focal WM lesions is associated with cortical atrophy, and is able to precisely predict the individual functional outcome over time together with disease progression. Thus, early identification of clinical phenotypes associated with a specific lesion distribution allows patient stratification for disease progression and clinical impairment.

Disclosure

Nothing to Disclose

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Decreased tract integrity in normal appearing white matter correlates to increased microglial activation and disability in multiple sclerosis *in vivo*

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Background: Neuroinflammation and microglial activation are hallmarks in the pathology of multiple sclerosis (MS). Diffusion tensor imaging (DTI) is a sensitive marker for assessment of pathology related structural alterations in the brain. Quantification of microglial activation with translocator protein (TSPO) binding radioligand [^{11}C]PK11195 positron emission tomography (PET) allows the measurement of neuroinflammation.

Objective: To evaluate structural and molecular brain changes and their correlation to clinical disability using combined *in vivo* magnetic resonance (MR) and PET imaging in MS patients

compared to healthy controls (HC), with correlational analyses of DTI parameters to TSPO radioligand binding.
Methods: A cohort of 55 MS patients (40 RRMS, 15 SPMS, age 28-64 years, EDSS 1-6.5) and 15 HC (age 21-58 years) were imaged with 3T MRI and [^{11}C]PK11195 PET. Mean fractional anisotropy (FA) and mean (MD), axial (AD) and radial (RD) diffusivities were calculated with ExploreDTI within whole normal appearing white matter (NAWM) and segmented NAWM regions (deep WM, cingulate, frontal, temporal, occipital, parietal) derived with Freesurfer. T2 hyperintense lesions were excluded from the WM by segmentation with Lesion Segmentation Tool. Microglial activation was evaluated as the distribution volume ratio (DVR) of [^{11}C]PK11195 from dynamic PET images. Spearman correlations of DTI, PET and clinical data were considered significant at the level of $p < 0.05$.
Results: Mean FA was significantly decreased in NAWM ($p=0.06$), occipital ($p=0.009$) and cingulate WM($p=0.004$) of the MS patients compared to HC. MD and RD were significantly increased ($p=0.005$ and $p=0.004$, respectively) in cingulate WM of MS patients vs. HC. White matter structural abnormalities (decreased FA and increased MD/AD/RD) correlated with increased TSPO binding in the whole NAWM ($p< 0.05$ for all correlations), in temporal WM ($p< 0.01$ for all correlations), and deep WM ($p=0.02$ for FA). Decreased white matter integrity and increased TSPO binding in NAWM also correlated significantly with higher EDSS disability (with strongest correlation with NAWM FA and RD, $p< 0.0001$, and with NAWM DVR, $p< 0.001$).
Conclusion: Microglial activation is strongly linked to widespread disruption of white matter in the NAWM and both associated strongly with clinical disability. Combination of both PET and DTI imaging modalities may enable a better understanding of hidden MS pathology not visible using conventional MRI.

Disclosure

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Large-scale normative volumes of brain structures as assessed by SIENAX

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Introduction: A number of MS studies have used MRI-derived methods to estimate brain volumes (BV), demonstrating clinically relevant atrophy in numerous brain structures. Despite the growing clinical interest, the lack of normative reference data has greatly limited the clinical implementation of BV measures.
Objective: To provide, in a large population of healthy subjects (HS) covering the whole adulthood, MRI-derived normative volumes of different brain structures to be used as reference in clinical studies.
Methods: A multi-centre MRI dataset of 1950 HS was collected from 10 research groups worldwide and from 5 open-source datasets (i.e., ADNI; IXI; MMRR; NKI and OASIS). Normalized (for head size) volumes of the whole brain (NBV), neocortical grey matter (NCV), white matter (NWMV) and brain structures such as hippocampus, thalamus and other subcortical structures were assessed by using an updated version of the SIENAX method (SIENAX2.0). The new implementations in SIENAX are: i) a new brain extraction; ii) FSL-FIRST for assessment of hippocampus

and subcortical structures; and iii) a new scaling factor for a more accurate head size normalization. Models predicting BV were produced including age, sex, scanner vendor, magnetic field strength (i.e., 1.5T and 3T) and interactions as predictors. For each selected final model, the fitting was assessed using R^2.

Results: All the assessed structures showed age, sex and their interaction as significant predictors and, with increasing age, significantly smaller volumes in men than in women. With increasing age, volume decrease was nearly linear for NBV (R^2=0.49, p< 0.0001) and NCV (R^2=0.57, p< 0.0001) and quadratic for NWMV (R^2=0.1, p< 0.0001) and thalamus (R^2=0.29, p< 0.0001). Generally, these measures were independent of the scanner vendor and magnetic field strength. Interestingly, in both women and men hippocampal volumes increased between 20 and 40 years of age (on average, 0.42 and 0.23 cm^3), but showed a rapid reduction between 40 and 80 years of age (1.15 cm^3 and 1.53 cm^3, respectively).

Conclusions: This work provides large-scale, age-related physiological BV of different brain structures as assessed by an improved version of SIENAX. These data can allow a better discrimination between physiological and pathological volumes of brain structures both at group and individual level.

Disclosure

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Gadolinium-induced changes in T1 relaxation time on 7-Tesla MRI in non-enhancing MS lesions may reveal chronic inflammation linked with disability and progressive phenotypes

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Introduction: Gadolinium contrast reveals blood brain barrier (BBB) breakdown in newly developed multiple sclerosis (MS) white matter lesions (WMLs), resulting in visually apparent T1 shortening. Previous attempts at quantification of

gadolinium-induced T1 shortening in non-enhancing WMLs, suggestive of sub-visual BBB breakdown, have had mixed results.

Objectives: Our goals were to find associations of contrast-induced T1 shortening in non-enhancing WMLs at 7-Tesla (7T) with clinical measures and demonstrate its potential as a biomarker of MS disease progression.

Aims: We aimed to evaluate the ability of quantitative T1 maps acquired at 7T to reveal subtle inflammatory changes in non-enhancing WMLs in MS.

Methods: Forty-seven participants with MS underwent brain MRI on a 7T MRI scanner (Philips, Achieva) with a volume transmit/32-channel receive coil. Magnetization prepared 2 rapid gradient echo (MP2RAGE) images were acquired before and after contrast and processed for T1-weighted images and T1 maps. T1 difference (delta T1) maps were generated by subtracting post-contrast T1 maps from pre-contrast T1 maps. WML masks were delineated manually on the pre-contrast T1 maps for all WMLs and enhancing WMLs separately and a non-enhanced WML mask was created by subtraction. T1 values in these masks were then compared to clinical and demographic data. Group differences were assessed by Mann-Whitney U-test and correlations were assessed by Spearman or Pearson correlations, as appropriate.

Results: Only 5(10.6%) participants had enhancing lesions. Delta T1 in non-enhanced WMLs correlated with Expanded Disability Status Scale (EDSS; rho=0.314, p=0.032) scores. Delta T1 was greater (p=0.022) in participants with EDSS ≥5.0 (median: 0.192, range: -0.003 to 0.386) than those with EDSS< 5.0 (median: 0.127, range: -0.079 to 0.574). Delta T1 in non-enhanced WMLs was greater (p=0.001) in participants with progressive MS phenotypes (median: 0.198, range: 0.132 to 0.386) than those with relapsing-remitting MS (median: 0.121, range: -0.079 to 0.574).

Conclusions: Greater changes in T1 relaxation time due to gadolinium in non-enhancing WMLs were seen in participants with higher levels of disability and progressive phenotypes. This suggests that clinically-significant, sub-visual BBB breakdown, potentially due to chronically inflamed WMLs, can be measured by T1 mapping on 7T MRI. This data supports further exploration of this technique as a novel treatment outcome measure in MS.

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Four-week in-patient multidisciplinary rehabilitation program in multiple sclerosis: behavioural and fMRI results

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Background: Although there is evidence supporting the efficacy of multidisciplinary rehabilitation in improving daily activities in people with multiple sclerosis (MS), the brain mechanisms underpinning this improvement are still poorly understood.

Aims: We aimed at investigating the efficacy of a multidisciplinary in-patient rehabilitation program and at studying brain mechanisms underpinning the potential improvement induced by it.

Methods: We included 24 patients with relapse-onset MS (16 female; mean age: 47.7±10.1 years; median EDSS: 5, range 1-6.5; mean disease duration: 17.4±8.9 years) and 24 healthy controls (HC, 16 female, mean age: 45.0±10.1 years). The MS group underwent a pre- and post-rehabilitation session including clinical, cognitive and motor assessments and magnetic resonance imaging (MRI). HC had two sessions four weeks apart, including MRI and cognitive assessments. MS patients underwent an in-patient rehabilitation program (mean duration 16.6±3.2 days, mean: 46.1±15.3 hours of training). The patient-specific program included physical (mean: 32.8±8.6 hours), cognitive (mean: 1±1.7 hours), psychological (mean: 5.3±4.3 hours) and social rehabilitation (mean: 4.5±4.6 hours). Performances were compared between sessions using t-tests. Task-related functional MRI data were acquired by multi-band echo planar imaging (voxel size=2mm isotropic, TR=768ms) on a 3 Tesla scanner (Siemens Prisma). A motor sequence learning (MSL) task with a training and random condition was presented during the fMRI. fMRI data were analysed using FSL.

Results: Patients showed improved walking speed (T25-FW; $t(18)=3.13$, $p< 0.05$), reduced perceived fatigue (FSMC; $t(19)=2.3$, $p< 0.05$) and a trend towards improved right hand dexterity (9-HPT; $t(22)=1.8$, $p=0.08$) after the rehabilitation. At baseline, patients performed less accurately ($t(27)=2.8$, $p< 0.01$) in the training condition of the MSL task compared to HC. However, no differences between groups in the number of mistakes were found post rehabilitation. Improved accuracy went along with a decreased activity in the left cerebellum and right frontal lobe post-rehabilitation. No changes between sessions were observed in HC.

Conclusion: Our results show that rehabilitation can improve walking ability, reduce perceived fatigue and lead to a higher accuracy in performing a motor tasks. The reduction of task-related brain activity after the rehabilitation program may reflect a more efficient recruitment of brain regions.

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Precision of manual vs. automated corpus callosum atrophy measurements in multiple sclerosis

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Introduction: The corpus callosum connects the two hemispheres and is resistant to age-related change. In multiple sclerosis (MS), however, it is affected by both focal lesions and Wallerian degeneration, making it a strategic biomarker for neurodegeneration in MS. While manual delineation is the gold standard for corpus callosum measurements, there are now promising automated methods, but their robustness compared to manual measurements remains to be studied.
Aim: To compare the precision of FreeSurfer's automated volumetric corpus callosum measurements, both cross-sectional and longitudinal, against manual measurements.
Methods: A cohort of 9 MS patients (6 females, age 38±13 years, disease duration 7.3±5.2 years, 6 RR, 2 SP, 1 PP) was scanned twice with repositioning using 3D T_1-weighted MRI on 3 scanners (Siemens Aera 1.5 T, Avanto 1.5 T, Trio 3.0 T), a total of 6 scans per patient, on the same day. For every scan, the normalized corpus callosum area was measured independently by two raters, a medical student and a neuroradiologist, in a randomized order. FreeSurfer's cross-sectional and longitudinal processing streams were used to measure the corpus callosum volume.
Results: For the manual measurements, there was high intra-rater (medical student 0.96, neuroradiologist 0.99) and inter-rater agreement (0.91), as measured by the intra-class correlation coefficient (all $P< 0.001$). The coefficient of variation of the neuroradiologist was 2.3% within scanners and 2.4% between scanners, as compared to FreeSurfer's cross-sectional method (3.7%, $P=0.20$; 3.8%, $P=0.27$) and FreeSurfer longitudinal (0.96%, $P=0.025$; 2.0%, $P=0.48$), by paired t-test. Expanded disability status scale scores were correlated with measurements from both the neuroradiologist (-0.36, $P< 0.01$) and longitudinal FreeSurfer (-0.36, $P< 0.01$) by Spearman rank. Age/sex-normalized single digit modality test scores showed similar results (neuroradiologist 0.60, $P< 0.001$, longitudinal FreeSurfer 0.65, $P< 0.001$) by Pearson correlation. Cross-sectional FreeSurfer only provided spurious or non-significant clinical correlations.
Conclusions: The manual method performs well, but FreeSurfer's longitudinal stream is significantly more precise than the manual method for within-scanner measurements. These initial results indicate that, even in a small cohort, FreeSurfer's longitudinal method outperforms manual gold standard measurements and could thus be suitable to study corpus callosum atrophy in MS.

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Brain complexity and damage in patients with multiple sclerosis using fractal analysis: a new imaging outcome for monitoring MS severity

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Background: Quantitative brain Magnetic Resonance Imaging (MRI) is nowadays the gold standard for monitoring Multiple Sclerosis (MS). Lesion load is used as a surrogate endpoint of disease activity and brain volume change is being pursuit as a marker of neuro-axonal injury. Nevertheless, there is a significant unmet need of better surrogate endpoints for monitoring the disease. As such, we have previously described that the analysis of the Fractal Dimension (FD) of the brain is significantly altered in MS patients and its subtypes.
Aim: To assess the accuracy of Fractal Analysis of the grey matter (GM) and white matter (WM) for classifying patients with high disease severity.
Material and methods: We analysed a prospective cohort of MS patients (n=126) and matched healthy volunteers (HV) (n=36) with yearly clinical (EDSS) and brain MRI assessment for 3 years (4 assessments). The population of analysis was the Per Protocol population (n=72, age: 43±9, disease duration: 9±7.5, 67% women). MS lesion masks were manually created and tissue segmentation was performed using SIENAX and FIRST. FD and Lacunarity were computed for GM and WM segmentation images in the standard space. We developed a classifier of EDSS=4 milestone using a Random Forest with 10-fold cross-validation and data augmentation, using the software WEKA.
Results: A random forest classifier was trained for discriminating between i) the condition of MS vs HV, and ii) for disability severity using the milestone of EDSS 4.0. First, we observed that the classifier using the Fractal Analysis of the GM and WM obtained an area under the ROC curve (AUC) of 0.83 for classifying subjects as MS or HV. The random forest classifier for predicting EDSS $\geq$ 4.0 (n=34) or < 4.0 using Fractal Analysis achieved an AUC of 0.90 (precision (P): 0.86, recall (R): 0.85), which was higher than the classifiers using volumetric analysis (AUC: 0.80, P: 0.78, R: 0.77). The combination of Fractal Analysis and volumetric analysis did not achieve higher accuracy than the one with the Fractal Analysis alone (AUC: 0.91, P: 0.83, R: 0.82).
Conclusion: Fractal Analysis of the brain is able to capture disease damage and may become a prognostic biomarker.

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Abnormal individual finger movement control in MS: a neurophysiological and neuroimaging study

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Introduction: Motor surround inhibition (mSI) is a neural mechanism that allows neural activity to focus during voluntary movement, thus facilitating selective motor execution and favoring hand dexterity.
Objectives: Aim of the present study was to evaluate whether mSI is altered in MS and to investigate whether damage to specific brain structures correlates with mSI reduction.
Methods: Thirty-three patients with relapsing-remitting MS (mean age 40,2±7,2 years) and a median Expanded Disability Status Scale of 1.5 (range 0-3.5) and 24 age-matched healthy subjects (HC) were recruited. Transcranial magnetic stimulation was used to assess mSI. By delivering single magnetic pulses we recorded motor evoked potentials (MEPs) from abductor digiti minimi (ADM; surround muscle) during the voluntary activation of the first dorsal interosseous (FDI; active muscle). MEPs from ADM and FDI were recorded at rest and at FDI activation onset. All participants underwent a 3T MRI protocol including 3D-T1 and T2-FLAIR images (Siemens, Verio); we used the semi-automated software Jim (v5.0) for white matter (WM) lesions detection and FSL-FIRST and SPM12-CAT12 for subcortical and primary sensorimotor cortices (M1 and S1) volumes calculation.
Results: mSI (expressed as the ratio between ADM MEP amplitudes during movement and at rest) was significantly reduced in patients compared to HS ($p < 0.002$), while the expected facilitation of FDI muscle during movement was similar in the two groups ($p > 0.05$). In patients, abnormal mSI correlated with left putaminal volume, i.e. the worse the mSI the more severe the putamen atrophy ($r = -0.578$, $p = 0.02$). Lastly, mSI did not correlate either with WM lesion load or with left M1 and S1 volumes.
Conclusions: Altered mSI in MS does not depend on WM damage or on sensorimotor cortices involvement. The relationship between abnormal mSI and putaminal volume suggests a key role of basal ganglia in mSI. Our findings may represent the background for new rehabilitation approaches in MS.

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Spinal cord volume in multiple sclerosis patients with dissociation of disability and intracranial white matter lesion load

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Background: The number and volume of white mater intracranial lesions explain only a fraction of the diversity of clinical outcomes in multiple sclerosis (MS). Little is known about brain and spinal cord volume in MS patients with pronounced dissociation between intracranial lesion load (LL) and disability.
Objective: To explore regional brain volumes and spinal cord volume in MS patients with dissociation between LL and disability.
Methods: Similarly to Healy et al., we assigned 1245 relapsing-remitting MS patients into three groups based on the clinical disability and cerebral white matter LL (estimated by FreeSurfer). The first group consisted of patients with low LL, but high disability (LL < 3 ml, EDSS ≥ 3.5). The second group represented patients low disability despite high LL (LL > 6 ml, EDSS ≤ 1.5). The remaining MS patients were considered "nonparadox". We compared global and regional brain volumes (gray and white matter, lateral ventricles, cortex, thalamus, cerebellum and corpus callosum normalized by total intracranial volume) estimated automatically by MorphoBox prototype and raw mean upper cervical cord area (MUCCA) measured semiautomatically by ScanView software between the three groups (overall and separately for men and women) by using ANOVA or Kruskal-Wallis test respectively.
Results: Patients with low LL, but high disability (n= 53; 46 female, mean age 43.33±10.62 years, mean disease duration 11.25±7.0 years, median EDSS 4.0) demonstrated significantly higher total brain volume, thalamus and corpus callosum volume and smaller lateral ventricles volume than those with low disability despite high LL (n=71; 42 female, mean age 38.26±9.61 years, disease duration 11.18±8.13 years, median EDSS 1.5). Thalamus volume was higher and lateral ventricles volume was lower in patients with low LL, but high disability than in nonparadox patients (n= 1121; 801 female, mean age 40.40±9.55 years, disease duration 11.06±7.66 years, median EDSS 2.0). Besides this, we found no other difference in brain volumes between these two groups. Importantly, patients with low LL, but high disability had significantly lower MUCCA (80.39±8.44 mm^2) than both remaining groups (low disability despite high LL 85.75 mm^2±7.58 mm^2 and nonparadox 84.02±9.82 mm^2).
Conclusion: Reduced spinal cord volume may explain part of the clinical-radiological paradox in patients who have high disability despite low intracranial lesion load.

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Imaging correlates of thalamic volume in a large multiple sclerosis cohort

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Background: Thalamic volume loss develops early in multiple sclerosis (MS) and is a potential marker of disease worsening. Because of functional and structural connectivity, it is likely that thalamic volume reflects overall injury in the brain and spinal cord.
Goal: To estimate the extent to which imaging measures of brain and spinal cord describe thalamic volumes in a large MS cohort.
Methods: We used standardized clinical MRIs of MS patients at Cleveland Clinic (n=2727) and publicly-available MRI datasets of healthy individuals (n=1952). Healthy datasets were from IXI, ICBM, NKI, and OASIS-1. Normalized thalamic volume (NTV) was measured to establish the normal thalamic volume trajectory

over a large age span (18-96 years). For MS, clinical data (age, sex, disease duration [DD]) were extracted from our comprehensive clinical database, and clinical MRIs were pulled from Cleveland Clinic picture archiving and communication system. From 3D T1-weighted MPRAGE, 3D SPACE FLAIR, and 2D T2-weighted spin echo, we measured NTV, normalized T2 lesion volume (T2LV), normalized whole brain volume (WBF), gray matter fraction (GMF), white matter fraction (WMF), and upper spinal cord area (CA) automatically using in-house (NTV, T2LV, WBF, and CA) and publicly available (SPM and FSL) software. Extreme values were inspected and removed (n=56). Linear models with NTV as dependent variable were modeled with demographic and imaging measures for healthy and MS datasets.

Results: Age/sex-adjusted mean NTVs were 18.3 ml for healthy controls (mean age = 44 ± 20 years, 55% women) and 16.3ml for MS (mean age 48 ± 12 years, mean DD 11 ± 8 years, 72% women). The univariate coefficient for age was -42mm^3/year in healthy, and -45mm^3/year for MS ($p< 0.0001$). The coefficient of DD was -104mm^3/year ($p< 0.0001$). The standardized coefficient, represent relative contributions, for age and sex were -0.62 and 0.23, accounting for 39% of healthy NTV variability. In model with all image and demographics in MS, the standardized coefficients were 0.47 (WBF), -0.25 (T2LV), 0.12 (WMF), -0.12 (DD), 0.11 (age), 0.08 (CA), and 0.01 (GMF); the model R2 was 0.63. All coefficients were significant ($p< 0.0001$) except for GMF.

Conclusion: Thalamic volume is smaller in MS and reflects pathology within brain but also from spinal cord. The reduction was correlated with several other MRI markers. Thalamic volume may be a useful marker of global health of the central nervous system.

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Effect of different doses of gadolinium contrast agent on clinical outcomes in multiple sclerosis

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Introduction: Gadolinium-based contrast agents (GBCA) commonly used in routine neuroimaging can accumulate in the brain's deep gray matter structures despite chelation. A clinical trial of secondary progressive multiple sclerosis (SPMS) patients included an infrequent (IFR) and a frequent (FR) MRI cohort who received 1-4 or 5-11 GBCA injections over 104 weeks. By evaluating the clinical outcomes of these two cohorts, this retrospective study was performed to assess the potential dose-dependent effect of GBCA on MS progression.

Objective: To evaluate the potential dose-dependent effect of GBCA on MS progression

Materials and methods: Clinical outcomes from a cohort of 612 SPMS patients, enrolled in a 2-year placebo-controlled (negative) trial assessing the efficacy of MBP8298, were acquired. Patients received 1-4 (infrequent cohort; IFR) or 5-11 (frequent cohort; FR) GBCA injections between screening (week -4) and week 104. The primary clinical outcome was the change in Expanded Disability Status Scale (EDSS) and time to confirmed EDSS progression and secondary outcomes included the changes of Multiple Sclerosis Functional Composite (MSFC), Timed 25-Foot Walk (T25FW), the 9-Hole-Peg Test (9HPT), the Paced Auditory Serial Addition Test (PASAT) from baseline to week 104.

Results: The 512 IFR and 100 FR participants showed no differences in baseline demographics or disease history. The mean change from baseline to week 104 in EDSS was +0.21(IFR) and +0.13(FR); MSFC -0.38(IFR) and -0.14(FR); T25FW +1.28(IFR) and +0.55(FR); 9HPT -0.06(IFR) and -0.08(FR); PASAT +0.22(IFR) and +0.20(FR). The FR to IFR progression hazard ratio was at 0.68 (p=0.09) favouring the FR cohort. There were no significant differences in any of the outcomes between the FR and the IFR cohorts.

Conclusion: There were no differences in the clinical outcome measures of disability progression between the two groups for different GBCA exposure indicating that gadolinium does not result in greater clinical worsening in SPMS in the short term, after two years of follow up.

Disclosure

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a company advisory board, board of directors or other similar group of Actelion, BayerHealthcare, BiogenIdec, Hoffman La-Roche, Merck Serono, MedDay, Novartis, Sanofi-Aventis and is on speaker's bureau for Genzyme. David Li has received research funding from the Canadian Institute of Health Research and Multiple Sclerosis Society of Canada. He is the Emeritus Director of the UBC MS/MRI Research Group which has been contracted to perform central analysis of MRI scans for therapeutic trials with Novartis, Perceptives, Roche and Sanofi-Aventis. The UBC MS/MRI Research Group has also received grant support for investigator-initiated independent studies from Genzyme, Merck-Serono, Novartis and Roche. He has acted as a consultant to Vertex Pharmaceuticals and served on the Data and Safety Advisory Board for Opexa Therapeutics and Scientific Advisory Boards for Adelphi Group, Celgene, Novartis and Roche. He has also given lectures which have been supported by non-restricted education grants from Biogen-Idec, Novartis, Sanofi-Genzyme and Teva. Roger Tam has received research support as part of sponsored clinical studies from Novartis, Roche, and Sanofi Genzyme. Shannon Kolind has received a research / educational grant funding from Genzyme; received honoraria or consultation fees from Acorda and Genzyme; she is member of a company advisory board, board of directors or other similar group of Acorda and Genzyme. Dr. Robert Carruthers has received grants/research from MedImmune, Teva and Guthy Jackson; received speaking fees for unbranded lectures from Biogen, Genzyme and Teva and received consulting fees from Novartis, EMD Serono and Genzyme. Carolyn Taylor and Heejun Kang have nothing to disclose.

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Inter-scanner variability may lead to differences in detection rate of leptomeningeal enhancement on 3D-FLAIR MRI in multiple sclerosis

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Introduction: B-cell lymphoid aggregates have been implicated in meningeal inflammation, cortical grey matter demyelination, and disability progression in multiple sclerosis (MS) (1). Gadolinium-enhanced 3D-FLAIR (Gd-3D-FLAIR) MRI has been shown to identify foci of leptomeningeal enhancement (LME) in MS (2), thought to be an imaging biomarker for leptomeningeal inflammation. However, there has been considerable variability in the rate of LME detection by different investigators.

Objectives: To determine if MRI scanner variability can cause different rates of LME detection by different investigators.

Aims: To add to the knowledge base of LME as a biomarker of meningeal inflammation in MS, in the hope of identifying disease modifying therapies that can attenuate meningeal inflammation.

Methods: A phantom was made containing vials of increasing concentrations of Gd from 0.01 to 3.0 mmol, as previously described by Mathews et al, 1999 (3). The phantom was placed over the forehead of one volunteer, and scanned using 3D-FLAIR on all imaging platforms available. Signal intensity was normalized by dividing by thalamic signal, and concentration-intensity curves were generated and compared by scanner type, including type of FLAIR and field strength. The effects of various surface coil intensity correction algorithms and fat suppression were also assessed.

Results: Scanners using CUBE FLAIR showed notably higher signal intensity compared to scanners using SPACE FLAIR. When using CUBE, 3T produced a moderate increase in signal intensity over 1.5T, whereas there was no difference between 1.5T and 3T when using SPACE.

Conclusions: There appears to be different sensitivity in signal detection by 3D-FLAIR between different scanners. Controlling for scanner variability will be essential in future studies of LME.

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Disclosure

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Dr. Lathi has no relevant disclosures

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Leptomeningeal gadolinium enhancement lesions in multiple sclerosis are not related to different brain volume measures

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Background: Leptomeningeal gadolinium enhancement lesions (LGEL) are the expression of the chronic meningeal inflammation of several inflammatory diseases of the central nervous system. LGEL have been described in multiple sclerosis, mainly in the progressive MS forms, but there are contradictory results on the impact of LGEL in brain atrophy phenomena.

Objective: To explore the relationship between LGEL and global and regional (grey/white matter atrophy, thalami, amygdalae, cerebellum) brain volume.
Methods: This is a transversal study over a consecutive series of MS patients studied with the following 3.0T MR images sequences: 3D T1-weighted images were acquired 5 minutes before and immediately after a single dose of intravenous bolus of 0.1 mmol/kg gadolinium injection, 3D-FLAIR for enhanced lesion detection (3D-FLAIRED) sequence was acquired 10 min post-contrast. Additional pre-contrast sequences included 2D T2/PD-WI and 3D high-resolution T1-WI. This latter sequence was used for measuring the brain volume measures with FreeSurfer. LGEL were defined as the presence of enhancement on the surface of the cortex only in the 3D-FLAIRED when comparing with the post-contrast T1 weighted images.
Results: One hundred and forty-six MS patients (67.1% females) were analysed. Demographic characteristics included: mean age 44.1 (SD 10.3); 13.5 (SD 9.5) years of evolution; mean EDSS 2.8 (SD 1.); mean MSSS 3.3 (2.3). Patients were divided into relapsing-remitting (101 patients, 69.2%) and progressive (36 secondary progressive MS, 24.7%; 9 primary progressive MS, 6.2%). LGEL presence was observed in 38 patients (26%); 15 of them in the SPMS form (p=0.038). We calculated the normalized brain volume (mean 1437.7, SD 153.0) and brain parenchymal fraction (mean 69.1 SD 4.5), the cortex volume (mean 420.5, SD 47.7), the total grey matter volume (mean 567.9, SD 60.5), the total white matter volume (mean 405..8, SD 62.1) and the volume of thalami (mean 12.3, SD 1.9), amygdalae (mean 3.0, SD .4) and cerebellum (mean 123.2, SD 15.7). No differences in all these brain volume measurements between patients with and without LGEL were found.
Conclusions: LGEL presence was more frequent in SPMS, but no relation with clinical or brain volume measurements was observed. Despite this, the presence of LGEL could be a radiological sign for detecting a secondary progressive course.

Disclosure
We declare not conflict of interest

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Baseline cerebellar volume as predictor of clinical disability in multiple sclerosis: MRI Findings from the CombiRx trial

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Objective: To investigate whether cerebellar volume is a predictor of disability in patients with relapsing-remitting multiple sclerosis (RRMS).
Background: The cerebellum is a predilection site of demyelination in MS and cerebellar atrophy is a strong contributor of clinical impairment. Cerebellar volume loss over one-year has been reported as predictor of disease worsening in progressive MS patients. However, the role of baseline cerebellar volume as predictor of disability has never been tested in a large group of RRMS patients.
Methods: MRI data from 838 of 1,008 RRMS patients who participated in the multi-center, randomized, phase III CombiRx Trial were analyzed. All patients were under immuno-modulatory treatment with either glatiramer acetate (n=210), interferon β-1a (n=213) or glatiramer acetate+interferon β-1a (n=415). On the baseline MRI scans, whole brain and cerebellar T2 and Gd-enhancing lesion number where obtained using MRIAP, while grey matter fraction (GMF) and cerebellar volume were measured using SPM12. Clinical measures included EDSS, Multiple Sclerosis Functional Composite (MSFC) and its subcomponents, evaluated at baseline and 36 months follow-up. Changes in clinical scores were assessed via repeated measure ANOVA. Ordinal and hierarchical multiple linear regression analysis were performed to assess the relationship between MR metrics and clinical disability at baseline and follow-up.
Results: The regression model including T2 and Gd-enhancing lesion number, GMF and cerebellar GM volume, explained about 15% of the variance in EDSS and MSFC scores at baseline ($p< 0.0001$ for both models), with cerebellar volume being significant predictor of MSFC (Beta=0.188, $p< 0.0001$). The only clinical score showing significant worsening over the follow-up period was the 25-foot walk test (25-FWT) (p=0.013). Although only 8% variance in 25-FWT at month 36 was explained by the regression model ($p< 0.0001$), baseline cerebellar volume was the only MRI metric to significantly predict 25-FWT scores at follow-up (Beta =-0.172, $p< 0.0001$).
Conclusions: These results suggest that cerebellar volume is an independent predictor of clinical disability in MS patients as measured by 25-FWT.

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Alterations of individual cortical networks in clinically isolated syndrome: a multi-centre MAGNIMS study

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Introduction: Coordinated patterns of cortical morphology in structural MRI scans can be described as a cortical networks (CNs). Alterations of CNs have been found in multiple sclerosis (MS), but only one study has included clinically isolated syndrome (CIS) patients, for which the CNs were constructed at group level. Here, we compared CNs between CIS patients and healthy controls (HCs) at the individual level.

Objectives: (i) to compare global and regional CNs' parameters determined at the individual level between CIS and HCs;(ii) to determine the association between CNs' metrics and clinical parameters.

Methods: We used a multi-centre MAGNIMS dataset: 60 CIS patients (recruited within 3 months from the onset) and 38 HCs. All subjects underwent a 3T brain MRI, including 3D FLAIR, 3D T1 and post gadolinium T1 (patients only) scans. Patients were assessed with Expanded Disability Status Scale (EDSS) and with Symbol Digit Modality Test (SDMT). Cortical grey matter (GM) was automatically segmented and parcellated into 98 defined regions with GIF. We then constructed CNs at the individual level. We used linear regression to compare global and regional CNs' metrics adjusting for age, gender, cortical GM volume and study centre. P values for the regional CNs' metrics were computed with permutation tests and false discovery rate.

Results: Patients had median lesion volume of 0.8 mL (range 0-19.4), median EDSS of 1.5 (range 0-3) and mean SDMT of 54.91±14.45. 5 patients fulfilled the McDonald 2010 criteria for MS. Patients and controls showed significant differences in small-world coefficient (s-w) (1.36±0.02 vs 1.35±0.02, p=0.02). An higher s-w was correlated with higher lesion volume (p=0.02). It was also correlated with worse cognitive performance (SDMT, p=0.03), independently of the lesion volume. Patients diagnosed with MS had higher s-w (1.38±0.02) than the other patients (p=0.015). At the regional level, patients showed lower betweenness centrality in the right postcentral gyrus ($p< 0.0001$) and higher clustering coefficient in the right superior frontal gyrus ($p< 0.0001$) as well as in the right medial orbital gyrus ($p< 0.0001$) in comparison to HCs.

Conclusions: Our findings suggest network alterations in line with previous CNs' studies showing a more regular network in MS/CIS. In our study a high s-w was correlated with a worse disease burden (high WM lesion load, diagnosis of MS and worse cognitive performance).

Disclosure

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Amyloid PET as a marker of normal-appearing white matter early damage in multiple sclerosis: correlation with CSF β-amyloid levels and brain volumes

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Background: Demyelination is the pathological hallmark of multiple sclerosis (MS). Positron emission tomography (PET) with amyloid tracers (AβT) is a promising tool to evaluate white matter (WM) damage and repair since AT bind to WM and the uptake decreases with demyelination. Reduced CSF β-Amyloid$_{1-42}$ (Aβ) levels have been suggested as prognostic biomarker in MS.
Objectives: To investigate AβT uptake in damaged WM (DWM) and in normal-appearing WM (NAWM) of MS patients and to evaluate possible correlations between AβT uptake and other clinical and radiological markers of disease progression.
Methods: Twelve patients with MS were recruited and divided according to their disease activity into active and non-active. All participants underwent neurological examination, neuropsychological testing, lumbar puncture, brain magnetic resonance imaging (MRI), and ^{18}F-florbetapir-PET. Aβ levels were determined in CSF samples. MRI and PET images were co-registered and mean standardized uptake values (SUV) were calculated for each patient in the NAWM and in the DWM. WM lesion load was derived using the Lesion Segmentation Tool for Statistical Parametric Mapping (SPM12). To calculate brain volumes, brain segmentation with SPM12 was performed. Non-parametric statistical analyses for between-group comparisons and regression analyses were conducted.
Results: DWM-SUV was lower compared to NAWM-SUV in each patient ($p< 0.001$). Dividing patients according to their disease activity, we found a reduced NAWM-SUV in active patients compared to non-active ($p< 0.05$). Considering only active patients, NAWM-SUV correlated with NAWM volume ($r=0.82$, $p=0.01$) and NAWM volume resulted the best predictor of NAWM-SUV ($r=0.87$, $p< 0.01$). Interestingly, CSF Aβ concentration was a predictor of both NAWM-SUV ($r=0.79$; $p< 0.01$) and NAWM volume ($r=0.81$, $p< 0.01$). CSF Aβ levels correlated with Expanded Disability Status Scale score ($r=-0.72$; $p< 0.05$), Paced Auditory Serial Addition Test (PASAT)-2 ($r=0.85$; $p< 0.01$) and PASAT-3 ($r=0.71$; $p< 0.05$).
Conclusions: The AβT uptake in the largest lesion of each patient is reduced compared to their NAWM and is lower in active patients compared to non-active, suggesting a link between early WM damage and disease activity. MS patients with a smaller NAWM volume display a lower AβT uptake in the NAWM and lower CSF Aβ levels. These findings suggest a predictive role of CSF Aβ levels in MS disease progression that may be linked to myelin (microscopic) damage.

Disclosure
All authors report no disclosure

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Microstructural damage in cortico-subcortical white matter tracts in patients with clinically isolated syndrome: prediction of cognitive functioning and follow-up of its change for 1 year

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Background: Damage to select limbic and associative cerebral cortical areas and deep grey matter (DGM) structures have been associated with cognitive impairment in multiple sclerosis (MS). However, structural integrity of white matter (WM) tracts connecting these brain regions and their association with cognition have not been investigated at the earliest stage of the disease.
Objectives: (1) To investigate longitudinal diffusion changes in WM tracts connecting limbic and associative parts of the cerebral cortex with DGM over one year in patients with clinically isolated syndrome (CIS). (2) To investigate the association of microstructural changes to these tracts with cognition.
Methods: 41 patients recruited less than 6 months after a CIS and 55 matched healthy controls (HC) underwent neuropsychological assessments, including episodic memory (EMem) and information processing speed (IPS). All patients and a subgroup of 19 HC were scanned using 3T T1-weighted and diffusion tensor (DT) brain MRI. Freesurfer was used to segment the brain in cortical (associative, limbic and sensori-motor) and subcortical (thalamus, hippocampus and striatum) regions. Two-tensor unscented Kalman filter tractography was used to trace tracts connecting limbic/associative cortex with DGM and both fractional anisotropy and mean diffusivity (MD) were used to assess the microstructural integrity in CIS and HC at each time-point. Linear regression models were used to assess cognitive impairment by altered tracts.
Results: Baseline: IPS and visual EMem were worse in CIS vs. HC. MD was significantly higher in right hippocampal-associative and right striatal-associative tracts in CIS compared to HC. MD of the striatal-associative tract could explain 27% of the IPS impairment (beta=-0.39).
After one year of follow-up, cognitive impairment was no longer detected in CIS. However, the cortico-subcortical tracts showed more widespread damage (increased MD) in the bilateral hippocampal-associative, the right hippocampal-limbic, the bilateral thalamo-associative, the right thalamo-limbic and the right striatal-associative tracts.
Conclusion: Damage to the tracts connecting DGM and associative/limbic cortex appears early in the evolution of MS and is associated with early cognitive impairment. However, normal cognitive performances at follow-up in spite of widespread microstructural damage suggests that compensatory mechanisms are deployed at this early stage of the disease.

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

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Background: Several studies have characterized thalamic structural damage in patients at the early stages of MS, while no study has explored thalamic resting state (RS) functional connectivity (FC) abnormalities. We investigated subregional thalamic RS FC abnormalities in patients with clinically isolated syndrome (CIS) suggestive of MS and their correlation with disability.
Methods: Structural and RS fMRI data were acquired from 59 CIS patients and 13 healthy controls (HC) at baseline (< 3 months from first attack) and after 2 years. Five thalamic sub-regions (SR) (frontal, motor, postcentral, occipital, temporal) were parcellated according to their cortico-thalamic structural connectivity and used for seed-based RS FC analyses. Baseline thalamic RS FC abnormalities and their changes over time were assessed and correlated with EDSS and its changes.
Results: Forty-nine (83%) patients developed MS at year 2. At baseline, compared to HC, CIS patients showed reduced thalamic RS FC with frontal cortices for the frontal and occipital SR, the temporal cortices for the temporal SR, and the cerebellum for the whole thalamus and all SR. At year 2, compared to baseline, CIS patients had increased subregional thalamic RS FC with frontal, temporal and cerebellar cortices for all SR, whereas no changes were detected in HC. Despite such connectivity increasing in patients, at year 2, CIS patients *vs* HC, still showed reduced thalamic RS FC with frontal cortices for the occipital SR, the temporal cortices for temporal SR, and the cerebellum for the motor SR. Increased temporal thalamic RS FC was observed with the cerebellum.
In CIS, significant correlations were found between: 1) higher EDSS at baseline and reduced baseline thalamic RS FC with temporal cortices for the frontal and temporal SR, and with the cerebellum for the temporal SR; 2) EDSS worsening at follow-up with concurrent increasing of thalamic RS FC with frontal and temporal cortices for the frontal and temporal SR; and 3) EDSS worsening at follow-up with reduced baseline thalamic RS FC with temporal cortices for the frontal and temporal SR.
Conclusions: Dynamic alterations of subregional thalamic RS FC with frontal, temporal and cerebellar regions occur in CIS patients and correlate with disability and its worsening, evidencing the contribution of thalamic dysfunction from the first stages of MS in explaining disability.
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INSPIRATION: An approach to quantitative MRI assessment of MS patients in daily clinical practice

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Background: Qualitative and Quantitative standards of MRI scans for multiple sclerosis have mainly been in use in clinical trials. In daily clinical practice standards in MRI acquisition are in discussion but largely not applied yet. Tools for quantitative data analysis do exist but are not available for daily clinical practice. INSPIRATION is a non-interventional study conducted in Germany, to validate the feasibility and explore the potential benefit of standardized MRI acquisition and centralized quantitative MRI reading including brain volume in clinical practice for RRMS patients.
Objectives: To implement standardized protocols and investigate qualitatively and quantitatively the results of standardized MRI scans obtained from multiple centers.
Methods: INSPIRATION included 253 patients in 15 centers until July 2015. MRI and clinical data were documented over 3 years. Sites underwent expert training and standardized sequence implementation. A centralized quantitative MRI data analysis was performed. The results were visualized and reported to the neurologist and radiologist.
Results: 99.7% of the obtained data sets passed the quality analysis. < 0.3% of cases led to site inquiries or data exclusion. The mean number (±SD)/mm^3 volume (±SD) of T2 lesions at baseline was 30.1 (±2.8)/11033.1 (±1578.9) and black holes 4.0 (±0.9)/490.3 (±136.6). Over 36 months the mean number (±SD)/mm^3 volume (±SD) of T2 lesions increased to 34.2 (±7.5)/11490.5 (±3300.3) while black holes remained rather stable at 4.1 (±2.1)/494.8 (±329.2). Whole brain volume at baseline was 1,142,125 ± 16,043 mm^3. Brain volume loss after 12 and 36 months was 2,757 ± 923 mm^3 (0.28 ± 0.1%), 7,600 ± 1,705 mm^3 (0.67 ± 0.2 %) respectively.Patients with high (≥10mL; n=33) and low (< 10ml; n=44) T2/Flair hyperintense lesion load at baseline were separated and brain volume loss was assessed over 3 years. Patients with high lesion load lost significantly more brain volume vs. patients with a low lesion load at baseline (0.30 ± 0.11% vs. 0.16 ± 0.10%; p=0.0067).
Conclusions: A centralized quantitative MRI-analysis is provided in a real-world situation and might improve the comparability of MRI scans in daily clinical routine. The quantification of lesion volumes and visualization of MRI abnormalities may facilitate MRI data integration by the responsible neurologist to support patient management.

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The contribution of microglial activation to cortical demyelination in multiple sclerosis: a multimodal ^{11}C-PBR28 MR-PET and quantitative 7 Tesla imaging study

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Introduction: Neuropathology shows that cortical demyelination in multiple sclerosis (MS) is often accompanied by microglia activation. The role of microglia activation, however, is still uncertain.
Aim: To assess, using 3T magnetic resonance-positron emission tomography (MR-PET) with ^{11}C-PBR28, a tracer for activated microglia, and quantitative 7T T_2*, a marker of myelin and iron content, whether 1) neuroinflammation in MS colocalizes with cortical demyelination, 2) the relation between the two processes.
Methods: Ten cases with secondary-progressive, 9 with relapsing-remitting MS (SPMS, RRMS), and 14 matched controls (HC) underwent 90' ^{11}C-PBR28 MR-PET to obtain 60'-90' normalized standardized uptake value maps (SUVR, 1.25 mm resolution) for sampling SUVR at mid-cortical depth. MS and HC also underwent multi-echo 7T T_2* imaging (0.33 mm resolution) for estimating T_2* at 25%, 50% and 75% depth from the pial surface, and for cortical lesion (CL) segmentation. Cortical demyelination in MS was defined as CL and clusters with significantly increased T_2* at all depths in RRMS and SPMS vs HC at general linear model (GLM, $p < 0.05$). In these areas mean SUVR were extracted and compared to i) mean SUVR in the normal appearing cortical grey matter (NACGM) within patients (by paired t-test), and ii) mean SUVR in HC cortex (by linear regression). A vertexwise GLM ($p < 0.05$) was run to assess the relation in MS between laminar T_2* and SUVR. Age and binding affinity were included as nuisance factors.
Results: RRMS and SPMS showed, relative to HC, clusters of increased, but not decreased, T_2* (myelin/iron loss) at all 3 depths. In RRMS mean SUVR in CL and clusters with increased T_2* were higher than mean SUVR in NACGM ($p < 0.02$) and HC cortex ($p < 0.05$); there were no differences in patient NACGM SUVR vs HC cortex. In SPMS, mean SUVR in CL and clusters of increased T_2* were higher than NACGM SUVR ($p < 0.05$) and HC cortex ($p < 0.003$). SUVR in NACGM in SPMS were also higher than HC cortex SUVR ($p=0.01$). Cortical SUVR and laminar T_2* were positively correlated in many cortical areas, and inversely associated in fewer regions.
Conclusions: Cortical microglia activation predominantly affects cortical lesion areas in RRMS, while it extends to the NACGM in SPMS. In most regions, microglia activation seems to contribute detrimentally to cortical demyelination. The inverse relation between SUVR and T_2* found in fewer cortical areas could reflect protective effects of microglia.

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Investigating the relationship between meningeal enhancement on 7T MRI and cortical gray matter lesions in multiple sclerosis

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Background: Post-contrast FLAIR MRI has emerged as a potential biomarker of meningeal inflammation in multiple sclerosis (MS). Autopsy studies suggest a link between cortical lesions (CLs) and meningeal inflammation.
Objective: To determine if meningeal inflammation and cortical demyelination have a true, in vivo relationship in MS.
Aim: We aimed to utilize the greater sensitivity at 7-Tesla (7T) for visualization of both leptomeningeal enhancement (LME) and CLs to explore this relationship.
Methods: Thirty-five participants with MS underwent brain MRI on a 7T scanner. Magnetization prepared 2 rapid acquisition gradient echo (MP2RAGE) and magnetization prepared fluid attenuated inversion recovery (MPFLAIR) images were acquired pre- and post-contrast. CLs were identified as hypointensities on MP2RAGE. Hyperintensities on post-contrast MPFLAIR located in the subarachnoid space, which were not present on pre-contrast images were notated as foci of LME. These were characterized as "nodular" (small spherical pial foci), "spread/fill - gyral" (contrast in the subarachnoid space from a gyrus out to dura), and "spread/fill - sulcal" (contrast filling a sulcus). Relationships were explored with Spearman correlation and Wilcoxon rank-sum analyses.
Results: Twenty-eight (80%) participants had at least one focus of LME. Only 9 (26%) participants had nodular LME, whereas 21 (60%) had spread/fill - gyral LME and 20 (57%) had spread/fill - sulcal LME. All were found to have CLs, with a median of 24 (range 9 - 79) lesions per subject. A non-significant trend was seen for a higher number of CLs in those with spread/fill - sulcal LME compared (median 27.5 (9 - 79) vs. 22 (10 - 54), p = 0.08). The number of spread/fill - sulcal foci trended towards a correlation with the number of CLs (rho = 0.26, p = 0.13). No differences were seen in the number of CLs for those with or without nodular or spread/fill - gyral LME.
Conclusions: Of the 3 patterns of LME visualized by 7T MRI in this cohort, only spread/fill - sulcal LME appeared to have any relationship with CLs. This relationship was weak; therefore, this study does not strongly support a causative relationship between meningeal inflammation and CL development. MRI identification of CLs is heavily weighted towards leukocortical CLs, which likely have a similar perivascular etiology to white matter lesions, explaining this result. Further work will be necessary to evaluate the relationship between LME and subpial demyelination.

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Early predictors of brain atrophy among MS patients

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Introduction: Brain atrophy occurs from the early phase of relapsing remitting (RR) MS and it is an important determinant of disease progression. We set out to explore factors affecting the rate of cortical thinning in the long-term.
Methods: Among 219 RRMS patients, followed from onset for 7.9 mean years, we used regression analysis to assess early factors affecting the rate of global cortical thickness (Cth) loss/year and predicting the most severe global cortical damage (worst 25Th percentile loss) over time.
Results: Within the observation period, 27% (59 of 219) of patients converted to secondary progressive (SP) MS, in 6.1 mean years; this subgroup had, at disease onset, significantly lower mean global Cth (SP=2.51 mm, RR=2.58 mm p=0.004) and higher number of cortical lesions (CLs) (SP=6.5, RR=1.8 mean lesions; p< 0.001), and displayed faster cortical thinning over time (SP=-1.31%/year, RR=-0.96%/year mean loss; p< 0.001). In the total population, at disease onset, a higher number of CLs was associated with a significantly lower mean global CTh (r = -0.188, p = 0.005). Factors associated with a larger proportion of grey matter loss/year were gender (male=-0.74%, female=-0.60%; p=0.03), number of CLs at onset (0 CLs=-0.56%, 1-3 lesions=-0.63%, 4-6 lesions=-0.73%, ≥7 lesions=-0.78%, p< 0.001) and number of relapses during the first two years (1 relapse=-0.47%, 2 relapses=-0.79%, ≥3 relapses=-0.94%; p< 0.001). The white matter lesions number at onset did not affect the rate of brain atrophy (lesions: ≤ 4=-0.68%, 5-8=-0.60%, 9-11=-0.67%, ≥12=-0.72%; p=0.13). In the multivariate model, a larger accumulation of CLs volume (OR=3.47; p=0.01), a more rapid cortical thinning during the first two years (OR=1.43; p=0.001), and ≥3 early relapses (OR=8.41; p< 0.001) independently predicted a higher risk of more severe global Cth loss at the end of the follow up.

Conclusions: Patients at higher risk of converting to SPMS have more severe global and focal cortical pathology at onset but also demonstrate a faster rate of cortical thinning. The extent of the early focal cortical damage affects the severity of grey matter loss in the long term, suggesting common mechanisms driving CLs and brain atrophy. Early relapse frequency and the extent of early focal cortical damage can be used for selecting groups at high risk of developing severe cortical atrophy, who may potentially benefit from early aggressive treatment.

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Normal appearing white matter damage detected by standardized T1w/T2w ratio

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Introduction: In patients with early multiple sclerosis (MS), the ratio of T1 weighted/T2 weighted image signal intensities (T1/T2) has been demonstrated to reflect MS-related changes in normal appearing white matter (NAWM). A standardised version of this T1/T2 ratio (sT1/T2) has been validated in the healthy population (Misaki et al., 2015). It was demonstrated that sT1/T2 reduces cohort variability in white matter values in healthy control (HC) subjects. The reduced cohort variability has the potential to lead to more sensitivity to detect pathological changes in NAWM in MS. However, the sT1/T2 ratio has not yet been evaluated in MS.
Objectives: To assess the advantages of sT1/T2 over the classic T1/T2 ratio in a comparison of MS patients and HC.
Aims:

1) To evaluate cohort variability of sT1/T2 values and classic T1/T2 values in NAWM by comparing their coefficient of variation (CoV).
2) To evaluate whether sT1/T2 and classic T1/T2 is more sensitive to MS-related pathology in NAWM by comparing MS and HC.

Methods: 3D T1w- and 3D T2w- MRI scans (1 mm isotropic resolution) from 45 patients with relapsing-remitting MS (median EDSS = 2.5 (0-6)) and 45 HC were included in the study. sT1/T2 was calculated as described by Misaki et al. (2015). MS lesions were segmented semi-automatically (LST toolbox with manual corrections) and median NAWM values were calculated. CoV in NAWM was calculated for T1/T2 and sT1/T2 and compared using the Feltz & Miller test. A linear model was used to assess group differences in NAWM with age as a covariate.
Results: CoV in NAWM for sT1/T2 was significantly lower compared to the classic T1/T2 ratio (sT1/T2 = 11.52, T1/T2 = 19.04, $p < .001$). Both ratios were significantly lower in MS compared to HC, with a larger effect size in sT1/T2 (sT1/T2 $r^2 = .234$, $p < .001$; T1/T2 $r^2 = .071$, $p = .013$).
Conclusions: Standardization of T1/T2 ratio increases tissue discriminability of NAWM in MS and HC. Moreover, sT1/T2 emphasises MS-related changes in NAWM compared to the classic T1/T2 ratio.

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Investigating the potential of high angular resolution diffusion imaging metrics and texture angular entropy for monitoring de- and remyelination in a cuprizone model of multiple sclerosis

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Background: The lack of established in vivo methods for monitoring de- and remyelination is well recognized in multiple sclerosis (MS). High angular resolution diffusion imaging (HARDI) and texture alignment measures have shown promise in probing subtle structural changes following brain white matter injury.
Aim: To investigate the sensitivity and power of high-resolution diffusion MRI and texture analysis methods for tracking de- and remyelination induced in mouse brain.
Methods: Sequential brain MRI was acquired using a 9.4T scanner from 5 C57BL/6 male mice before and after being fed with 0.2% cuprizone (Cu). Imaging protocols included 2-shell HARDI (b1/b2=1000/2000; 15 and 30 directions) and T2-weighted MRI (TR/TE=4000/48 ms; pixel size=0.05×0.05 mm^2; and slice thickness=0.5 mm), at 4 and 6 weeks on Cu (demyelinating), and at 1 and 3 weeks of normal diet after stopping Cu (remyelinating). A control mouse was also scanned at 2,7, and 12 weeks for comparison. The diffusion MRI was first analyzed to obtain the orientation dispersion index (ODI), and neurite density index (NDI) using a software (NODDI toolbox, UCL, UK) and then processed to get the fractional anisotropy (FA). Image analysis focused on the corpus callosum at select slices of genu, body, and splenium. The T2 MRI was used to evaluate texture alignment complexity using an in-house program (genu only). Diffusion images were co-registered to the T2 MRI within a time point, and then between T2s over time to ensure position alignment. All metrics were normalized using intra-slice values of 3rd ventricle. Data analysis used two-way ANOVA; $p \leq .05$ as significance.
Results: All normalized diffusion and texture metrics showed significant changes over time ($p \leq .05$). There was a 29% increase in ODI ($p \leq .0001$) and 49% in angular entropy from 4 to 6 weeks on Cu diet, and a 17% recovery in FA ($p=0.03$), and 6% in NDI ($p \leq .0005$) from 1 to 3 weeks of normal diet. Control mice week 2 FA (10.6±2.4), ODI (-.89±.05), and NDI (-.39±.03) compared to the average of all mice week 6 on Cu FA (3.74±.19), ODI (-.29±.18), and NDI (-.59±.04) also showed significant changes ($p \leq .0001$).
Conclusion: The Cu mouse model is well understood featuring a progressive de- and remyelination course before and after ceasing the toxic diet. Corresponding changes in MRI suggest that high angular resolution diffusion and texture alignment analyses may be promising methods for monitoring de- and remyelination that occurs frequently in MS patients.

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Comparison of Pittsburgh compound-B and fractional anisotropy as white matter integrity markers: correlations with cognitive function

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Introduction: Fractional anisotropy (FA) from diffusion tensor MRI (DTI) is used as a white matter (WM) integrity marker. Similarly, Pittsburg compound-B (PiB) uptake on PET has been proposed as a WM integrity marker, particularly in demyelinating diseases. We have shown that PiB uptake in WM hyperintensities (WMH) and normal appearing WM (NAWM) correlate with cognitive function in patients with MS (Zeydan et al. MSJ-2017).
Objectives: To compare WM PiB binding and FA as WM integrity markers.
Aims: To evaluate the association of PiB-PET and DTI-FA in WMH and NAWM with cognitive function.
Methods: Healthy adults (n=537) from the population-based Mayo Clinic Study of Aging were included. MRI-FLAIR images were segmented into WMH and NAWM via a semi-automated algorithm. After registration of DTI, FLAIR and PET images to the T1-weighted image, FA values and PiB standard uptake value ratios (SUVr; referenced to cerebellar crus) were calculated for regions within the WMH and NAWM masks. Global cognitive z-scores were calculated in each participant from nine cognitive tests. Paired t-test was used for comparisons within subjects. Linear regressions and correlations were adjusted for age and global cortical PiB-SUVr.
Results: The WMH PiB-SUVr (mean±SD=1.88±0.20) was lower compared to NAWM PiB-SUVr (mean±SD=2.08±0.20; $p < 0.001$). The WMH FA (mean±SD=0.37±0.05) was lower compared to NAWM FA (mean±SD=0.45±0.02; $p < 0.001$). In the WMH, there was a correlation between PiB-SUVr and FA ($r=0.22$; $p \leq 0.001$), with a trend in the NAWM ($r=0.08$; $p=0.052$). In the WMH, both the PiB-SUVr ($r=0.14$; $p=0.002$) and FA ($r=0.11$; $p=0.018$) correlated with global cognitive z-scores without a significant difference in slopes ($p=0.17$). In the NAWM, PiB-SUVr correlated with global cognitive z-scores ($r=0.1$; $p=0.022$), while a trend was observed with FA ($r=0.09$; $p=0.058$).
Conclusion: As a potential WM integrity marker, PiB-PET appears to be as informative as DTI-FA when utilized for associations with global cognitive function in adults.

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Manual delineation of only one image in unseen databases is sufficient for accurate performance in automated multiple sclerosis lesion segmentation

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Background: Convolutional Neural Network (CNN) methods are being proposed for automated white matter lesion segmentation increasing the performance of typical state-of-the-art methods. However, their accuracy decreases significantly when using them on other image domains that those used for training, showing lack of adaptability to unseen imaging data and limiting its applicability in non-specialized hospitals.

Aim: To analyze the effect of domain adaptation on multiple sclerosis (MS) lesion segmentation, investigating how transferable a CNN model is when applied to other unseen image domains.

Methods: An automated lesion segmentation method based on a 11-layer CNN classifier was firstly fully-trained using 35 T1-w and FLAIR scans from the MS lesion segmentation challenges (MICCAI 2008 and 2016). Then, domain adaptation was independently evaluated on two different datasets composed of 60 and 61 T1w and FLAIR images from a clinical hospital and from the public ISBI2015 challenge, respectively. For each unseen dataset, the same source model was fine-tuned re-training only the last layers but using a single image (we tested the use of images with different lesion load). The Dice overlap (DSC) coefficient between the resulting segmentations and manual lesion annotations was compared with respect to the same model when was fully trained on the target domain and with respect to other methods such as LST.

Results: On the clinical dataset, the performance of the model fully-trained with data from the target domain was DSC=0.53. When using the source model without readaptation, the performance dropped to DSC=0.25, while when adapting the source model using a single image the performance ranged between DSC=[0.30-0.48] depending on the lesion load of the image used. In all cases, showed a significant increase in the accuracy with respect to LST (DSC=0.29). On the ISBI2015 challenge, our fully-trained CNN method was ranked 3rd among 59 methods, showing human like segmentation performance. Interestingly, adapted models trained with only one image still yielded a remarkably higher performance than other state-of-the-art methods like LST or lesionToads, showing also a very similar performance to other CNN models trained on larger number of images.

Conclusions: Domain adaptation allows to use pre-trained CNNs on unseen clinical settings. A manual delineation of the lesions in only one image is sufficient to obtain accurate automated lesion segmentation performances.

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P495

Validation of brain atrophy measurements in multiple sclerosis: a physical phantom study

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Background: Global and regional brain atrophy assessment is fundamental in multiple sclerosis (MS) patient monitoring and research. However, the validation of segmentation algorithms still remains an open issue due to the lack of a ground truth.

Aim: Validating the quantification of white matter (WM), grey matter (GM), and total brain volumes of two commonly used automatic algorithms using a ground truth derived from a multimodal physical brain phantom.

Methods: The anthropomorphic phantom was built with two agar gels that resembled the WM and GM compartments of a real brain tissue, both in terms of signal intensity characteristics and shape. The ground truth volumes of WM, GM and total brain were derived from high-resolution computed tomography (CT) images. T1-weighted magnetic resonance (MR) images acquired at 3T were used as input for automatic segmentation carried out using FMRIB Software Library (FSL v5.0; FMRIB´s Automated Segmentation Tool, FAST) and Statistical Parametric Mapping (SPM v12; 'Segment'). Accuracy of the two algorithms was assessed by computing the percentage volume difference (VD) between the segmentation output and the ground truth for each compartment. Two additional T1-weighted MR images were acquired (without/with repositioning) to assess the scan-rescan reliability by comparing the computed volumes of those two scans to the ones calculated for the first scan.

Results: The ground truth volumes derived from the CT scan were: 237.60 mL for the WM, 737.92 mL for GM, and 975.52 mL

for the total brain. FSL and SPM performed comparably in terms of accuracy and reliability. For the accuracy, FSL slightly prevailed in computing the volumes of WM, GM, and whole brain, yielding lower absolute values of VD than SPM ($VD_{FSL\text{-}WM}$ = 3.4%, $VD_{FSL\text{-}GM}$ = 2.3%, $VD_{FSL\text{-}Brain}$ = 2.6%; $VD_{SPM\text{-}WM}$ = -4.4%; $VD_{SPM\text{-}GM}$ = -2.6%; $VD_{SPM\text{-}Brain}$ = -3.0%). Regarding the reliability, instead, SPM provided slightly less variable results compared to FSL ($VD_{SPM} \leq 0.5\%$ without repositioning, $VD_{SPM} \leq 1.0$ with repositioning; $VD_{FSL} \leq 0.2\%$ without repositioning; $VD_{FSL} \leq 2.0$ with repositioning).

Discussion and conclusions: The brain phantom, with its structural and intensity properties, allowed the validation of two popular automatic segmentation algorithms. Since the variability in computed volumes between the two software packages is comparable to the atrophy rates observed in MS, our study underlines the huge impact of software choices for quantifying brain volumes.

Disclosure

There are no conflicts of interest to report.

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Alteration of visual cortical microstructure is associated with pathology along the optic radiation in patient with MS: an asymmetry analysis of posterior visual pathway

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Introduction: Brain tissue loss, particularly in grey matter, has been recognized as the primary cause of irreversible neurological disability in multiple sclerosis (MS). While cortical inflammatory demyelinating lesions are common, damage in connected white matter tracts and/or other mechanisms may contribute to grey matter atrophy. The visual pathway is frequently affected by MS and constitutes an ideal model for probing these patho-mechanisms, primarily due to retinotopic organization and advances in magnetic resonance imaging (MRI) that facilitate the simultaneous assessment of optic radiation (OR) and primary visual cortex (V1) damage.

Objective: To elucidate the relationship between OR and V1 structural integrity in RRMS patients.

Methods: diffusion MRI, 3D T1, and FLAIR sequences were acquired on a 3T GE MRI scanner from patients with relapsing MS, recruited at a single centre. The OR was constructed individually using probabilistic tractography. OR diffusion metrics (AD, RD, MD, FA) and OR lesion volume were assessed. V1 structure was parcellated using FREESURFER; and both cortical thickness and MD assessed. Asymmetry analysis was conducted between left and right hemisphere to minimise inter-subject variation. Patients without OR gadolinium-enhancing lesions and with OR lesion length differences > 1mm were included in the analysis. Pearson's correlation was used to assess the relationships between the imaging metrics.

Results: Twenty relapsing MS patients with asymmetrical OR T2 lesions were included in the study; 75% female; mean age 37.3(10.5) years; mean disease duration 4.8(5.2) years and mean EDSS 2.0 (1.5) were evaluated. OR lesion volume was associated with V1-ΔMD (r=.60, p=.005), but not with V1-ΔFA (r=-.26, p=.27) nor V1-Δthickness (r=.09, p=.7). OR-ΔMD/ΔAD/ΔRD were also correlated with V1-ΔMD, however, the relationships were no longer significant after correction for OR lesion volume.

Conclusion: By asymmetry analysis, a higher visual cortex MD was identified in the hemisphere with the higher OR lesion volume. This relationship may reflect the consequences of both Wallerian degeneration along the OR and subsequent trans-synaptic degeneration within the V1. The absence of correlation between OR lesion volume and V1 thickness suggests that MD may be a sensitive biomarker for early stage cortical tissue loss, indicative of microstructural injury that occurs prior to overt tissue collapse and measurable cortical thinning.

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Magnetic resonance imaging parameters as predictors of physical and cognitive changes over the course of 8 years in patients with relapsing forms of multiple sclerosis

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Introduction: Limited data are available on the ability of magnetic resonance imaging (MRI) parameters to predict cognitive changes or improvements in physical ability in multiple sclerosis (MS).

Objectives: Assess the predictive value of MRI parameters for physical and cognitive outcomes in MS at ≤8 years.

Methods: *Post hoc* analyses of data from patients with relapsing MS on fingolimod in the placebo-controlled, phase 3 FREEDOMS

and FREEDOMS II trials and their extensions. Baseline (BL) MRI predictors analysed included T1 hypointense lesion volume (T1LV), T2 lesion volume (T2LV), presence of gadolinium-enhancing (Gd+) lesions and normalized brain volume (NBV). Other predictors included new T2 lesions, change in T2LV and annualized rate of brain atrophy (ARBA), all from BL to months 12 (M12) or 24 (M24), and change in T1LV from BL to M24. Outcomes were transition to secondary progressive MS (SPMS), confirmed disability improvement (CDI; a decrease in Expanded Disability Status Scale score of 1.0 or 0.5 points, if baseline score ≤5.5 or ≥6.0, respectively, confirmed at 6 months), CDI+ (CDI or improvement of ≥20% in 9-hole peg or timed 25-foot walk tests, confirmed at 6 months) and cognitive worsening (a decrease of ≥20% in the paced auditory serial addition test confirmed at 6 months). Predictors were categorized by quartile, except for Gd+ and new T2 lesions, which were dichotomized by presence/absence. Baseline-adjusted Cox proportional hazards model compared risk of worst vs best category; log-rank test determined predictive value of MRI parameters.

Results: For CDI and CDI+, the only significant predictors were baseline NBV and T1LV: low NBV (hazard ratio [HR]: 0.59 and 0.63; $p< 0.01$) and high T1LV (HR: 0.56 and 0.73; $p< 0.05$) predicted less CDI and CDI+, respectively. High baseline T1LV and T2LV predicted increased SPMS risk (HR: 2.88 and 2.83; $p< 0.01$), as did greater change in T1LV at M24 (HR: 2.32; $p< 0.05$). Risk of cognitive worsening correlated with high baseline T1LV and T2LV (HR: 3.00 and 2.51, respectively; $p< 0.01$), low NBV (HR: 3.51; $p< 0.001$), high ARBA at M12 (HR: 1.87; $p< 0.05$) and high Gd+ lesions (HR: 1.9; $p< 0.01$). By log-rank test, NBV was significantly predictive of all parameters tested ($p< 0.001$); T1LV was the second most robust parameter ($p< 0.01$ for all except CDI+).

Conclusions: Overall, disease burden measures, particularly NBV, are more robust prognostic parameters of long-term disease progression than MRI lesion activity.

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Association between baseline brain volumes and future change in EDSS in a cohort of early MS patients

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Background: Brain volume loss measurements over a period of several years determined by structural magnetic resonance imaging (MRI) are increasingly used for patient monitoring and treatment optimization in multiple sclerosis (MS). However, often brain volume measurements at a single time point are available only.

Methods: 71 early relapsing MS patients (median age at baseline: 33.0 years, interquartile range (IQR) [28.9, 40.0], median disease duration at baseline: 0.6 years, IQR [0.2, 3.2]) from the Neuroimmunology and MS Research Section at the University Hospital Zurich and 14 healthy controls received standardized MRI examinations including a high resolution gradient echo T1 sequence at baseline. EDSS scores were assessed by an experienced neurologist at baseline and approximately every 6 months. Median follow-up time was 2.5 years (IQR [1.6, 3.3]). Baseline brain parenchymal volume (BPV), thalamus volume, total T2 lesion load, and total lesion number were computed using an automated processing pipeline. BPV and thalamus volumes were transformed into z-scores using a publicly available cohort of healthy controls. Data from the 14 controls recruited locally were used to correct z-scores for inter scanner effects. For each patient, EDSS change over time was computed as the slope of the regression line fitting the age-EDSS measurements. As a second measure, the area under the curve (AUC) of the EDSS was divided by the length of the individual observation period for each patient. MRI measures were tested for correlation (Pearson's) with EDSS change and EDSS AUC.

Results: Mean EDSS AUC and EDSS change in the entire cohort was 1.1 (1.0 SD) and 0.0 (0.7 SD), respectively. Mean z-scores for thalamic volumes were significantly lower than z-scores for the BPV (-0.92 vs -0.34, $p=0.01$). The EDSS AUC correlated with thalamus z-scores ($r=-0.25$, $p=0.01$), the lesion load ($r=0.35$, $p< 0.001$), as well as with total lesion number ($r=0.42$, $p< 0.001$) but not with BPV z-scores. EDSS change showed a correlation with the thalamus z-scores only ($r=-0.32$, $p=0.006$).

Conclusions: In newly diagnosed MS patients, z-scores for thalamus volumes were significantly lower than z-scores for BPV indicating early involvement of the thalamus in neurodegenerative processes in MS. Our results suggest that lower thalamus volumes at baseline are associated with a higher risk of EDSS worsening over on average 2.5 years in early MS.

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Multi-shell diffusion imaging reveals progressive axonal pathology in early multiple sclerosis

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Background: Axonal loss is a main determinant of long-term disability and disease progression in multiple sclerosis (MS), however its non-invasive *in vivo* detection is challenging. The Composite Hindered and Restricted Model of Diffusion (CHARMED) is an advanced multi-shell diffusion-weighted magnetic resonance imaging (MRI) method that estimates a restricted diffusion fraction (FR) - a surrogate marker for axonal density. We previously provided cross-sectional evidence for the presence of widespread low axonal density in the normal appearing white matter (NAWM) of early MS cases that is, at least in part, unrelated to focal demyelinating lesions. The longitudinal application of CHARMED axonal density estimates, however, remains to be evaluated.
Objective: We aimed to investigate the longitudinal potential of FR axonal density estimates in tracking MS disease progression after 1 year.
Methods: A prospective cohort of 12 early MS subjects (disease duration ≤5 years) were scanned on an ultra-high gradient strength Siemens 3 T Connectom MRI scanner (300 mT/m maximum gradient strength) at baseline and at 1-year follow-up with multi-shell diffusion imaging (b=1k, 5k, 10k s/mm^2, 64, 64, 128 directions; 1.5 mm isotropic resolution). Additional imaging included a 3D multi-echo MPRAGE for anatomical segmentations in FreeSurfer and a 3D T2-SPACE-FLAIR (both 1 mm isotropic resolution). Diffusion-weighted data was pre-processed with FreeSurfer and FSL. FR maps were obtained with CHARMED using in-house developed scripts. Lesion masks were drawn by a radiologist using the FLAIR images from both time points independently, and lesions smaller than 12 voxels in diffusion space were discarded. The longitudinal change in FR values was assessed in the NAWM using voxel-wise tract-based spatial statistics (TBSS) while controlling for age, gender and multiple comparisons across clusters. Additionally, the change of FR within lesions was evaluated using one-sample t-tests.
Results: At 1-year follow-up, TBSS analysis revealed decreases in FR in widespread NAWM regions compared with the baseline ($p< 0.01$). There was also a reduction of the FR within lesions at follow-up ($p=0.02$).
Conclusion: Our findings show *in vivo* evidence of progressive axonal loss in both lesions and NAWM of early MS cases. The CHARMED axonal density estimate FR is a sensitive marker for longitudinal change in MS pathology and holds promise as a novel biomarker for early diagnosis and disease-monitoring purposes.

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Spatial distribution of white matter lesions in neuromyelitis optica spectrum disorder and multiple sclerosis

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Introduction: The characteristic brain abnormalities on MRI play an increasingly important role in differentiating neuromyelitis optica spectrum disorder (NMOSD) from multiple sclerosis (MS).
Objectives: The aim of this study was to compare brain lesion distribution and frequency on MRI in patients with NMOSD and MS using voxel-wise comparison procedures.
Methods: We collected MRI and clinical data of 91 patients with NMOSD and 54 patients with MS attending at the institutional referral center, Korea. Automated lesion segmentation was performed using T1 and FLAIR image modalities on publicly available lesion segmentation toolbox (LST) implemented for the SPM (http://www.fil.ion.ucl.ac.kr/spm). Blinded to clinical information, white matter (WM) lesions were manually modified by two independent raters. Voxel-wise statistics were examined for group-level comparison of lesion distribution using permutation-based cluster analysis ($p < 0.05$, cluster-corrected).
Results: Of 91 patients with NMOSD, 90% of patients were positive for anti-AQP4 antibody and 61 (65%) patients had brain MRI abnormalities. Patients with NMOSD had a longer disease duration (mean 8±5 vs. 7±4 years, $p=0.041$) and a higher EDSS score (median 2.5 [0-7.0] vs. 2.0 [0-6.5], $p=0.011$) compared with MS patients. In patients with MS, WM lesions tended to have a more widespread distribution than in NMOSD patients. The maximum local probability for lesions was higher in MS patients (39% peak probability in the posterior thalamic radiation) than in NMOSD patients (20% peak probability in the posterior corona radiata). The voxel-wise analysis showed that lesion frequency was higher in MS patients than in NMOSD patients with significant bilateral clusters in the posterior thalamic radiation, anterior and posterior corona radiata, sagittal stratum (including inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) and cingulum ($p< 0.05$, corrected).
Conclusion: Lesion probability mapping supports more frequent association of specific lesion locations with MS than NMOSD.

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P501

Transient enlargement of brain ventricles in the course of neuroinflammatory disease

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We previously reported an increase in cerebral ventricle volume (VV) prior to onset of clinical signs in the experimental autoimmune encephalomyelitis (EAE) model of MS. Here we extended these findings in EAE and investigated VV in MS patients.

We performed serial MRI scans in EAE mice to monitor longitudinal changes in VV during remission and relapse. SJL EAE mice were imaged every 2-3 days from d0 to d64 post-immunization, on a 9.4T animal MRI scanner. In MS patients, we investigated VV changes by analyzing MRI data that was acquired in a previous clinical study. Patients with definite MS (n=33) and at least one contrast-enhancing lesion (CEL) had each undergone a total of 13 MRI examinations over 1 year. A reference cohort of n=8 healthy individuals who had undergone multiple serial MRI scans over a period of several months served as controls. Absolute VV for mouse and human was quantified using FSL5.0 and corrected manually.

In mice we observed a robust increase in VV during the first disease peak, accompanied by CEL. Upon remission of clinical signs, VV of all mice returned to normal. Subsequent VV enlargements occurred in parallel to clinical exacerbations. We also observed fluctuations in the VV of MS patients, with substantial heterogeneity in the volatility of changes. The coefficient of variation in MS VV was significantly greater than that of controls. The range of VV changes in the control group was ±6% relative to baseline; 21/33 MS patients showed VV changes exceeding this threshold, and a majority of these showed VV contraction following expansion. Sequential VV measurements were analyzed as a time series and compared with CEL, T_2- and black hole lesion volumes and counts. Half of the patients showed significant temporal relationships between VV fluctuations and changes in lesions (cross correlations between time series). Additional significant cross correlations with VV were seen for cognitive and motoric tests.

These results show that the dynamic VV changes during the course of disease in EAE may also occur in some MS patients. The fact that VV often contracted following expansion argues that these variations are not merely the result of brain atrophy due to neurodegeneration, but rather reflect some process related to the inflammatory status. The mechanisms underlying this phenomenon, and the potential prognostic and diagnostic value of VV as a contrast-free MRI parameter for MS patients, remain topics for further investigation.

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Coordinate based network meta-analysis: localised regions of consistent GM atrophy form networks

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Background: Coordinate based meta-analysis of voxel-based morphometry (VBM) studies of grey matter (GM) density shows consistent regional atrophy in MS; where the coordinates reported by the studies form dense clusters. Between regions the effect size (reported Z scores normalised by the number of subjects), which quantifies relative degree of atrophy, is correlated. These regions may form networks of GM atrophy.

Objective: use novel Coordinate Based Network Meta-Analysis (CBNMA) to look for GM atrophy networks.

Methods: Search for VBM studies comparing MS or CIS to healthy controls. Use CBNMA to locate regions (clusters of reported coordinates, which form the network nodes) where atrophy is reported consistently across the studies, then estimate a correlation (of effect size to form the network edges) matrix between the regions; computed by fitting (pairwise) bivariate normal distributions to the effect sizes. The likelihood ratio test provides asymptotic p-values for each edge, and thresholding the p-values by false discovery rate (FDR) produces an adjacency matrix that defines network connections. Research into the thresholds needed to create brain networks is ongoing. Here FDR was chosen to create, as far as possible, symmetric networks.

Results: 43 studies met the inclusion criteria and reported 523 foci in total. Two separate networks were identified. An FDR of 0.1 was chosen as it produced symmetric networks. Other FDR levels resulted in the same nodes (regions of consistent GM atrophy), but some edges were missing at lower FDR and extra edges added at higher FDR. Network 1 involved (bilaterally) the thalamus, Postcentral Gyrus (Brodmann area 3), and the Claustrum. In this network the most connected nodes were the postcentral gyri, where atrophy was correlated with atrophy in every other node. The second network involved bilateral insula.
Conclusions: Multiple GM regions are reported as atrophied consistently by VBM studies comparing CIS and MS to healthy controls. These regions form independent networks of atrophy, where knowing the degree of atrophy in one region can indicate atrophy in others from the same network. Clinical trials using GM atrophy as an outcome might then test for significant networks, rather than significant voxels or regions of atrophy. The single statistical test of a network would require no correction for multiple comparisons, and thus be more powerful necessitating smaller sample sizes.

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^{11}C-PBR28 imaging in multiple sclerosis is reproducible and able to disclose progression of neuroinflammation

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Background: Microglia activation plays a main role in multiple sclerosis (MS) pathogenesis. Activated microglia upregulate expression of the 18kDa translocator protein (TSPO), which can be imaged in vivo with ^{11}C-PBR28, a second-generation TSPO positron emission tomography (PET) radioligand. Cross-sectional ^{11}C-PBR28 PET studies in MS have disclosed microglial pathology in the white matter (WM) and grey matter (GM) of the brain at different disease stages. The ability of ^{11}C-PBR28 imaging to detect progressive TSPO expression in MS is still unknown.
Aim: To assess test-retest and longitudinal changes in TSPO expression in the brain of 10 healthy controls (HC) and 4 MS subjects using integrated 3 T ^{11}C-PBR28 magnetic resonance-PET (MR-PET).
Methods: Ten HC (mean±SD age=28±6 years) underwent two 90-minutes ^{11}C-PBR28 MR-PET sessions, 3 months apart, to evaluate the test-retest variability in tracer uptake. Four MS subjects (mean±SD age=54±4 years) underwent 90-minutes ^{11}C-PBR28 MR-PET at baseline and 1-year follow up. During each session, anatomical MR scans were simultaneously acquired for: a) FreeSurfer cortical surface reconstruction, b) FIRST-FSL for deep GM segmentation (thalamus, hippocampus and basal ganglia) c) MR-PET image registration. Normalized standardized uptake value (SUVR) maps were created for 60-90-minute PET frame (1.25 mm isotropic voxels). In patients, WM and cortical lesions (CL) were segmented on 7T T_2* images (0.33x0.33x1 mm^3) from a separate scan. Lesional, cortex, deep GM and normal appearing WM (NAWM) masks were co-registered to ^{11}C-PBR28 maps. In these areas mean SUVR were extracted and compared at baseline and follow up (by paired t-test). In HC, the within-subject coefficient of variations (CV) was estimated across brain regions as the ratio between the standard deviation and the mean of each couple (Scan 1, Scan 2) of measurements (SUVR).
Results: In HC, CV were 8% in cortex, 7% in WM, 9% in thalamus, 8% in hippocampus and 9 % in basal ganglia. Relative to baseline, MS had increased ^{11}C-PBR28 SUVR at follow up in the cortex (~15%, p=0.006), CL (~10%), thalamus (~10%), hippocampus (~16%) and basal ganglia (~10%). Increased SUVRs were also detected at follow up in NAWM (~12% p=0.03) and WM lesions (14%, p=0.009). In HC, mean % SUVR change across brain regions was < 3%.
Conclusions: ^{11}C-PBR28 MR-PET shows good test-retest reproducibility and proves to be a sensitive tool for assessing neuroinflammation and its progression in MS.

Disclosure
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P504
Characterizing grey-matter multiple sclerosis lesions using double inversion recovery, diffusion and contrast-enhanced MRI

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Background: While white-matter (WM) lesions have been well-characterized in multiple sclerosis, cortical grey-matter (GM) lesions remain largely unexplored because they are usually non-conspicuous on conventional MRI (FLAIR). The aim of our study is to use double-inversion recovery (DIR) MRI to better identify MS lesions in cortical GM, determine their prevalence, and characterize their contrast-enhancement and diffusion. Comparisons were made with WM lesions and correlated with atrophy.

Methods: Relapsing remitting multiple sclerosis (RRMS) patients (N=44) with DIR data were identified. 3T MRI pre- and post-contrast, fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI) and DIR were acquired. Lesion segmentation was based on DIR into cortical GM, subcortical WM and periventricular WM, and whether they were enhancing and not, and hyper- or hypo-intense on apparent diffusion coefficient (ADC).
Results: Most (86%) RRMS patients had cortical GM lesions. Compared to WM lesions, GM lesions were fewer in count (328 versus 1604) and volume (32,831 versus 511,125). Of the 328 GM lesions, 97% were not enhanced of which 89% had high ADC. Of the 1095 subcortical WM lesions, 98% were not enhanced, of which only 40% had high ADC. Of the 509 periventricular lesions, 97% were not enhanced, of which 82% showed high ADC. These findings indicate that GM and WM have similar prevalence of enhancement. GM lesions showed similar susceptibility to cytotoxicity as periventricular WM lesions but differed from subcortical WM lesions.
GM lesion count was correlated with GM atrophy (p=0.004) and total brain atrophy (p=0.005), but not with WM atrophy. GM lesion-volume correlated with GM, WM and total brain atrophy (p=0.01, 0.04, 0.006, respectively).
Conclusion: This study identified the prevalence of GM lesions based on DIR, described diffusion changes and contrast-enhancement and compared them with WM lesions. GM and WM had similar percentage of contrast-enhanced lesions. Most enhanced lesions showed higher ADC, suggesting more oedema and/or atrophy. GM lesion count and GM lesion volume, correlated with total brain, WM and GM atrophy. Improved understanding of grey-matter multiple sclerosis pathology is important because it could be better correlated with cognitive and physical disability.

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P505

Can MR spectroscopy predict multiple sclerosis and its clinical symptoms?

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Objective: Advanced MR technologies, such as 1D magnetic resonance spectroscopy (MRS) have been applied to multiple sclerosis previously to investigate metabolic changes in the brain of multiple sclerosis (MS) patients and to offer potential biomarkers for disease monitoring. For the first time, we have applied *in-vivo* two-dimensional (2D) Localized COrrelation SpectroscopY (2D L-COSY), an innovative MRS technique in relapsing and remitting multiple sclerosis (RRMS) in order to identify the optimal MR biomarker to monitor disease activity.
Methods: 2D L-COSY MRS spectra was prospectively acquired from a 3x3x3cm^3 voxel located in the posterior cingulate gyrus (PCG) from 45 stable RRMS patients undergoing treatment with Fingolimod and 40 age and gender-matched healthy control participants (HC). Mean metabolites and clinical correlates including cognitive, fatigue and mental health parameters were calculated and compared using parametric and non-parametric tests. Whole brain volume and voxel morphology were evaluated using SIENAX and SPM LST toolbox.
Results: Mean lesion volume was 6.8mls. Out of all metabolites measured, the NAA metabolic fingerprints most accurately distinguish MS from healthy controls using the Wald test for logistic regression (12.9; $p < 0.001$ after adjusting for age and sex). NAA peaks are closely correlated with most atrophy measures (r=0.487; $p< 0.01$). In a cohort with only minimal cognitive impairment, only visuospatial function and attention were correlated with metabolites in the brain (NAA_1 Pearson's correlation -0.42; $p< 0.01$; GABA and NAA_3 -0.36; $p< 0.05$; Glx -0.37 $p< 0.01$). Out of all brain volume measurements grey matter volume (GMV) and total lesion volume (TLV) are most closely associated with cognitive function (GMV: 0.39; TLV: -0.401; $p< 0.01$) and disease severity (GMV: -0.495; TLV 0.463; $p< 0.01$). None of the parameters tested predicted fatigue, depression, anxiety or stress.
Conclusions: 2D L-COSY has the potential to detect metabolites that distinguish healthy from MS brain even if the lesion load is minimal. Despite only examining a localized region, we could detect metabolic variability associated with symptoms. In future, whole brain MRS might offer additional essential information to monitor MS.

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P506

Neuroinflammation in progressive multiple sclerosis: *in vivo* assessment using [^{18}F]DPA714

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Introduction: Over the past decades positron emission tomography (PET) imaging has progressed in the field of MS research, as PET can visualise molecular processes, such as neuroinflammation, *in vivo*. The second generation PET radioligand [^{18}F]DPA714 binds with high affinity to the 18-kDa translocator-protein (TSPO), which is expressed on activated microglia.
Objectives: The aim of this study was to evaluate this *in vivo* marker of neuroinflammation in primary and secondary progressive MS.
Methods: All subjects were genotyped for the rs6971 polymorphism within the TSPO gene and low affinity binders were excluded from participation in this study. Eight progressive MS patients and seven age and genetic binding status matched healthy controls underwent a 60 minutes dynamic PET scan using [^{18}F] DPA714, including both continuous on-line and manual arterial blood sampling to obtain metabolite-corrected arterial plasma input functions.
Results: The optimal model for quantification of [^{18}F]DPA714 kinetics was a reversible two tissue compartment model with additional blood volume parameter. For genetic high affinity binders, a clear increase in binding potential (BP_{ND}) was observed in MS patients compared with age matched controls. For both high and medium affinity binders, a further increase in BP_{ND} was observed in T2 white matter lesions compared with non-lesional white matter. Volume of distribution, however, did not differentiate patients from healthy controls, as the large non-displaceable compartment of [^{18}F]DPA714 masks its relatively small specific signal.
Conclusions: The TSPO radioligand [^{18}F]DPA714 can reliably identify increased focal and diffuse neuroinflammation in progressive MS when using plasma input derived BP_{ND}, but observed differences were predominantly visible in high affinity binders.

Disclosure

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P507
Estimation of brain cerebrospinal fluid components in CIS patients

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Background: Brain atrophy is usually quantified through global and regional brain volume fractions such as the grey and white matter fraction (GMF, WMF) and the brain parenchymal fraction (BPF). The differential role of the ventricular (V) and sulcal (S) cerebrospinal fluid (CSF) components has not been studied so far.
Objective: The aim of this study was to obtain an estimation of VCSF and SCSF, and to assess their relationship with GMF, WMF and BPF as well as with disease burden.
Material and methods: A convenience sample of 114 patients with a clinically isolated syndrome was included in this study. Images were acquired with a 3.0T system (Siemens, Trio, Erlangen, Germany) and included: 3D-T1-weighted (MPRAGE) and 2D-T2-FLAIR images. Brain lesion volume (LV) was estimated with the Lesion Segmentation Toolbox, global brain volume measures were obtained with Statistical Parametric Mapping (v12), and the estimation of VCSF, with the ALVIN tool (v1). Estimation of SCSF was done after subtracting VCSF from total CSF volume. The corresponding brain fractions (grey matter fraction -GMF-, white matter fraction -WMF- and brain parenchymal fraction -BPF-) were obtained after dividing tissue volume estimations by the total intracranial volume (GM+WM+CSF). Associations were tested with partial correlations, controlling for age and gender.
Results: VCSF and SCSF fractions were poorly correlated ($r=0.21$, $p=0.03$). VCSF correlated moderately with BPF ($r=-0.50$, $p< 0.001$) and WMF ($r=-0.49$, $p< 0.001$); while SCSF showed only a poor correlation with BPF ($r=-0.27$, $p=0.005$). LV correlated with VCSF ($r=0.40$, $p=0.001$), BPF ($r=-0.50$, $p< 0.001$) and WMF ($r=-0.44$, $p< 0.001$).
Conclusions: Regional components of CSF do not seem to be strongly associated with brain volume global measures. Further studies are needed to assess their value as additional biomarkers in atrophy dynamics.

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P508

QUANTUM - Standardized MRI acquisition with centralized quantitative MRI reading in daily clinical routine of MS patients

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Background:In Multiple Sclerosis (MS) clinical trials quantitative MRI analyses are carried out based on highly standardized protocols, while such levels of standardization are not yet available in clinical routine. Tools for quantitative data analysis including brain volumetry do exist, but are not yet available for daily routine practice.
Objective: To validate the feasibility and explore the potential benefit of standardized MRI acquisition and centralized quantitative MRI reading including brain volumetry and lesion segmentation in day-to-day MS patient management.
Methods: Within the QUANTUM project approximately 9.000 MRI analyses will be performed in 300 centres in Germany. The standardized MRI data (3D T1 gradient-echo sequence and 2D/3D FLAIR) are analysed by means of a centralised automatic processing pipeline (Biometrica MS®, jung diagnostics GmbH). The analysis comprises a volumetric quantification of brain volume, as well as T2 lesion load and number. Percentage brain volume change is computed (using optimized SIENA pipeline) when follow-up scans are available. The results are visualised and provided to the participating physicians as a report. The value and feasibility are evaluated using a questionnaire.
Results:Since July 2016 130 radiological centres across Germany have been qualified and 1600 quantitative MRI analyses been accomplished in 190 neurological centres.A preliminary analysis of the first 276 questionnaires revealed good acceptance and usability of the QUANTUM reports among neurologists**:** 73% of the neurologists report a strong or very strong correlation between the quantitative MRI parameters in the QUANTUM report and the clinical presentation of the patients. 87% of the neurologists state that the report was very helpful to classify the disease activity. 89% of the neurologists rate the additional benefit of quantitative MRI parameters in the context of assessing all four NEDA-criteria as high or very high. The data included into the preliminary analysis were acquired between July 2016 and May 2018. Until mid-2018 approx. 2200 questionnaires will be available for analysis.
Conclusion: In QUANTUM, standardized MRI acquisition and centralized MRI evaluation are broadly being made available in a real-world setting. Brain volume change and quantification of lesion load can be assessed in routine clinical practice based on validated protocols. This could provide new opportunities for individual MS patient monitoring in daily care.

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OCT

P509

Annualized inner retinal layer atrophy rates show a flooring effect in longstanding MS; a limitation for longitudinal OCT studies?

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Introduction: Atrophy of the inner retinal layers (peripapillary retinal nerve fibre layer [pRNFL], ganglion cell-inner plexiform layer [GCIPL]) is common in multiple sclerosis (MS), but data on annual atrophy rates are inconsistent and seem to be dependent on disease stage.
Objective: To define the annualized atrophy rates of the pRNFL and GCIPL in a cohort of patients with longstanding MS and to investigate the effect of disease duration on these rates.
Methods: In this longitudinal observational study, spectral-domain optical coherence tomography (OCT) and clinical data (EDSS score and MS-associated optic neuritis [MSON] during the study) were collected in 114 patients with relapsing-remitting, secondary progressive and primary progressive MS (64.9% female, age 53.6±9.6 years) and 30 healthy control subjects (HCs, 50.0% female, age 51.2±5.9 years). Mean follow-up duration was 4.4 years (range 2.1 to 6.1). Following OCT quality control, automated segmentation of the pRNFL (µm) and GCIPL (µm) was performed. Annualized atrophy rates were calculated for each eye. Disease duration was categorized into quartiles. Generalized estimation equations were used to analyze atrophy rates and associations with disease duration and clinical measures.
Results: Patients had a mean disease duration of 20.5±6.4 years (range 9.2-38.4) at baseline. In this patient group, the annualized atrophy rate for the GCIPL was -0.31 µm ($p< 0.001$), which was only slightly higher than in HCs (-0.25 µm, $p< 0.001$). For the pRNFL, there was significant annualized atrophy in MS patients (-0.30 µm, $p< 0.001$), but not in HCs (0.12 µm, $p=0.41$). Eyes with an episode of MSON during the study (25/228 MS eyes) demonstrated a higher GCIPL atrophy rate compared to eyes without MSON (-0.78 µm and -0.25 µm respectively, $p=0.06$). Annualized pRNFL and GCIPL atrophy rates were significantly more pronounced in patients with the shortest disease duration (1st quartile) compared to longer disease duration (3rd and 4th quartile, $p< 0.05$, adjusted for baseline OCT value and MSON).
Conclusion: This study showed that in longstanding MS, the annualized atrophy rates of the pRNFL and GCIPL are lower than previously reported values. Atrophy rates were highest in patients with a relatively short disease duration, suggesting a flooring effect in longstanding MS, potentially limiting the use of OCT in longstanding progressive MS.

Disclosure

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3D fovea morphometry reveals distinct foveal changes in neuromyelitis optica spectrum disorders

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Introduction: Neuromyelitis optica spectrum disorders (NMOSD) are chronic autoimmune conditions associated with optic neuritis (ON) and myelitis, and characterised by pathogenic serum autoantibodies against aquaporin-4 (AQP4-IgG) in the majority of cases. We and others recently reported foveal thinning as detected by optical coherence tomography (OCT) in AQP4-IgG positive NMOSD independent of ON.

Objectives: To further investigate the fovea in AQP4-IgG pos. NMOSD in comparison to healthy controls (HC) and the most common differential diagnosis multiple sclerosis (MS) by applying a novel 3D fovea morphometry analysis.

Aims: To establish a biomarker based on 3D fovea morphometry for supporting the diagnosis of NMOSD.

Methods: OCT scans from 150 subjects (28 AQP4-IgG pos. NMOSD, 60 MS, 62 HC) were included. We applied our recently developed model-driven 3D macula shape analysis based on cubic Bézier parametric modelling on standard macular OCT volume scans. This morphometry describes the fovea in 19 parameters and allows evaluation of depth, pit shape, diameter, slope, area, and volume of different regions of the fovea. Combined ganglion cell and inner plexiform layer (GCIPL) and peripapillary retinal nerve fiber layer (pRNFL) thicknesses were measured to determine neuro-axonal damage.

Results: Slope disk area (NMOSD: 0.46±0.17, HC: 0.34±0.12, MS: 0.34±0.17 mm^2), major axis slope disk (NMOSD: 0.080±0.028, HC: 0.059±0.022, MS: 0.058±0.030 mm), minor axis slope disk (NMOSD: 0.068±0.026, HC: 0.050±0.018, MS: 0.049±0.025 mm), and average slope disk diameter (NMOSD: 0.74±0.14, HC: 0.64±0.11, MS: 0.63±0.15 mm) were significantly higher in NMOSD in comparison to both HC ($p=0.002$, $p=0.004$, $p< 0.001$, $p=0.001$) and MS patients ($p=0.012$, $p=0.017$, $p=0.005$, $p=0.004$), independent of history of ON. Six further fovea parameters were different in NMOSD but also dependent of ON. Two additional fovea parameters were mainly dependent on a history of ON and independent of the disease type.

Conclusions: The fovea shape differs in AQP4-IgG pos. NMOSD in contrast to HC and MS. The cause, functional relevance, and potential diagnostic value of these changes, considering ON dependency, need to be further investigated. Fovea shape analysis might provide important additional information for AQP4-IgG pos. NMOSD diagnosis and monitoring.

Disclosure

SM is named as inventor on "Method for estimating shape parameters of the fovea by optical coherence tomography" (EP 17182192.9) patent application, related to this work. FCO is employee of Nocturne UG, unrelated to this work. JH reports an OCT research grant from the Friedrich-Baur-Stiftung, personal fees and non-financial support from Merck, Novartis, Roche, Bayer Healthcare, Santhera, Biogen, Sanofi Genzyme and non-financial support of the Guthy-Jackson Charitable Foundation and NEMOS, all unrelated to this work. SY is named as inventor on "Method for estimating shape parameters of the fovea by optical coherence tomography" (EP 17182192.9) patent application, related to this work, and is co-founder, employee, and shareholder of Nocturne UG, unrelated to this work. EMK is named as inventor on "Method for estimating shape parameters of the fovea by optical coherence tomography" (EP 17182192.9) patent application, related to this work, and is co-founder, employee, and shareholder of Nocturne UG, unrelated to this work. HZ received grants from Novartis during the conduct of the study, related to this work, and received speaking fees from TEVA, unrelated to this work. KR was supported by the German Ministry of Education and Research (BMBF/KKNMS, Competence Network Multiple Sclerosis) and has received research support from Novartis and Merck Serono as well as speaking fees and travel grants from Guthy Jackson Charitable Foundation, Bayer Healthcare, Biogen Idec, Merck Serono, sanofi-aventis/Genzyme, Teva Pharmaceuticals, Roche and Novartis. JBS has received travel grants and speaking fees from Bayer Healthcare, Biogen Idec, Merck Serono, sanofi-aventis/Genzyme, Teva Pharmaceuticals, and Novartis, all unrelated to this work. TK received travel expenses and personal compensations from Bayer Healthcare, Teva Pharma, Merck, Novartis Pharma, Sanofi-Aventis/Genzyme, Roche and Biogen as well as grant support from Bayer-Schering AG, Novartis and Chugai Pharma, all unrelated to this work. FP received research support from the Guthy Jackson Charitable Foundation and National Multiple Sclerosis Society, research grants and speaker honoraria from Bayer, Teva, Genzyme, Merck,

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P511

Reductions in retinal vascular plexus densities in multiple sclerosis are associated with visual dysfunction and global disability

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Background: Central nervous system inflammation may lead to alterations in vascular function. Studies of the cerebral microvasculature in multiple sclerosis (MS) reveal hypoperfusion in gray and white matter. MS lesions also exhibit elevated hypoxia inducible factors. Retinal vasculature may be altered in MS, and can be evaluated with optical coherence tomography angiography (OCT-A).

Goals: To (1) compare retinal vascular plexus densities in relapsing remitting MS (RRMS) and healthy controls (HCs), and (2) examine the relationships of these measurements with retinal layer thicknesses, visual function and global disability.

Methods: In this cross-sectional study, 116 people with RRMS [225 eyes; 98 eyes with a history of optic neuritis (ON)] and 50 HCs (97 eyes) underwent Heidelberg Spectralis OCT-A and spectral-domain OCT (with automated segmentation of retinal layer thicknesses). Superficial vascular plexus (SVP) and deep vascular plexus (DVP) densities were quantified using ImageJ software, and poor quality OCT-A images were excluded. People with RRMS also underwent assessment of visual function and expanded disability status scale (EDSS) scores. Multivariate linear regression models were adjusted for age, sex and ON history. Mixed-effects models were additionally adjusted for within-subject inter-eye correlations.

Results: Mean SVP density was 24.4% (SD 5.5%) in RRMS eyes [26.2% (SD 4.7%) in non-ON eyes vs. 22.4% (SD 5.6%) in ON eyes, $p< 0.001$], as compared to 29.2% (SD 3.3%) in HC eyes (all RRMS, non-ON, and ON eyes vs. HC eyes; $p< 0.001$ for all). DVP density did not differ significantly between groups. In individual RRMS eyes, lower SVP density was associated with lower peripapillary retinal nerve fiber layer (pRNFL) thickness ($R^2=0.53$, $p< 0.001$), lower ganglion cell + inner plexiform layer (GCIP) thickness ($R^2=0.75$, $p< 0.001$) and lower letter acuity ($R^2=0.22$ for 100%-contrast, $R^2=0.36$ for 2.5%-contrast, $R^2=0.26$ for 1.25%-contrast; $p< 0.001$ for all). Using mixed-effects regression, lower SVP density, pRNFL and GCIP thickness were independently associated with longer disease duration ($p=0.02$, $p=0.03$ and $p=0.008$, respectively) and higher EDSS ($p=0.04$, $p=0.05$ and $p=0.04$, respectively).

Conclusions: RRMS eyes, both with and without a history of ON, demonstrate reduced retinal SVP density as compared to HCs. Furthermore, lower SVP density in RRMS correlates with lower retinal layer thicknesses, poorer visual function and higher levels of global disability.

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OCT intra-retinal layer segmentation unveils grey and white matter pathology in primary progressive MS

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Background: It's critical to develop new biomarkers of disease progression in primary progressive (PP) MS. There is evidence that deep grey matter (DGM) atrophy drives disability worsening in MS representing an early biomarker of neurodegeneration. Optical coherence tomography (OCT) has also emerged as a possible surrogate of disease progression and brain atrophy, but its relation with regional brain atrophy outside the visual system has not been investigated yet. Moreover, very little is known about the association between OCT-derived metrics and diffuse inflammatory white matter pathology, which is predominant in PPMS.
Objective: To assess whether OCT-derived intra-retinal layer thickness correlates with DGM atrophy and white matter pathology in PPMS.
Methods: We collected data from 41 PPMS patients (age 51±9 y, median EDSS 4, mean disease duration 9 y) and 26 matched healthy controls (HC) from 2 MS centres. All subjects underwent brain MRI (including 3D-T1/T2-weighted and DTI sequences) using a 3T Philips scanner and spectral-domain OCT (Heidelber Spectralis). Brain volumes were estimated with SIENAX and FSL FIRST on lesion-filled 3D-T1 images. 4 OCT exams were excluded from the analysis due to poor quality. Statistical analyses were performed with SPSS 23.0.
Results: Compared to controls, thickness of the ganglion cell layer (GCL) and inner plexiform level (IPL) was significantly lower in patients (p=0,003 and p=0,007 respectively) as well as normalized brain volume (NBV) and DGM volumes (p< 0,05 for all the comparisons). In PPMS patients, correlations (after correcting for age, sex and center) were found between GCL and NBV (r=0,37: p=0,03), thalamus (r=0,58:p< 0,001), caudate (r=0,4:p=0,02), putamen (r=0,5:p=0,003) and globus pallidus (r=0,37:p=0.03) volumes and between IPL and white matter volume (r=0,325:p=0,04), NBV (r=0,41:p=0,017), thalamus (r=0,53:p< 0,001), caudate (r=0,36:p=0,003) and putamen (r=0,46:p=0,006) volumes. Correlations were found between GCL and mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) of the whole normal appearing white matter and between both GCL and IPL and MD, AD and RD of the grey matter (r ranging from -0,25 to 0,59:p< 0,05 for all the comparisons).
Conclusion: Thickness of GCL and IPL strongly correlates with DGM volumes and with diffuse white matter pathology, representing a sensible and reproducible marker to monitor early neurodegeneration and widespread neuroinflammation in PPMS.

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The effect of tobacco use on retinal structures in vitamin d deficient patients with relapsing remitting multiple sclerosis

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Objective: To assess the correlation between tobacco use and retinal layer thickness in patients with relapsing remitting multiple sclerosis (RRMS) who are vitamin D deficient.
Background: It has been shown that retinal layer thickness decreases over time in MS patients. Previous studies have indicated that MS patients with vitamin D deficiency experience a higher relapse rate than MS patients with normal vitamin D serum levels. Other studies have noted that both tobacco use and insufficient vitamin D serum levels were correlated with higher disease disability. In this study, we are trying to determine whether there is a synergistic effect of vitamin D deficiency and tobacco use on the retinal layers and volumes.
Design/Methods: Twenty-two patients with RRMS (17 women, 5 men, mean age 43.7: range 24-65 y) were included in this single-center, retrospective study. Optical coherence tomography (OCT) was performed by an experienced technician to quantify the papillomacular bundle (PMB) and the peripapillary retinal nerve fiber layer (pRNFL) quadrant thicknesses: superior, inferior, temporal, nasal. Intra-retinal segmentation was performed to obtain total macular volume (TMV), retinal nerve fiber (RNFL), ganglion cell (GCL), inner plexiform (IPL), inner nuclear (INL), outer plexiform (OPL), outer nuclear (ONL) and photoreceptor (PR) layer thickness. Tobacco use was self-reported in three out of the twenty-two MS patients who had an OCT scan within 6 months of vitamin D serum levels being measured. General linear multivariate analysis was used to establish a possible relationship between retinal volumes, and tobacco use in RRMS patients with vitamin D deficiency. Age, disease duration, sex, and ethnicity were included as covariates.
Results: A significant direct correlation was found between retinal nerve fiber layer (RNFL) and vitamin D deficiency in RRMS patients who use tobacco (p=0.036). Similarly, there was a direct correlation between the thickness of the PR layer, vitamin D deficiency and tobacco use (p=0.024). There were no significant relationships between GCL, IPL, INL, ONL, RPE, TMV, pRNFL, serum vitamin D deficiency and RRMS patients who smoke tobacco and non-smoking RRMS patients.

Conclusions: Our data suggests that there is a significant direct correlation between PR, RNFL thickness and vitamin D deficiency in RRMS patients who smoke tobacco. Further longitudinal studies should be conducted to confirm these findings.

Disclosure

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P514

Has the prevalence of uveitis in patients with multiple sclerosis been overestimated?

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Introduction: The occurrence of intermediate uveitis in patients with multiple sclerosis (MS) may be a sign of coexistent inflammatory central nervous system (CNS) disease activity. Intermediate uveitis is characterized by the presence of vitreous inflammation resulting in vitreous haze (VH). Studies on uveitis in MS patients have reported varying prevalences (ranging from 0.4 to 44%) which is partly due to the subjective manner of assessment by slit lamp examination. Recently, a new algorithm has been developed for the quantification of VH on optical coherence tomography (OCT) scans, making it possible to objectively assess the presence and activity of uveitis.
Objective: To investigate whether there is evidence of VH in patients with MS and whether this VH is associated with inflammatory CNS disease activity.
Methods: This cross-sectional study included 315 MS patients and 87 healthy controls (HCs) from the Amsterdam MS Cohort who had previously undergone an OCT scan. Macular volume scans were analysed for the presence of VH using an automated algorithm. All VH scores were log transformed before analysis. The relationship between VH and clinical, retinal OCT and MRI parameters of inflammatory disease activity was investigated using generalized estimating equations.
Results: The mean VH scores were low in both MS patients and HCs (respectively -0.96 and -0.93) and did not differ between these two groups (mean difference 0.03, p=0.419). There was no difference in VH score between relapsing remitting and primary progressive patients (mean difference 0.14, p=0.471) nor between relapsing remitting and secondary progressive patients (mean difference 0.12, p=0.251) after correcting for age. A history of optic neuritis (n= 171 eyes) did not affect the amount of VH (mean difference 0.05, p=0.132). In addition, VH was not associated with inner nuclear layer volume on OCT (β=-0.00009, p=0.990) or cerebral T2 lesion load on MRI (β=-0.089, p=0.219).
Conclusion: Using an objective measure to detect the presence of uveitis in a large cohort of MS patients, this study could not find evidence of increased vitreous inflammation in MS patients compared to HCs nor was there any association between VH and measures of inflammatory disease activity. The results might indicate that uveitis in MS is less prevalent than previously thought.

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Obesity and retinal integrity in relapsing remitting multiple sclerosis

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Objective: To assess the effect of obesity on retinal structures in patients with Relapsing Remitting Multiple Sclerosis (RRMS).
Background: It has been previously shown that obesity may be a risk factor for MS and has a negative effect on disease severity. In MS patients, it has been well established that retinal layers thin over time. Optical coherence tomography (OCT) is utilized to quantify retinal thickness. In this study, we are further exploring the direct effect of obesity on retinal structures in RRMS patients.
Desgin/Methods: Ninety- two patients with RRMS (66 women, 26 men, mean age±SD: 44.5±9.7) were included in this single-center retrospective study. Fifty-six RRMS patients were classified as obese (BMI ≥30, 42 women, 14 men, mean BMI±SD: 35.6±4.6, mean disease duration±SD: 8.1±7.0). Thirty- six RRMS patients were classified as non-obese (BMI<30, 24 women, 12 men, mean BMI±SD: 24.6±3.2, mean disease duration±SD: 10.4±7.1).OCT was performed on each patient by an experienced technician to quantify the peripapillary retinal nerve fiber layer

(pRNFL) thickness and volumetric macular scans. Peripapillary retinal nerve fiber layer (p RNFL) within superior, inferior, temporal, nasal along with TMV and papillomacular bundle (PMB) were measured. Intra-retinal segmentation was performed to obtain retinal nerve fiber (RNFL), ganglion cell (GCL), inner plexiform (IPL), inner nuclear (INL), outer plexiform (OPL) and outer nuclear (ONL) layer thickness. The BMI for each patient was calculated and they were classified as either obese or non-obese. A generalized linear model with OCT parameters as dependent variables and BMI groups as independent variable was used to analyze our data. Age and disease duration were included as covariates.

Results: In obese RRMS patients, there was a significant direct correlation between BMI and INL thickness (p= 0.029). The mean global pRNFL thickness was 90.5±16.4 and 93.0±12.9 in obese RRMS patients and non-obese RRMS patients, respectively (p=0.30). There were no significant correlations between BMI and PMB, TMV, GCL, IPL, ONL, OPL, PR and RPE.

Conclusions: Our data suggests that obesity can adversely affect retinal integrity, specifically the INL. Follow-up OCT measurements may be beneficial in combination with BMI calculations to monitor the course of MS disease in RRMS patients.

Disclosure

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P516

Neurodegeneration of macular ganglion cells and maculo-papillary bundle is present early in radiologically isolated syndrome and reflects brain atrophy

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Objective: To study peripapillary retinal nerve fiber layer (pRNFL), macular RNFL (mRNFL) and ganglion cell and inner plexiform layer (GCIPL) thickness within their association to volumetric brain magnetic resonance imaging (MRI) measurements in individuals with radiologically isolated syndrome (RIS).

Methods: 15 RIS individuals and 15 age and sex matched healthy controls (HC), total 60 eyes, underwent spectral-domain optical coherence tomography (OCT) (Spectralis, Heidelberg Engineering), and MRI (1.5 Tesla Magnetom scanner, Siemens) scans. Peripapillary and macular scans and macular retinal segmentation was performed for both eyes of each participant. Voxel based morphometric measurements were done by using Statistical Parametric Mapping (SPM) 12 and brain volumetric measurements were normalized to intracranial volume before analysis. Generalized estimation equation models accounting for within-subject inter-eye effects and corrected for age and sex were used to compare OCT results between the study cohorts and for the analysis of association between OCT measures and brain parenchymal volumes.

Results: GCIPL (78.5 (71-80.5) vs 80 (76.75-85), p=0.032) and mRNFL (28 (26.75-30) vs 30 (28-32), p=0.012) thickness, as well as normalized total brain volume (nTBV) (0.817±0.056 vs 0.854±0.025, p=0.028) and normalized thalamic volume (nTV) (0.0047±0.0006 vs 0.0053±0.0004, p=0.007) was reduced in the RIS group compared to HC. Moreover, GCIPL and mRNFL measurements were correlated with nTBV (SB=0.73, p>0.001 and standardized beta (SB)=0.52, p>0.001), nTV (SB=0.78, p=0.005, only GCIPL), normalized gray (SB=0.84, p=0.019 and SB=0.59, p=0.044) and white matter (SB=0.51, p=0.018 and SB=0.36, p=0.005) volumes in the RIS group, but not in HC. Although pRNFL thickness was not different between RIS and HC, there was an association between pRNFL, nTBV and nWMV in the RIS group. Further analysis showed that retinal nerve fiber layer atrophy is more pronounced in temporal pRNFL and nasal mRNFL, showing that selective involvement of the maculo-papillary bundle occurs in RIS.

Conclusion: GCIPL, mRNFL and temporal pRNFL, but not global pRNFL thickness is reduced in RIS in parellel to brain volumetric measurements, indicating that common inflammatory and neurodegenerative processes affect brain and maculo-papillary region of the retina, even before the onset of clinical relapses. Assessment of these layers by OCT may have a potential to predict prognosis in RIS.

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Neuropsychology

P517

Prevalence of isolated cognitive decline in a large, heterogeneous multiple sclerosis population

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Introduction: Performance on the symbol digit modalities test (SDMT) is associated with employment status and activities of daily living. However, most constructs of MS disease progression do not take into account cognitive changes; potentially underestimating disease progression in MS.

Objectives: Describe the prevalence of cognitive decline in multiple sclerosis (MS) in the absence of motor function decline.

Methods: Patients with MS and clinically isolated syndrome were enrolled in MS PATHS, a network of 10 healthcare institutions in the US (7) and EU (3). During routine visits, patients used the Multiple Sclerosis Performance Test (MSPT) to complete the Processing Speed Test (PST), Manual Dexterity Test (MDT) and Walking Speed Test (WST), which are electronic adaptations of the SDMT, Nine-hole Peg Test and Timed 25 Foot Walk. Patients also completed the Patient Derived Disease Steps (PDDS). This analysis included all patients enrolled in MS PATHS with two or more completed MSPT assessments. Decline between timepoints was defined as a 4 point change on the PST, 20% change on the MDT or WST, or a 1 point change on the PDDS.
Results: 2289 patients had 2 or more complete MSPT assessments. At baseline, the average age was 44.9 yrs (SD: 11.2 yrs) and the average disease duration was 10.7 yrs (SD: 8.1 yrs). The average duration of follow-up was 7.5 mos (SD: 4.5 mos) and the average number of MSPT assessments was 2.5 (SD: 0.93). When comparing a patient's first and last MSPT assessment, 33.7% of patients had a decline on either the PST, MDT, or WST. 15.2% of patients had a decline on the PST only, 13.6% had a decline on the WST or MDT only (i.e. motor tests), and 4.9% of patients had decline on both the PST and a motor test. There were no meaningful differences in the distribution of baseline demographics, socioeconomics, or MS sub-types between patients who did or did not experience any decline and within decline sub-groups. PDDS progression was observed in 16.9% of patients with PST decline only, 22.5% of patients with motor decline only, and 30.4% of patients with both PST and motor decline. Further results will be reported at conference.
Conclusions: The prevalence of cognitive decline was as common as motor decline. 75.7% of patients with cognitive decline did not have concurrent motor decline. These results highlight the importance of cognitive monitoring in routine clinical care and the need for effective treatment strategies for cognitive decline in MS.

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Evaluation of the cognitive-affective syndrome in subjects with RRMS

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Background: The cerebellum is frequently involved in patients with multiple sclerosis (MS), and indeed the presence of cerebellar symptoms is one of the leading causes of motor disability in MS. Recent years have seen an increase in the awareness of the contribution of the cerebellar system to cognitive performances in healthy subjects and in patients with neurodegenerative conditions (i.e. the so called cerebellar affective-cognitive syndrome), however the possible contribution of the cerebellar system to cognitive performance in MS remains to date poorly characterized.
Objective: To evaluate the presence of the cerebellar affective-cognitive syndrome in MS using the recently validated cerebellar cognitive affective scale (CCAS).
Methods: A convenience sample of 50 subjects with a diagnosis of relapsing remitting MS (RRMS) were included in this study. Patients were selected from those followed in our center based on the following characteristics: (i) age between 18 and 50 years, (ii) no other comorbid neuropsychiatric conditions, (iii) an EDSS score between 2 and 6. Based on the cerebellar functional system score (FSS), patients were divided into cerebellar-impaired (cerebellar FSS => 2) or cerebellar-not-impaired (cerebellar FSS < 2). All patients were asked to complete the CCAS and the BiCAMS. Moreover, we asked an informant to complete the MS neuropsychological screening questionnaire (MSNSQ). The CCAS is a 10-item scale with a maximum score of 120, with higher scores representing a better performance.
Results: The "*cerebellar-impaired"* group included 20 RRMS patients (age 35.4±6.5; EDSS range 3-5) and "*the cerebellar-not-impaired"* group included 30 RRMS patients (age 36.6±7.8; EDSS range 3-5.5). Patients with a more severe motor cerebellar impairment also presented with more pathological scores at the CCAS (79±10.2, vs. 87±6.2; p=0.002). This difference remained significant correcting for EDSS and total BiCAMS score (p=0.01). We observed a significant correlation between CCAS and MSNSQ scores (r= -0.45, p=0.008) that remained significant correcting for BiCAMS score (p=0.01).
Discussion: Our data provide preliminary evidence of a contribution of the cerebellar system to cognitive deficits in subjects with MS. Indeed the CCAS was able to capture some facets of cognitive decline not completely assessed by the BICAMS. More studies are warrented to better characterize the cerebellar cognitive-affective syndrome in MS.

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Physical exercise and cognitive training improve self-perceived cognitive deficits and information processing speed in multiple sclerosis

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Background: A recent European survey impressively showed that 71% of patients with multiple sclerosis (MS) report cognitive deficits which have tremendous effects on working ability (Kobelt et al., 2017). Due to a lack of effective pharmacological therapies for patients suffering from cognitive impairment, non-pharmacological treatment approaches are warranted.
Objectives: To evaluate the effectiveness of physical exercise and cognitive training as single and combined treatment options on subjectively perceived cognitive deficits and objective information processing speed as primary outcomes.
Methods: Included patients received one of the following interventions for 3 months: physical exercise training twice a week for 45 min. each (treadmill walking), computer-based training twice a week for 45 min. each (using the software BrainStim) or a combination of both. Before and after the training period a comprehensive neuropsychological assessment was administered. To determine self-reported deficits, the perceived cognitive deficits questionnaire (PDQ-20) was applied including the following cognitive subscales: attention and concentration; retrospective memory; prospective memory; planning and organization. To measure information processing speed the symbol digit modalities test (SDMT) was used. The Wilcoxon signed-rank test was applied to evaluate treatment effects.
Results: In total, 44 MS patients (39 relapsing-remitting MS and 5 secondary-progressive MS, 33 female; mean age 43.70, *SD* = 10.35; mean EDSS 2.44) were included so far. First analyses indicate a significant improvement in both primary outcomes over all three training groups: PDQ-20: z= -3.093, *p*= .002; SDMT: z= 1.961, *p*= .05. Cohen's *d* supports these findings by strong effect sizes for both measures: PDQ-20 (*d*= -1.63) and SDMT (*d*= 0.87), with no differences between the different training groups. The analysis of the PDQ subscales showed significant improvement on the following cognitive domains: attention and concentration (z = -2.890, *p*= .004); retrospective memory (z= -2.589, *p*= .010); prospective memory (z= -2.894, *p*= .004). Planning and organization showed no significant improvement (z= -.969, *p*= .333).
Conclusions: Physical exercise and cognitive training improve patients' self-perceived cognitive deficits and the ability to quickly process information (objective measure). Thus, physical exercise and computer-based cognitive training can be recommended to treat cognitive problems in MS patients.

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P520

A 5-year follow-up study of the correlation between quality of life and the symbol digit modalities test

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Background and objective: Cognitive impairment is common in multiple sclerosis (MS) and it has shown to have important implications on patient's quality of life (QOL). Our objective is to assess the correlation between the symbol digit modalities test (SDMT) and QOL in a 5-year follow-up study.
Method: A group of MS patients underwent a neuropsychological evaluation with the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) that includes the SDMT. They also answered the Functional Assessment of Multiple Sclerosis (FAMS) scale, used to assess QOL. A second and a third evaluation were performed one year and 5 years later respectively.
Results: A total of 358 patients were included, 87,7% had relapsing remitting MS. There were 242 females, with a mean age of 39,83 years (SD=11) and a mean of 96,85 months of evolution of the disease (SD=97,62).The second evaluation included 284 patients and the third one 94. This last evaluation was performed 7,85 years (SD=2,02) after the first one. In the first and second assessments, from all the BRB-N's subtests, the higher significant correlation was observed between the SDMT and the total score of the FAMS (FAMST) (r=0,415, p< 0,001 and r=0,410, p< 0,001). In the third evaluation, most of the BRB-N subtests had no significant correlations with the FAMST score, except for the immediate and delayed spatial recall test (r=0,298, p=0,004 and r=0,278, p=0,007) and the SDMT (r=0,248, p=0,017). Significant differences were observed between the first and the third evaluation with lower results in the last one for the SDMT (p=0,032) and the FAMST score of (p=0,004). Other tests as the immediate visual recall test, the PASAT 3 seconds and the semantic fluency test, showed significant better scores in the second assessment when compared to the first one (p=0,002, p=0,047 and p=0,005).
Conclusions: The SDMT showed a significant positive correlation with the QOL score in a follow-up period of approximately 5 years. It was the only test from the BRB-N that showed significant lower scores in the last evaluation when compared to the first one, which supports previous findings regarding its sensitivity to detect cognitive impairment in MS patients. The significant higher scores of some tests in the second assessment may be explained because of the previous described practice effects of some of the tests. These findings support the SDMT as a unique tool to assess MS patients when a comprehensive assessment is not possible.

Disclosure
Authors have nothing to disclose.

P521
Premorbid physical activity, cognitive reserve and trait personality modulate rehabilitation effect in multiple sclerosis

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Background: Although factors associated with improved functional recovery through rehabilitation in multiple sclerosis (MS) are largely unknown, premorbid physically and intellectually enriching lifestyles have increasingly been recognized as able to mitigate the risk of disease-related disability. Our work hypothesis is that premorbid physical activity, cognitive reserve and trait personality may also contribute to rehabilitation outcome in people with MS.
Methods: We sought to identify each of the 36 patients from the 24-week, randomized, crossover pilot trial investigating the effect of home-based video game training on balance impairment due to MS (Prosperini L et al. Neurorehabil Neural Repair 2013). We achieved 94% ascertainment (34/36). In early 2018, identified patients underwent the following assessments: premorbid Historical Leisure Activity Questionnaire (HLAQ), Cognitive Reserve Index (CRI) and Temperament and Character Inventory (TCI). Non-parametric correlations and ordinal regression analysis were estimated to test association of premorbid HLAQ, CRI and TCI with training effect, expressed as percentage improvement in balance control (static posturography).
Results: No association between baseline patients' characteristics (sex, age, disease duration, disability level) and premorbid HLAQ and CRI and TCI was found. Larger training effect was associated with higher HLAQ values (rho=0.386, p=0.029), but not with CRI or TCI. This finding remained unaltered even after controlling for the aforementioned baseline variables (rho=0.456, p=0.018).
Ordinal regression model confirmed larger training effect as associated with higher HLAQ values (odds ratio [OR]=2.26, p=0.006), and also showed greater benefit in patients with higher score in persistence temperament (OR=3.30, p=0.034) and in those with lower score in self-transcendence character (OR=0.60, p=0.015). The model was significant (Chi-squared=37.85, p=0.001) and explained 45% of the variance in training effect (McFadden pseudo R-squared=0.448).
Discussion: Our study suggests that the rehabilitation outcome in MS is modulated by premorbid level of physical activity, as well as by specific temperament and character. These findings have a two-fold implication: (i) physical activity should be promoted in children by health authorities, in order to strengthen motor reserve; (ii) assessment of patients' character traits and temperaments may help neurologists to tailor rehabilitation strategies.

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P522
A randomized trial of cognitive behavioural therapy for improving psychological distress and cognitive impairments in multiple sclerosis

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Background: there is some evidences that Cognitive Behavioural Therapy (CBT) can be an effective treatment for mood disorders in Multiple Sclerosis (MS). Several studies suggest that some methods of the third wave of CBT could improve cognitive performance in others populations. Taking this into account, we designed and evaluated the efficacy of a CBT program to reduce mood disorders and cognitive impairments in MS.

Method: 120 patients with relapsing forms of MS were randomly assigned to CBT therapy (n=40), psychophysiological training (PT) (n=40) or wait list control condition (n=40). Both treatments consisted of 14 weekly 1.5-hour group sessions with post-intervention assessment one week after the end of training. Outcomes included anxiety, depression and neuropsychological impairments. Assessment measures: Hospital Anxiety and Depression Scale (HADS); Multiple Sclerosis Neuropsychological Questionnaire (MSNQ); Multiple Sclerosis Quality of Life-54 (MSQOL-54); Cognitive Triad Inventory (CTI); Brief Repeatable Battery of Neuropsychological Test (BRB-N).

Results: discriminant analysis over gain scores (post-intervention minus pre-intervention) showed a significant function [λ =0,73, F(2,81)=13,54; p< 0,0001]. This function clearly separates CBT group from PT and control groups, revealing the most important variables for group differences: Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), MSQOL-54, MSNQ, HADS, CTI.

Conclusions: the findings here reported allow us to conclude that the application of the CBT was particularly effective in improving emotional distress and cognitive functions in MS.

Disclosure

Study Group: nothing to disclose.

P523

Cognitive impairment in benign MS: a multiparametric structural and functional MRI study

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Background: The definition of benign MS is based on the limited accumulation of locomotor disability over long periods of time, without considering cognitive impairment. We applied a multiparametric MRI approach to investigate whether cognitive impairment in BMS patients is associated with specific patterns of structural and functional abnormalities.

Methods: Dual-echo, high-resolution 3D T1-weighted, diffusion tensor (DT) and resting state (RS) functional MRI sequences were acquired from 38 BMS patients (EDSS score $\leq$3.0 and disease duration >15 years) and 50 age- and gender-matched healthy controls (HC). All patients underwent neuropsychological assessment, using the BRB-N, and a cognitive impairment index (CII) was calculated. Regional gray matter (GM) atrophy was estimated using a voxel-based-morphometry analysis, white matter (WM) fractional anisotropy (FA) and mean diffusivity (MD) abnormalities were investigated with tract-based-spatial-statistical analysis, while RS functional connectivity (FC) was assessed using independent component analysis. A linear regression analysis was performed to investigate the correlations between CII and regional structural and functional MRI abnormalities.

Results: In BMS patients, the median CII was 9 (IQR:4-16). Compared to HC, BMS patients showed: a significant GM atrophy of several deep GM nuclei, fronto-temporal regions and cingulate cortex; decreased FA of supratentorial/infratentorial WM tracts, and increased MD in supratentorial WM tracts only; a widespread increase of RS FC in fronto-temporo-parietal regions involved in attention and executive function networks. At correlation analyses, higher CII, indicating cognitive dysfunction, was correlated with right (R) thalamic atrophy and more severe microstructural abnormalities (decreased FA and increased MD) in cognitive-relevant WM tracts, including bilateral posterior thalamic radiation, corona radiata, splenium of corpus callosum, inferior fronto-occipital fasciculus, forceps major, inferior, superior longitudinal fasciculus and R fornix. Positive associations between higher CII and increased RS FC of the R precuneus in the default mode network and R middle frontal gyrus in the executive control network were also found.

Conclusions: These findings support the need for a new clinical definition of BMS, which should include including cognitive features.

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P524

Cognitive decline in MS over a period of six years: subtle or substantial?

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Introduction: Cognitive deficits are common in multiple sclerosis (MS) and occur in all stages of the disease. Longitudinal studies on the course of cognitive decline are scarce. Here, we studied cognitive changes in cognitively preserved (CP) and impaired (CI) MS patients over a period of approximately 6 years.
Methods: 37 MS patients (mean age 47.3±8.6 years, 22 females and mean disease duration at baseline 12.0±7.1 years; 11 CI and 26 CP) and 20 healthy controls (HCs; 44.9±9.5 years, 15 females) underwent neuropsychological evaluation at baseline and follow-up (FU; median FU duration 5.95 years). Tests for verbal memory, visuospatial memory, working memory (WM), information processing speed (IPS) and verbal fluency were administered. Cognitive change was calculated using the modified practice adjusted reliable change index (RCI), corrected for FU duration, resulting in yearly cognitive change per test. This was averaged over all tests to obtain a composite cognition score. Cognitive decline was defined as an RCI of < -0.25/year on two or more cognitive tests. Group differences were calculated using independent t-tests.
Results: At baseline, MS patients performed significantly worse than HCs on tests for verbal memory (p=.01), visuospatial memory (p=.001), WM (p=.013) and IPS (p< .001). This pattern was still present at FU. Patients' yearly cognitive change did not differ significantly from that of HCs (change in composite cognition/year MS = -0.05; HC = 0.00, n.s.) However, nine persons with MS (24.3%) showed cognitive decline. Most prone to deterioration were memory function (visuospatial and/or verbal) and IPS. Of the declining patients, seven were CP at baseline, while two were already CI. Cognitively declining MS patients did not differ on age, sex, education level and disease duration from the non-declining MS patients.
Conclusion: MS patients with a mean disease duration of 12 years did not differ significantly from HCs on yearly cognitive change. This has been described previously (Roy et al., 2016) and could suggest subtle changes after initial cognitive decline has set in. However, at closer inspection, almost 25% of the MS patients showed substantial cognitive decline, emphasizing the need for interventions for cognitive deficits in MS at all stages of the disease. MRI analyses are currently ongoing to elucidate the underlying neurobiological mechanisms of these cognitive changes in MS.

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Environmental and lifestyle risk factors for cognitive impairment in multiple sclerosis

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Introduction: Together with genetic factors, a number of environmental, potentially modifiable risk factors for MS are increasingly investigated; some of them may also play a role as prognostic factors. It is not known, however, if these risk factors and prognostic factors also apply to MS-related cognitive impairment (CI), a frequent and debilitating consequence of MS, affecting 40% to 70% of patients at any time in their disease course.
Objective: to assess risk factors for CI in MS patients, focusing on environmental exposures, lifestyle and comoborbidities.
Methods: We included RR, SP and PP MS patients referred to Florence MS Center between 2014 and 2017. Neuropsychological assessment was performed on the Rao's battery and Stroop test, fatigue was assessed on the Fatigue Severity Scale (FSS) and depression on the Montgomery-Asberg Rating Scale for Depression (MARSD). Potential risk factors were investigated through a semi-structured questionnaire, administered to the patients at the presence of the caregiver. Stepwise multivariable logistic and linear regression models were employed to evaluate differences in exposure to hypothesized risk factors in patiens classified as cognitively preserved or cognitively impaired (impairment in one cognitive domain).
Results: 150 MS patients were included (103 women, age 44.8 +/- 1.79, median EDSS 2.79). CI was detected in 95 (63%) subjects. Cognitively impaired patients were older, had a younger age at MS onset (p=0.005) and exhibited higher fatigue and

depression levels (p< 0.005). In cognitively impaired compared with cognitively preserved patients, diabetes (p< 0.05) and history of brain trauma (p=0.05) were significantly more represented; thyroid disease tended to be more frequently reported. Daily caffeine intake and physical activity in childhood and adolescence, on the contrary, were more represented in cognitively preserved patients (p< 0.05). In the multivariable analysis, diabetes and history of brain trauma remained significantly associated with CI (p< 0.05); the trend of association with thyroid disease was confirmed (p=0.07).

Conclusions: our findings suggested a number of potential risk factors or protective factors for MS-related CI, related with comorbidities and lifestyle, potentially susceptible to preventive and management strategies.

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Cognitive dysfunction in patients with multiple sclerosis: evaluation of cognitive reserve and other predictive factors

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Cognitive dysfunction(CD) in multiple sclerosis(MS) is one of the most disabling symptoms, affecting 30-65% of patients. Most commonly affected cognitive domains are memory, attention and processing speed. The protective effect of cognitive reserve(CR) has been demonstrated. We aim to analyze the prevalence of CD and the domain impairment in a Spanish MS cohort. Besides, we examine the effect of CR, mood disorders, fatigue, psychiatric drugs, demographic and clinical variables on cognitive performance(CP).

We enrolled health controls and MS patients over 24 years old diagnosed according to the McDonald-criteria 2010, matched by age, gender and years of education. We used Rao abbreviated Neuropsychological battery to analyze the prevalence of CD; educational level, years of education(YE), profession, vocabulary knowledge and leisure activities to evaluate CR; and validated questionnaires for demographic variables, clinical forms of MS, EDSS, fatigue, anxiety and depression.

We included 82 patients(73.2% women) with a mean age of 40.93 years and 14.32 YE and 74 controls(68.9% women) with a mean age of 43.55 years and 14.57 YE. The prevalence of CD in MS patients was 29.27%. There was a significant difference between MS patients with and without CD in all cognitive domains. In MS patients with CD, verbal memory was affected in 50%, visuospatial skills in 54.2%, verbal fluency in 70.8% and processing speed in 66.7%.

In univariate analyses, YE(p< 0.001), vocabulary knowledge (p=0.016), profession(p=0.016) and educational level(p=0.016) were associated with better CP. On the contrary, age(p=0.004), physical functioning(p=0.018), cognitive functioning (p=0.036), psychosocial functioning(p=0.036), fatigue (p=0.014), EDSS (p=0.001), male gender(p=0,012) and use of psychiatric drugs(p< 0.001) were associated with worse CP.

Multivariate logistical regression model showed that age (p=0.026), EDSS(p=0.030) and male gender(p=0.006) were independent risk factors of CD in MS, and that YE(p=0.042) and vocabulary knowledge(p=0.014) were independent protective factors of CD in MS.

We confirm a similar prevalence of CD in our MS cohort as previously described in the literature. Verbal fluency and processing speed were the most affected cognitive domains. We demonstrate age, male gender and disability as potentials risk factors for CD in MS. Meanwhile, we confirm a protective value of CR(measured by YE and vocabulary knowledge) in the onset of CD in MS.

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P527

Employment status of people with multiple sclerosis in Argentina

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Background: Cognitive and clinical symptoms can have significative negative effects on employment status. The identification of these factors will allow mitigating unemployment and improve quality of life of Multiple Sclerosis (MS) patients.
Objectives: To examine the relationship between employment status (no employment, part-time employment, and full-time employment) and clinical and cognitive variables of people with MS; to analyze the relationship between work hours and clinical and cognitive variables and to investigate the relationship between employment status and Quality of life.
Methods: The sample included 61 MS patients (93.2%RR, 1.7%SP and 5.1%PP). 59% were female; mean age: 38.89 ±10.38 years; education: 14.18 ±2.57 years; EDSS: 2.74 ±2.01; disease evolution 11.64 ±7.57; fatigue: 4.33 ±3.17; depression: 12.07 ±9.16. Outcomes measures: Argentina adaptation of the Buffalo Vocational Monitoring Survey; clinical outcomes; EDSS, Beck Depression Inventory II, Fatigue Scale & MS International Quality of Life (MusiQol). Cognitive outcomes: *BICAMS* comprises the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test - Second Edition (CVLT II) and the Brief Visuospatial Memory Test - Revised (BVMT-R); 7/24 Visuospatial Scale, PASAT 2"-3" and Verbal fluency. Of all the variables studied, two factors were obtained: Clinical factor (EDSS, fatigue and depression) with a Cronbach´s α 0.400 and cognitive factor (SDMT, CVLT, BVMT-R) with a Cronbach´s α 0.765.
Results: 14.75% are unemployed and 65.55% employees, of which 36.05% are full-time employees. SDMT (p= .044), Pasat2" (p= .008), 7/24 Visuospatial Scale (p= .006) and the Cognitive Factor (p= .033), differentiate the unemployed patients from the employed patients. EDSS (p= .032), disease evolution (p= .033) and with a trend the fatigue (p= .052) difference between employees full time and part time. According to working hours, it differentiates patients who work more or less than 32 hours per week, EDSS (p=.022), disease evolution (p=.008), SDMT (p=.027) and PASAT 3" (p=.009). Regarding Quality of life, only differences in the activities of daily life are found (p=.015)
Conclusion: Cognitive factors differentiate between employed and non-employed patients, while physical disability and disease evolution differentiate between full-time and part-time patients. Processing speed, together with the physical disability and disease evolution influence the number of hours worked.

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Putaminal and hippocampal involvement in cognitive performance: BICAMS and MRI assessment of multiple sclerosis patients without self-reported cognitive deficits

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Introduction: A high prevalence of cognitive deficit in multiple sclerosis (MS) patients has been widely described, however the mainly involved cerebral areas are still debated. The aim of our study was to correlate the Brief International Cognitive Assessment for MS (BICAMS) neuropsychological assessment with the MRI volume measurements in MS patients without self-reported cognitive deficits.
Patients and methods: A cohort of 45 relapsing-remitting MS (RRMS) patients, without self-reported cognitive deficits, underwent the BICAMS. Cognitive impairment was defined as a failure in at least 1 test out of 3. Demographic and clinical data, neuroimaging data at diagnosis and last follow-up (normalized volumes of total brain, gray matter, white matter, peripheral cortex and subcortical structures, computed by SIENAX and FIRST softwares from 2D T1-weighted MRI sequences), were compared between cognitive impaired (CI) and cognitive preserved (CP) patients. Pearson correlation was applied between neuroimaging and neuropsychological variables; finally, a multivariate model was applied to confirm the univariate analysis.
Results: In our cohort, 15/45 patients were CI (11/15 in Brief Visual Memory Test - BVMT, 3/15 in Symbol Digit Modalities Test - SDMT, and 1/15 in California Verbal Learning Test-II - CVLT-II). CI and CP patients did not differ in terms of clinical variables. A positive correlation between SDMT score and both age onset (r=0,295, p=0,05) and disease duration (r=0,307, p=0,04) was observed. Compared to CP patients, CI patients showed a significantly bilateral lower volume of putamen both at diagnosis (L putamen: 5158.15±550.51 vs 5851.67±1215,84, p=0.043; R putamen: 5003.31±892.97 vs 5829.72±1235.57, p=0.049) and at last follow-up (L putamen: 5184.29±913.74 vs 5988.94±1260.43 p=0.020; R putamen: 5081.81±1102.98 vs 5997.72±1389.59, p=0.032). Compared to baseline values, only CI patients showed a statistically significant reduction of hippocampal volume, bilaterally (L hippocampus: p=0.019, R hippocampus: p=0.042). Finally, L hippocampal volume correlated with SDMT score, as confirmed in a linear regression model including disease duration and age at onset (p=0.023).

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Biomarkers

P529
Serum intestinal fatty acid binding protein in multiple sclerosis as a marker of intestinal barrier integrity

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Background and purpose: Patients with Multiple Sclerosis (MS) have increased intestinal permeability.An altered intestinal barrier could lead to the translocation of gut commensals and associated molecules into the circulation that alter immunologic responses. Our aim was to measure the serum levels of Intestinal Fatty-Acid Binding Protein (IFABP), a marker of intestinal barrier integrity in patients with MS, and study if an altered intestinal barrier is associated with their clinical features.
Materials and methods: We included 112 patients with MS, 55 patients with RRMS (mean age 39.3 [range: 21-56] years, 69% female, mean EDSS 2.5 [range: 0-6.5], mean disease duration 10.1 [range: 1-37] years), and 57 patients with progressive MS (mean age 45.9 [range: 28-60] years, 63% female, mean EDSS 5.6 [range: 2-8.5], mean disease duration 13 [range: 3-36] years). We used 10 age and sex matched healthy individuals as controls. Blood-samples were used to measure IFABP by ELISA. Clinical, demographic and outcome measures were analyzed. A detectable serum IFABP was considered to be reflective of an altered intestinal barrier.
Results: In the progressive MS group, 57.9% of patients had SPMS and the rest had PPMS. In the RRMS group, 47.3% had recent (< 1 month) disease activity (enhancing lesion or a relapse). Patients with MS in either group had significantly higher concentrations of IFABP than controls (303±567 pg/mL in RRMS, 272.4±548 pg/mL in progressive MS, and 7.3±23 pg/mL in controls, respectively). IFABP levels were not associated with treatment, age or sex. At baseline, IFABP levels were not significantly different between active vs. non-active RRMS patients or between SPMS and PPMS. An altered intestinal barrier was found in 47.3% and 50.8% of patient with RRMS and progressive MS, respectively. In progressive MS patients, an altered intestinal barrier was not associated with disability progression. In RRMS, an altered intestinal barrier was significantly associated with the occurrence of a relapse within 1 year, even after adjusting for baseline disease activity and treatment.
Conclusions: Patients with MS have an altered intestinal barrier more often than controls. IFABP was not associated with clinical features in progressive MS. In RRMS, IFABP could not distinguish between active and non-active patients, but could predict a relapse within 1 year. More studies are needed to determine the clinical significance of having an altered intestinal barrier in MS.

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P530
Relationship between serum neurofilament light chain levels and cognitive decline over 9-years follow-up in patients after first demyelinating event suggestive of MS

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Introduction: Serum Neurofilament light chain (NfL) is a promising marker of neuronal injury and is associated with disease activity in multiple sclerosis (MS) patients. However, its predictive value for development of cognitive decline in early stages of MS has not been investigated.
Aims: To investigate relationship between serum NfL levels in the early MS and evolution of cognitive decline over 9-years.
Methods: 57 patients after a first demyelinating event suggestive of MS from the study of early interferon treatment (SET) were included. Serum NfL levels were measured at screening, at baseline (intramuscular interferon beta1a initiation) and at 1 year. Age-related pathological NfL levels were defined using 90th percentile cut-off (Disanto et al.; 2017). Cognitive performance was assessed by Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test Revised (BVMTR), California Verbal Learning Test Second Edition (CVLT2) and Paced Auditory Serial Addition Test-3 seconds (PASAT-3) at baseline, at 1, 2 and 8.9 (95% confidence interval 8.8-9.0) years. NfL levels were measured using a Single Molecule Array (Simoa) assay. We applied Spearman´s correlation, Odds ratio, Chi-square test, linear and logistic regression adjusted for age, sex, treatment and cognitive performance at baseline.
Results: Higher NfL levels at screening were associated with lower CVLT2 scores at baseline (rho=-0.28; p=0.032). We did not find other correlations between early NfL levels and cross-sectional or longitudinal cognitive measures. Age-related pathological NfL levels at 1 year were observed in 9 (15.8%) patients and were associated with 4.7-fold (p=0.037) greater risk of CVLT2

decrease between 1 and 9 years compared with patients with normal NfL levels. This relationship was confirmed in adjusted logistic regression (p=0.028). There was also a trend for an association between pathological NfL level at 1 year and PASAT-3 decline over 9 years (Odds ratio 4.7; p=0.053). BVMTR and SDMT scores decline were not associated with early NfL levels.
Conclusions: Pathological serum NfL levels at disease onset were associated with verbal memory decline over long-term follow-up. Similarly as in imaging studies, the association between paraclinical markers of disease activity and cognitive measures may be substantially stronger in more advanced disease stages. In this respect, future studies on larger cohorts and with higher disease burden are warranted.

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P531
Cerebrospinal fluid biomarkers dissect extreme phenotypes of clinically isolated syndrome and early multiple sclerosis

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Background: Studies of multiple sclerosis (MS) patients have proposed prognostic values for different magnetic resonance imaging (MRI) parameters and molecular biomarkers. The role of cerebrospinal fluid (CSF) analysis has been emphasized in particular in patients with a first episode suggestive of MS. We here evaluate disease activity biomarkers distinguishing benign from aggressive MS disease courses that should allow a stratification of patients aiming at best treatment strategies.
Objectives: To assess the value of CSF biomarkers including multiparameter flow cytometry, neurofilament light chain (NfL) and chitinase 3-like 1 (CHI3L1) levels along with serum NfL levels as indicators of extreme manifestations of clinically isolated syndrome (CIS) and early MS.
Methods: From a cohort of 1024 patients, we selected 102 patients diagnosed with either CIS or early relapsing-remitting (RR)MS. These were divided into three different severity groups defined by MRI criteria. High activity was defined as ≥ 20 T2 lesions and ≥ 2 gadolinium-enhancing lesions or 1 tumefactive lesion. Low activity was defined as ≤ 3 T2 lesions and no gadolinium-enhancing lesions. Intermediate activity referred to patients neither fulfilling the criteria for high nor low activity. Leukocyte subsets in the CSF were analyzed by flow cytometry. CSF NfL and CHI3L1 levels were measured by enzyme-linked immunosorbent assay. Serum NfL levels were examined using single molecule array technology. MS patients with particularly high or low MRI-activity underwent up to 3 years of follow-up.
Results: Univariate analysis demonstrated that B cell/monocyte (CD20/CD14) ratios in CSF as well as NfL levels in CSF and serum were associated with the MRI-based severity grouping, whereas this association was not found for CSF CHI3L1 levels. NfL levels in CSF and serum highly correlated. Multivariate logistic regression with backward selection showed the best prediction for a model combining B cell/monocyte ratios and CSF NfL levels to identify patients with particularly high or low MRI-activity. Data will be presented about the prognostic value of these biomarkers for predicting future disease courses.
Conclusion: Patients with extreme manifestations of CIS and early MS defined by MRI parameters can be distinguished with regards to a combined biomarker panel of CSF NfL and B cell/monocyte ratios. This could stratify individual treatment decisions towards a more personalized immunotherapy.

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P532
Temporal relationship of serum neurofilament light levels and radiological disease activity in patients with multiple sclerosis

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Introduction: Serum neurofilament light (sNfL) is a promising biomarker that correlates with disease activity and predicts outcomes in patients with multiple sclerosis (MS). However, the temporal relationship between radiological disease activity and sNfL levels is not well characterised.

Objectives: To evaluate the relationship between sNfL dynamics and radiologic disease activity using a dataset with frequent sample collection and MRIs.

Methods: A retrospective analysis was performed on a subset of 65 MS patients from the RESTORE study. In RESTORE, natalizumab-treated patients who were relapse-free in the prior year and had no contrast enhancing (Gd+) lesions at screening, were randomised (1:1:2) to continue natalizumab or switch to placebo or to other treatment (intramuscular interferon-β-1a, glatiramer acetate, methylprednisolone) for 24 weeks and then switched back to natalizumab for weeks 28-52. Patients who restarted natalizumab prior to week 28 per rescue criteria, entered the follow up period right away. Serum collection and MRI were performed at baseline (BL), every 4 weeks to week 28 (or rescue) and at week 52. sNfL levels were measured with a Single Molecule Array (SIMOA, Quanterix) assay.

Results: In patients continuing natalizumab (n=13) and in those who discontinued natalizumab and had no Gd+ lesions (n=21), sNfL levels remained low and stable. In patients with Gd+ lesions (n=31), sNfL increased significantly compared to those without Gd+ lesions (median change from BL to maximum sNfL 72% vs 11 %, $p < 0.0001$, Wilcoxon test). A higher number of Gd+ lesions was associated with higher sNfL levels, with median sNfL change of 29%, 135% and 503% in patients with 1-4 (n=17), 5-10 (n=8) and ≥11 (n=6) Gd+ lesions, respectively. Variability in sNfL levels among patients with similar number of Gd+ lesions was observed, consistent with varying degree of tissue damage between patients. Increase in sNfL levels coincided with or lagged behind the appearance of Gd+ lesions, reaching a maximum at about 7 weeks post Gd+ lesion detection, and in some patients remained elevated after resolution of enhancement.

Conclusions: These findings add to our understanding of the temporal relationship between Gd+ lesions and sNfL levels in MS patients, and suggest a complementary role of this biomarker and MRI in characterising and monitoring the differential evolution of tissue injury across individuals in MS.

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R. Gold serves on scientific advisory boards for Teva, Biogen, Bayer Schering and Novartis; has received speaker honoraria from Biogen, Teva, Bayer Schering and Novartis; serves as editor for *Therapeutic Advances in Neurological Diseases* and on the editorial boards of *Experimental Neurology* and the *Journal of Neuroimmunology*; and receives research support from Teva, Biogen, Bayer Schering, Genzyme, Merck Serono and Novartis.

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Spatial distribution of MS lesions: new insights into white matter damage

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Introduction: White matter (WM) lesion volume has been used to predict both disease course and disability progression in multiple sclerosis (MS). However, current analysis methods provide metrics averaged over the whole brain, thereby failing to capture the complexity of brain damage. Although there is evidence that the spatial distribution of brain damage is important for disability accumulation in MS, the impact of different spatial patterns of damage has never been formally quantified. In this study we have exploited the concept of spatial covariance, which indicates how changes of lesion load along a spatial direction relate to changes along different directions, to assess how WM lesions spread in space. Specifically, we aimed to identify spatial patterns of brain WM lesions through spatial covariance analysis and assess the ability of spatial covariance-derived metrics to distinguish between MS phenotypes.
Methods: Ninety-four relapse-onset MS (ROMS, age 47+/-11 yrs.) and 28 primary progressive MS (PPMS, 52+/-9 yrs.) consecutive patients underwent conventional brain MRI scans at 3T. We extracted WM T2 lesion masks and followed these steps: 1) Calculation of 3D (x,y,z) positions of lesional voxels for each patient; 2) calculation of the spatial covariance matrix of lesional voxels; 3) calculation of spatial covariance-derived metrics through Principal Component Analysis, performed with Python in-house code. These metrics describe the *shape* of the *whole-brain lesion mask* for each patient and are called *anisotropy* (ranging from 1=stick-like to 0=non-stick-like lesion mask shape) and *planarity* (ranging from 1=plate-like to 0=non-plate-like lesion mask shape). Linear regression assessed differences between groups.
Results: There were no differences in lesion load or disease duration between ROMS and PPMS (14mL vs. 17mL, and 16 yrs. vs. 14 yrs., respectively). Lesion anisotropy was similar for ROMS and PPMS (0.54 vs. 0.58, respectively, p=0.097), whereas lesion planarity was significantly higher in ROMS than PPMS (0.51 vs. 0.40, respectively, p=0.012), even after adjusting for lesion load and disease duration.
Conclusions: The finding of higher planarity in ROMS than PPMS with similarly low anisotropy suggests that in ROMS lesions spread more on a level whereas in PPMS lesions spread in a more spherical way, suggesting different disease mechanisms. This occurred even adjusting for total lesion load indicating its independence from the total burden of the disease.

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P534

Relationship between pathogenesis of spasticity in patients with secondary-progressive multiple sclerosis and neuromediators level: double-blind placebo-control study

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Backgrounds: The spasticity syndrome is a significant factor in the development of disability. However pathogenesis of spasticity is complex and not not fully understood.
Introduction. Our aim was to assess neuromediators level in motor cortex during effective treatment of spasticity in patients with secondary-progressive multiple sclerosis (SPMS).
Methods: Thirty four patients (14 males, mean age 47±11) with SPMS and lower spastic paraparesis were enrolled in double-blind

placebo-control study. To explore neuromediators level we used single voxel proton magnetic resonance spectroscopy (H-MRS). Voxel was placed in the senso-motorial region. Patients were divided into 3 groups: two of them received real repetitive transcranial magnetic stimulation (rTMS) (20 Hz or iTBS) of motor cortex and one - sham stimulation. For assessment spasticity level we used Modified Ashworth Scale (MAS), Subjective Evaluation Spasticity Scale (SESS) before and at the end of 10 rTMS sessions, SESS 2 weeks and 12 weeks after of 10 rTMS sessions.

Results: In contrast with sham group, in both treatment groups were statistically significant reduction of spasticity level on MAS and SESS. But in iTBS group the effect was stronger and persisted for 12 weeks, instead of 2 weeks in 20 Hz group. With this correlation we noticed significant increase N-acetilaspartat/creatin level only in iTBS group after treatment. This findings could indicate the relationship between the level of spasticity and neuromediators level in senso-motorial region of motor cortex.

Conclusions: Our results indicate that spasticity associated with neuromediators level. Future trials will provide us more evident information.

Disclosure

Nothing to disclose.

P535

Kappa free light chains Index: a diagnostic tool to assess intrathecal immunoglobulin synthesis in multiple sclerosis

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Introduction: The presence of CSF oligoclonal bands (OBs) is an important diagnostic and prognostic factor for Multiple Sclerosis (MS), expressing intrathecal inflammation and immunoglobulin synthesis. The measurement of the K free light chains index (KFLC index) has been recently proposed as a faster, cheaper and easier alternative test for the detection of intrathecal immunoglobulin synthesis.

Aim of our study was to assess the diagnostic accuracy of the KFLC index in MS and its relationship with other measures of intrathecal immunoglobulin synthesis.

Methods: KFLC index, IgG index and presence of OBs were assessed in 247 consecutive patients who underwent diagnostic lumbar puncture in a large university hospital (University Hospital AOU Città della Salute e della Scienza di Torino).

Results: KFLC index correlated strongly with the presence and number of OBs and with the IgG index (KFLC index-IgG index 0.559; $p < 0.0001$; KFLC index-OBs number 0.784; $p < 0.0001$). KFLC index was significantly higher in patients with MS compared to other patients (MS 94.45 ± 147.04; NMOSD 17.86 ± 16.32; other immune-mediated CNS disorders 32.06 ± 67.73; other non immune-mediated CNS disorders 4.79 ± 9.07; $p < 0.0001$). An inverse correlation was observed betweeen age and KFLC index, both in MS patients and in the whole population (KFLC index-age: - 0.169; $p = 0.008$). KFLC index showed a diagnostic accuracy for MS comparable to CSF OBs and higher than the IgG index (AUC 0.929, 95% CI 0.889 - 0.970; sensibility 88.5%, specificity 88%). Diagnostic accuracy was even higher in patients with age ≤ 40 years (AUC 0.970, 95% CI 0.928 - 1.000; sensibility 94.9% specificity 91.4%).

Conclusion: KFLC index is a reliable measure of intrathecal immunoglobulin synthesis and can accurately discriminate MS patients, with a sensibility and specificity comparable to the detection of CSF OBs.

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CSF neurofilament light concentration reflects cognitive impairment in multiple sclerosis

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Introduction and aim: Cognitive impairment (CI) is a common and disabling symptom of multiple sclerosis (MS), but its pathogenesis is controversial and there is no effective treatment. White and grey matter damage has been proposed as one of the possible causes of MS-related CI and the disruption of white matter neuronal pathways may contribute to the impairment of specific cognitive domains, such as information processing speed. Since cerebrospinal fluid (CSF) neurofilament light chain (NfL) is a reliable marker of neuroaxonal damage, the aim of our work was to examine the relationship between CSF NfL and cognitive performance in MS patients.

Patients and methods: We enrolled 28 consecutive newly diagnosed MS patients (mean age 39.1 ± 11.3 years, F/M =2.5). All of them underwent CSF analysis as part of the usual diagnostic work-up. CSF NfL was measured by means of a newly developed in-house ELISA. Neuropsychological evaluation with the Rao's Brief Repeatable Battery (BRB) was performed at the time of CSF collection (mean time between lumbar puncture and BRB execution: 25.5 ± 19.2 days). Normative values adjusted according to gender and education for Italian population were used. The presence of specific cognitive domains impairment was defined by the failure of ≥1 test exploring that domain.
Results: CSF NfL was higher in patients with global CI as defined by the presence of impairment in ≥2 cognitive domains explored by the BRB (947.8±400.7 vs 518.4±424.7 pg/mL, p< 0.01). Specifically, CSF NfL was higher in patients with impairment in the information processing speed (820.8±413.6 vs 513.6±461.4 pg/mL, p< 0.05) and verbal fluency (1292±511 vs 582.8±395.4 pg/mL, p< 0.05) tests. Finally, CSF NfL concentration was inversely correlated with the scores of the following BRB tests: SRT-LTS (r=-0.45, p< 0.05), SRT-DR (r=-0.52, p< 0.01) for verbal memory, SPART-IR (r=-0.49, p< 0.01) for visuospatial memory, SDMT (r=-0.45, p< 0.05), PASAT-3 (r=-0.57, p< 0.01) and PASAT-2 (r=-0.54, p< 0.01) for information processing speed.
Conclusions: CSF NfL concentration may reflect CI in MS patients and has a stronger negative association with information processing speed tests scores. However, CSF NfL seems to reflect also the performance in other cognitive domains during MS, such as verbal memory, visuospatial memory and verbal fluency. Degeneration of larger myelinated axons, as reflected by CSF NfL, may therefore be an important determinant of CI in MS patients.

Disclosure

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Ganglion cell layer volume and serum neurofilaments are associated with disability in multiple sclerosis

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Introduction: Both retinal integrity in optical coherence tomography (OCT) and neurofilament light chain levels in serum (sNfL) are promising markers of neuroaxonal loss in multiple sclerosis (MS).
Aim: To assess the relationship between serum NfL and retinal neuroaxonal integrity in patients with MS and their associations with disability. We hypothesized that sNfL levels are related to the integrity of the ganglion cell- and the peripapillary retinal nerve fiber layer (pRNFL) in OCT. Moreover, we hypothesized that sNfL together with the OCT measures are associated with disability.
Methods: Hundred MS patients (mean age: 50.4±11.6y, 61% women, mean disease duration 18.7±9.8y, median EDSS: 3, 80% RRMS, 20% progressive MS, 74% on disease modifying treatment) underwent: i) spectral-domain OCT, to assess the volume of the ganglion cell-inner plexiform layer (GCIPL) and mean pRNFL thickness, ii) measurement of sNfL concentration by single molecule array assay and iii) clinical assessment, including the expanded disability status scale (EDSS) and the symbol digit modalities test (SDMT). For GCIPL and pRNFL, the mean of both eyes was used, except for patients with optic neuritis, where only the non-affected eye was included. The Spearman method was used for correlation analyses and linear regression models for multivariate analyses.
Results: Serum NfL levels negatively correlated with GCIPL volume (Spearman´s rho=-0.23, p=0.03) and by trend with pRNFL thickness (rho=-0.19, p=0.06), although both relationships were not significant after adjusting for age.
GCIPL volume (rho=-0.54, p< 0.0001) and sNfL (rho=0.53, p< 0.0001) showed significant and similarly strong correlations with the EDSS, while the correlation was weaker for pRNFL (rho=-0.4, p< 0.0001). A multivariate regression analysis with GCIPL, sNfL and age as independent variables revealed both GCIPL (beta=-3.42, p< 0.0001) and NfL (beta=0.05, p=0.002) as significant predictors of the EDSS (adjusted R^2=0.47).
GCIPL volume (rho=0.35, p=0.0005), sNfL (rho=-0.31, p=0.002) and pRNFL (rho=0.27, p=0.006) were also correlated with the SDMT. In a multivariate analysis including age, only GCIPL remained a significant predictor of the SDMT (beta=15.5, p=0.007; adjusted R^2=0.26).

Conclusions: GCIPL volume and sNfL levels together explained approximately 50% of the EDSS-variance in our cohort. The results stress the complementary role of both measures as markers of neuroaxonal damage and disability in MS.

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Age immune related changes in multiple sclerosis according with their oligoclonal IgM band status

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Background: Intrathecal synthesis of lipid specific oligoclonal IgM Bands (LS-OCMB) predict an aggressive Multiple Sclerosis (MS) course. Our aim was to elucidate the immune mechanisms associated with the presence of these antibodies in MS patients and their changes with age.
Methods: CSF and serum samples were consecutively collected from 121 MS patients. Oligoclonal bands were detected by isoelectrofocusing and immunoblotting. Immune cell subsets and protein levels in the CSF were analyzed by flow cytometry and ELISA respectively. Neuropathological analysis of the presence IgM+ cells was performed in 10 secondary progressive MS (SPMS) cases and 5 controls.
Results: Of the 121 patients included in this study, 78 patients had LS-OCMB+ remaining were LS-OCMB-. LS-OCMB- ones showed a dramatic age associated decline of the adaptive immune response in the CSF. The total number of CD4 and CD8 T cells, B cells, dendritic cells decreased significantly with age. We also investigated specific subsets of T cells and we found that the number of CD4 T cells producing TNF-a, IL-22 and CD8 producing perforin significantly diminished with age. In contrast, this group showed a significant increase in the levels of chitinase-3 like 1 in the CSF and in the titers of antibodies against cytomegalovirus (CMV). In the OCBM+ we only observed an increase in the levels of superoxide dismutase (SOD). In general, both groups showed a significant increase in the levels of Activin A in the CSF. Remarkably, this decline in the immune response started to be observed after the 40 years in OCBM patients. Finally, we found the presence of IgM+ cells only in SPMS cases with high meningeal inflammation verifying its association with the chronic immune infiltration.
Conclusions: Our data suggest that patients lacking IgM antibodies in the CSF suffer a premature immunosenescence in contrast LSMCB+ maintain a chronic inflammatory response throughout the disease.

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Carmen Picon: Nothing to disclose

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International multi-site analytical validation of the Simoa NF-light assay in human serum samples from multiple sclerosis patients

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Introduction and Objective: Neurofilament light chain (NfL) is an exclusively neuronal protein showing increased levels in blood upon neuroaxonal injury in various neurological diseases. For the first time highly sensitive NfL measurements in blood open the option for a sensitive assessment of the consequences of brain tissue damage. Measurement of peripheral blood NfL levels in MS is emerging as a biomarker of disease activity, treatment response and short and longer-term prognosis. Establishing a normative multi-centre applicable database for NfL, including potential confounding by metabolic illnesses, other CNS diseases and age, is a key development step for a potential application in clinical trials and individual therapeutic decision making. As a prerequisite, we aimed at analytically validating the Simoa NF-light assay from Quanterix within the MSNfL Working group.
Methods: The single molecule array (Simoa) assay technology is significantly more sensitive compared to conventional detection systems like ELISA or electrochemiluminescence immunoassays. Simoa allows reliable detection of NfL in individual serum samples.
Results: As of May 2018, 11 centres have confirmed participation in the multisite analytical validation of the Simoa NF-light assay. All centres have agreed to perform 6 kit runs on individual days according to a standardized protocol and common materials. We will report data on assay sensitivity, parallelism (between calibrators and samples) and within- and across site comparability. We will also present results on centrally blinded serum samples from well-characterized MS patients in various different concentration ranges for analyzing consistency of NfL concentrations across sites.
Conclusions: Coordinated multicentre research activities are under way to develop NfL as a body fluid marker that may accurately reflect brain tissue damage and allows monitoring disease activity and drug effects in clinical practice. To date, the main limitations towards an application in individual disease monitoring is the lack of normative data for NfL across a broad range of age groups and understanding how comorbidities affect blood NfL concentrations. The goal of this assay validation is to establish standardized and accurate NfL measurements across sites. Our results will inform about the precision and robustness of the NfL assay in a multi-centre setting and will facilitate future establishment of broadly applicable NfL reference ranges.

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X Montalban has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Phramaceuticals, Almirall and Roche.
A Datwani is a Genentech employee.
M Fluck is a Merck employee.
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K Blennow is a cofounder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures - based platform company at the University of Gothenburg. Dr. Blennow has served at advisory boards or as a consultant for Alzheon, Eli Lilly, Fujirebio Europe, IBL International, Pfizer, Roche Diagnostics, Amgen, and Sanofi-Aventis (unrelated to the present study) and has received research support from Janssen Alzheimer Immunotherapy and Roche Diagnostics (unrelated to the present study).
H Zetterberg is a cofounder of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures - based platform company at the University of Gothenburg.
C Teunissen serves on the advisory board of Fujirebio and Roche, performed contract research for Shire, Boehringer, Roche, Probiodrug, PeopleBio, and Jansen Prevention Center.

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Association between multimodal evoked potentials, lesion burden and brain volumes in multiple sclerosis: searching for early axonal damage markers

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Introduction: Evoked potentials (EP) are useful for the diagnosis of multiple sclerosis (MS), but they are not mandatory. Previous studies suggest that they could be more useful in long-term prognosis. On the other hand, brain volume has a better association with disability than T2 lesion burden.
Objetives: In this study, we asses for the first time whether there is an association between EP results and magnetic resonance imaging (MRI) measures and if both tools used together would improve the prognostic value.
Methods: MS patients were randomly recruited along three months. We collected their EP results at diagnosis: visual evoked potentials, brain stem auditory evoked potentials, somatosensory evoked potentials and motor evoked potentials (MEP) and combined results: the evoked potential abnormality score (EPAS). In addition, we quantified number and volume of T2 lesions, black holes, number of enhancing lesions and number of spinal lesions with JIM software and whole brain (WB), white matter and gray matter (GM) volume with SIENAX. We collected the evolution of the disability measured by Expanded Disability Status Scale (EDSS) too. Correlations between MRI measures, EP results and EDSS were evaluated using correlation coefficients.

Results: We included 60 MS patients (39 were women). Among all variables tested, MEP results had the highest correlation coefficient with the disability (for average central conduction times with EDDS in the fifth year: R= 0.516, p< 0,01). The correlations with the disability improved when we used combined scale (EPAS) (in the fifth year: R=0,514, p< 0,01). We found the best correlations among all MRI and EP variables for MEP of lower limbs: average central conduction times with volume of T2 lesions (R=0,301, p< 0,05), WB volume (R=-0,306, p< 0,05), GM volume (R=-0,319, p< 0,05) and average of amplitudes with volume of T1 lesions (R=-0,499, p< 0,05), WB volume (R=0,726, p< 0,01) and GM volume (R=0,597, p< 0,01). We found significant positive correlations (p< 0,05) between EPAS results and T2 lesions, black holes and spinal lesions.
Conclusions: Early alterations in EP have a long-term predictive value. MEP data and EPAS score showed the best correlations with disability, better even than WB and GM volume. EP could be useful as predictors of neurodegeneration given the correlations with MRI parameters. The combination of both tools might be useful to determinate the risk of individual progression.

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mRNA-sequencing of blood platelets as a novel biomarker in multiple sclerosis

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Background: In Multiple Sclerosis (MS), clinical assessment and MRI play an important role in the diagnostic process. Cerebrospinal fluid assessment is often part of the diagnostic workup for MS and its value is supported by the latest 2017 revisions of the McDonalds criteria. So far, however, no blood biomarker has been convincingly confirmed as a useful tool in the diagnostic work-up of MS. Blood-based approaches harbor obvious advantages and recently, the long-neglected blood platelets, being the second most abundant cell type in peripheral blood, have shown emerging potential as a new source for biomarker discovery. Blood platelets contain a rich messenger RNA (mRNA) repertoire that can change during megakaryocyte development but also during platelet formation and circulation. In addition, platelets have the ability to bind and interact with numerous other cells, such as leukocytes and vascular cells. Platelets are also able to participate in the inflammatory response and could have an active role in MS.
Objective: To evaluate the diagnostic potential of blood platelets that contain a disease-specific mRNA signature profile.
Methods: We isolated and sequenced platelet mRNA of blood samples obtained from 58 relapsing-remitting multiple sclerosis (RRMS) patients and 67 healthy controls (HC) (age gender matched). Subsequently, 60% of the samples was used to train and evaluate a Support Vector Machine (SVM) learning algoritm, using differentially expressed genes identified by ANOVA analyses. Finallly, the remaining 40 % of the samples was validated in order to show the potential of a predictive diagnostic algoritm.
Preliminary results: The SVM algoritm based on differentially expressed platelet mRNAs correctly distinguished between HC and RRMS patients with minor overlap ($p < 0.0001$) and high accuracy (training accuracy 84%, evaluation accuracy 89%, validation accuracy 78%).
Interpretation: Processes involved in RRMS patients lead to significant changes in the platelet RNA profiles. The results further indicate that sequencing mRNA derived from blood platelets is a promising approach for the development of a novel blood-based biomarker for MS.

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New TRIDENT proteomic approach of CSF analysis at MS diagnosis: identification of complement and coagulation pathway associated to cortical damage

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Introduction: Cerebrospinal fluid (CSF) analysis is a powerful tool to identify specific biomarkers of multiple sclerosis (MS) diagnosis and prognosis. In addition to the study of inflammatory mediators involved in MS, a specific proteomic characterization of the presence and levels of proteins related to intrathecal inflammation and MS pathogenesis has been not fully examined.
Aims: In order to increase the diagnostic and prognostic role of CSF analysis in MS, we developed a new proteomic approach that allows deep examination of complex mixtures of proteins like CSF by identifying pathways probably involved in inflammation and tissue damage.
Methods: This study was performed on the CSF obtained by two MS populations stratified at time of diagnosis according to high (MSHigh) or low (MSLow) level of cortical lesion load detected by double inversion recovery 3T-MRI sequence and of CSF inflammation. CSFs from 3 MSHigh vs 3 MSLow patients were prepared by TRIDENT methodology by applying three-denaturation protocols, gradient SDS-PAGE separation and LC-MS/MS technologies. Bioinformatics analysis using Database for Annotation, Visualization and Integrated Discovery (DAVID) and search tools for the retrieval of interacting genes (STRING) software, were carried out analysis of total number of proteins identified and related pathways.
Results: A total number of 227 proteins have been identified as expressed onto CSFs of the two examined groups of patients. Eleven main pathways have been identified as key mechanisms discriminating the MSHigh and MSlow patients.Among them, complement and coagulation cascade (29% of the total identified 227 proteins) was identified as the most modified pathway across the two groups of patients. ELISA methodology was then used for validation analyses, indicating that sCD163 ($p < 0.0001$), free hemoglobin ($p < 0.05$), haptoglobin ($p < 0.0001$) and fibrinogen ($p < 0.01$) were significantly higher in the CSF of MSHigh compared to MSLow patients. The protein expression of these molecules positively correlated with both number and volume of cortical lesions. On the contrary, the CSF levels of sCD14 were found significantly ($p < 0.05$) higher in MSLow compared to MSHigh and inversely correlated with cortical lesion load.
Conclusions: New proteomic CSF analysis approaches, including TRIDENT analysis, in combination with clinical and imaging assessment, may strongly contribute to shed light on molecular mechanisms of MS pathogenesis and severity/progression.

Disclosure
Roberta Magliozzi: nothing to disclose

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Cerebrospinal fluid biomarkers of inflammation and neurodegeneration in acute optic neuritis

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Background: Optic neuritis (ON) is an inflammatory optic neuropathy causing demyelination and axonal injury. The relation between intrathecal markers of inflammation and markers of neurodegeneration in acute ON is incompletely understood.
Objective: To investigate neurofilament light-chain (NF-L) and inflammatory biomarkers in the cerebrospinal fluid (CSF) in patients with acute ON and their potential to predict a diagnosis of multiple sclerosis (MS).
Methods and patients: We recruited 40 patients with acute isolated ON (ION) in a population-based prospective cohort with a one-year follow-up. Paired serum and CSF samples were taken prior to glucocorticoid treatment with a median interval from onset of symptoms of 14 days (range 2-38). Overall, 12/40 patients were diagnosed with MS at onset of ON and additionally 4 were diagnosed at follow-up; 24 patients remained as ION. IL-1β, IL-6, IL-10, IL-17A, TNF-α (serum and CSF) and NF-L (CSF only) were measured by digital ELISA on the Simoa™ platform; CXCL13 in CSF was measured by ELISA (Euroimmun). Comparisons were made using Kruskal-Wallis test followed by the Benjamini-Hochberg FDR method.
Results: TNF-α, IL-10 and CXCL13 levels in CSF were significantly increased in MS-ON compared to ION patients (p-values: 0.006, 0.010 and 0.03, respectively). MS-ON patients had more CSF leukocytes than ION ($p=0.0018$) as well as more CSF-restricted oligoclonal bands ($p=0.015$). Levels of IL-10, TNF-α, IL-17A and CXCL13 in CSF were all significantly correlated with

leukocyte counts (r>0.69 and p< 0.002 for all). In MS-ON, but not in ION patients, a time-dependent increase in CSF NF-L levels was observed in the period between 7 to 14 days after disease onset (r=0.73, p< 0.0065). We detected no significant correlation between NF-L and markers of inflammation.

Conclusions: CSF levels of NF-L and inflammatory markers were associated with the development of MS at an early time point in acute ON, suggesting that the inflammatory and neurodegenerativeprocesses of MS occur already at the first demyelinating event.

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A wide cytokine analysis in cerebrospinal fluid at diagnosis identified MIP-1α as possible prognostic factor for multiple sclerosis

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Introduction: No specific marker of inflammation or neurodegeneration that can be used for prognostic purposes are currently available in Multiple Sclerosis (MS). Early and specific markers of local pathology should be identified in the cerebrospinal fluid (CSF).

Aim: To identify, among a wide spectrum of soluble molecules, CSF biomarkers associated with MRI parameters of white and grey matter damage at MS diagnosis and verify whether these biomarkers were predictive of clinical and radiological disease activity in the following 2 years.

Methods: At diagnosis, CSF examination, brain and spinal cord MRI (including 3D-T1, 3D-FLAIR and 3-DIR) and EDSS evaluation were performed. Multiplex technology (Bio-Plex Pro Human Cytokine, GF and Diabetes 27-Plex Panel, Bio-Plex Pro Human Chemokines 40-Plex Panel, Bio-Plex Pro Human Inflammation Assays 37-Plex Panel) was applied to analyse 87 cytokines in the CSF. Thereafter, clinical evaluation and MRI were performed biannually and annually, respectively, and EDSS changes, clinical relapses, evidence of new/enlarging white and grey matter lesions were scored.

Results: 51 Relapsing Remitting MS (RRMS) and 11 matched healthy controls (HC) were included the study. 11/87 molecules, namely CXCL13, CCL22, MIP-1α, CCL1, IL-16, CXCL11, CXCL10, CXCL6, CXCL9, CCL19, and CCL23, were increased in RRMS CSF compared to HC (p< 0.05 for all comparisons). Multivariate analysis disclosed that only MIP-1α (macrophage inflammatory chemokine) was associated with MS diagnosis (O.R.: 95.4, CI95% 1.9-4846.6, p=0.02). At baseline, grey matter lesion volume mildly correlated with IL-16 (r:0.41, p< 0.01) and global cortical thickness was inversely associated with both IL-26 (r:-0.34, p< 0.05) and CCL20 (r:-0.33, p< 0.05). No significant correlation was observed between white matter lesion volume and any cytokine. Based on the CI95% in HC (cut-off value: 0.707 pg/mL), MS patients were divided in RRMS-MIP1α^{high} and RRMS-MIP1α^{low}. Survival analysis revealed that RRMS-MIP1α^{high} had more frequently and earlier disease reactivation in the following two years compared to RRMS-MIP1α^{low} (OR 3.8, IC95% 1.3-11.0, p< 0.05). Finally, intrathecal IgG synthesis was inversely associated with CSF BAFF (p< 0.001) and directly associated with CCL23 (p=0.005) concentrations.

Conclusions: Our study points out a possible role of MIP1α, a chemokine intrathecally produced by astrocytes and acting as microglia activator, as candidate prognostic biomarkers for MS.

Disclosure

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The effect of disease modifying therapies on CD62L expression in multiple sclerosis

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Background: An increasing number of disease-modifying therapies (DMTs) is available for treating multiple sclerosis (MS); however, some immunomodulatory agents are associated with potentially severe side effects. The cell-adhesion molecule CD62L, which facilitates leukocyte extravasation, has been proposed as predictive marker for treatment tolerability. Nevertheless, pre-analytical procedures might increase the variability of the assay and limit its clinical usability. If the immediate analysis of CD62L expression of peripheral blood mononuclear cells (PBMCs) can aid in treatment decision-making is yet unclear.

Objective: We aimed to investigate the effect of various DMTs in MS on CD62L expression of CD3+CD4$^+$ PBMCs in freshly collected blood samples.

Methods: We collected peripheral blood samples of patients with clinically isolated syndrome (CIS) and definite MS (n = 48/186; 62.4 % female; age median 35.7, IQR 29.9-45.2 years; disease duration median 7.16 IQR 3.38-13.43 years; Expanded Disability Status Scale (EDSS) score median 1.5, IQR 0.0-2.5), and healthy controls (n = 51; 39.2 % female; age median 49.1, IQR 34.1-60.9 years). In 98 CIS/MS patients one or more samples were collected during follow-up (median 113, IQR 78-163 days). CD3, CD4 and CD62L were analysed by means of FACS flow cytometry within one hour after blood sampling.

Results: CD62L expression of CD3$^+$CD4$^+$ PBMCs was significantly decreased in patients receiving natalizumab (n = 26) and fingolimod (n = 20), and slightly increased in patients who were treated with dimethyl fumarate (n = 15) compared to patients who received interferon (n = 90), glatiramer acetate (n = 30) or no DMT (n = 53) and controls ($p < 0.001$). CD62L expression showed temporal stability in patients who did not change DMT usage, but increased after natlizumab withdrawal and decreased upon fingolimod introduction. CD62L expression did not correlate with demographic and clinical data (i.e., age, gender, age at disease onset, disease duration, therapy duration, EDSS at time of sampling and during follow-up, and annualised relapse rate).

Conclusion: CD62L expression of CD3$^+$CD4$^+$ PBMCs is altered in patients treated with different DMTs when measured in freshly isolated samples. The clinical implication of CD62L changes under various DMTs warrants further investigation.

Disclosure

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F Fazekas serves on scientific advisory boards for Biogen Idec, Sanofi Genzyme, Merck, Novartis, and Teva ratiopharm; serves on the editorial boards of the European Stroke Journal, Multiple Sclerosis Journal, Neurology, the Polish Journal of Neurology and Neurosurgery, and the Swiss Archives of Neurology and Psychiatry; provides consulting services for Actelion, Medday, Parexel and Teva ratiopharm and has received speaker honoraria from Merck, Genzyme-Sanofi and Teva ratiopharm.

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Multicenter sensory and motor evoked potentials: sample size estimation for differences in group change

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Background: Sensory and motor evoked potentials (SEP; MEP) quantitatively measure signal conduction in multiple sclerosis (MS). They may serve as outcomes in clinical trials. Here we estimate sample sizes to detect differences in longitudinal group changes.
Methods: 21 patients with MS (mean age: 47.3 years, median EDSS: 3.0, 74% relapsing, 26% progressive) were evaluated at 2 time points (tp) within a 30 day window with median and tibial SEP and upper (UL) and lower limb (LL) MEP in 3 centers[1-3]. Five neurophysiologists independently marked all curves using a custom server-based software, EPMark. N20, P40, cortico-muscular-latencies (CxM) and two quantitative EP-scores (qEPS=sum of z-transformed results/number of tests; unit=mean standard deviation) were analyzed. Modified qEPS (mqEPS) comprised all 8 tests, qMEP all 4 CxM.
From mixed effects linear models (outcome: tp 1 and 2 combined) total variance (V) and its components were estimated assuming 2 central readers. Subject related V (V_{sub}), intra-individual test-retest V (V_{TRT}), standard deviation of assumed longitudinal change (SD_{long}) and effect size e=SD_{long} were used to estimate sample sizes necessary to detect differences in mean group change (a=5%, b=90%) using: $\boldsymbol{n}$=(1.96+1.28)^2*(2*V_{TRT}+SD_{long}^2)/e^2. SD_{long} was calculated from the assumed change of V_{sub} over time (proportion of V_{sub} not explained by its inter-correlation over time: SD_{long}=sqrt[4*V_{sub}*(1-r)] with r=0.85 for correlation between true underlying baseline and follow-up values). High effect size is justified as it relates to SD_{long} and not to the larger observed longitudinal variance SD_{long}+V_{TRT}.
Results: For single EP tests, estimated sample sizes range between 50 and 60 subjects per arm to detect group differences in longitudinal change ***d*** ranging from 0.7 to 4.2ms (MEP-UL: n=59, d=2.4ms; MEP-LL: n=52, d=4.2ms; N20: n=59, d=0.7ms; P40: n=55, d=3.7ms). For qEPS, sample sizes and ***d*** are smaller (mqEPS: n=54, d=1.2; qMEP: n=45, d=1.7).
Conclusion: Our results corroborate the approach of using multimodal EP to assess therapeutic effects of remyelinating substances: the estimated sample sizes allow conducting efficient trials, the differences in mean group change are reasonable provided that an efficient drug shortens latencies. Multimodal EP optimizes sensitivity to change and has high construct validity.

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Immunosuppression

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Relapse-associated worsening and progression independent of relapse activity in patients with relapsing multiple sclerosis in the Phase III OPERA I and OPERA II studies

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Background: In OPERA I and II ocrelizumab (OCR) reduced the risk of 12- and 24-week confirmed disability progression (CDP) vs interferon (IFN) β1a. CDP may result either from relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA).
Objective: To report the risk of RAW and PIRA events in a pooled analysis of the OPERA I and OPERA II studies.
Methods: Patients with relapsing multiple sclerosis (RMS) from the OPERA I and OPERA II studies (NCT01247324; NCT01412333) were randomised 1:1 to receive intravenous OCR 600mg every 24 weeks (N=827) or subcutaneous IFN β1a 44µg three times weekly (N=829) for 96 weeks. RAW events were defined as a disability change occurring ≤90 days after onset of a protocol-defined relapse. RAW in Expanded Disability Status

Scale (EDSS) was defined as increase in EDSS score of ≥1.0 if baseline EDSS score ≤5.5 or ≥0.5 if baseline EDSS score >5.5; composite RAW was defined as RAW in EDSS or ≥20% increase in Timed 25-Foot Walk or 9-Hole Peg Test. Composite CDP and composite PIRA were previously defined and reported. Analyses were performed on the pooled intent-to-treat population of OPERA I and II. Hazard ratios were calculated by Cox regression and p-values by log-rank test, stratified by study, region and baseline EDSS score.

Results: OCR vs IFNβ1a reduced the relative risk of 12/24-week confirmed RAW in EDSS by 59% (IFNβ1a/OCR events, n [%], 34 [4.1]/16 [1.9]; p=0.003) and 66% (IFNβ1a/OCR events, n [%], 30 [3.6]/11 [1.3]; p=0.002]), respectively; reductions in 12/24-week confirmed composite RAW were 55% (IFNβ1a/OCR events, n [%], 37 [4.5]/19 [2.3]; p=0.004) and 58% (IFNβ1a/OCR events, n [%], 27 [3.3]/12 [1.5]; p=0.009), respectively. A large majority of overall disability accumulation corresponded to PIRA events (82.3/84.5% of 12/24-week confirmed composite CDP events). Defined events of RAW and PIRA appeared to be mostly non-overlapping (only 1.5/1.3% of patients with 12/24-week confirmed composite CDP events experienced both RAW and PIRA).

Conclusions: Ocrelizumab was superior to IFNβ1a in preventing confirmed accumulation of disability. Our results indicate that a considerable proportion of overall accumulation in disability in a typical RMS population might be related to an underlying progressive course, thus challenging the current phenotypical distinction of relapsing and progressive forms of the disease.

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Early versus delayed initiation of fingolimod or dimethyl fumarate in relapsing-remitting multiple sclerosis

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Introduction: Delaying treatment with interferon beta (IFNb) for two years in clinically isolated syndrome was associated with an increased relapse rate after eleven years (Kappos L et al.; 2016) suggesting that an early commencement of disease modifying treatment (DMT) might modify the immune response in the long run. Thus, a delayed initiation of dimethyl fumarate (DMF) or fingolimod (FTY) might also be associated with a higher disease activity compared with an early start, even when the delayed group is not treatment-naïve but has been exposed to a less effective DMT.

Objective: To compare the relapse rate of early vs. delayed initiation of DMF/FTY in relapsing-remitting multiple sclerosis (RRMS) when the delayed group is treated with IFNb or glatiramer acetate (GA) in the interval.

Methods: Data were derived from the Swiss MS treatment registry including 14726 patients initiating DMT between February 1995 and September 2017. Data were provided annually by board-certified neurologists and recorded prospectively using a specific case-report form. We included treatment-naïve RRMS patients commencing DMF/FTY as first-line treatment (early starters) and compared them with patients who commenced IFNb/GA, stayed on IFNb/GA for ≥2 years and then switched to DMF/FTY (late starters). To avoid including merely IFNb/GA non-responders, patients were required to be relapse-free in the year prior to switch. Propensity score-matching was used to select subpopulations with comparable baseline characteristics. Relapse rates were compared with negative binomial models in paired, pairwise-censored analyses.

Results: In total, 808 patients were included. The matching procedure retained 151 early and 151 late DMF/FTY starters. Median follow-up after pairwise censoring was 1.2 years (interquartile range 1.0-1.9). Late DMF/FTY starters had a higher risk of experiencing relapses compared with early starters (incident rate ratio 2.1; 95% confidence interval 1.2-3.8; p=0.01). The fractions of patients with relapses in the first four years of follow-up were 20/151, 11/62, 3/17 and 1/6 in the late, and 10/151, 5/62, 1/17 and 2/6 in the early group, respectively. Sensitivity analyses with various matching strategies and different inclusion criteria confirmed these results.
Conclusion: Early commencement with DMF/FTY seems to be associated with a better control of relapses relative to a late start even when late starters were treated with IFNb/GA beforehand.

Disclosure
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CLARITY: an analysis of severity and frequency of relapses in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets or placebo

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Introduction: In the CLARITY study, treatment with Cladribine Tablets 3.5 mg/kg (CT3.5) showed strong efficacy vs placebo (PBO) over 2 years in patients with relapsing multiple sclerosis (MS).
Objective: The effect of CT3.5 on the rate and severity of relapses (using hospitalisation and steroid use as proxy indicators), and the effect of adjusting for covariates was evaluated in *post hoc* analyses.
Methods: Qualifying relapse was defined by Kurtzke Functional Score status and specified clinical parameters. Qualifying relapse relative risk (RR) was estimated for patients treated with CT3.5 (N=433) and PBO (N=437) at Weeks 24, 48 and 96 by Poisson regression with treatment and various alternating covariates (gender, age, age at time of diagnosis, disease duration, and pre-treatment) as main effects and by adding treatment by covariate interaction effects. All relapses were also analysed; analyses were post hoc and exploratory.
Results: Risk of qualifying relapse was significantly lower for CT3.5 vs PBO at Weeks 24, 48 (both p< 0.001) and Week 96 (Week 96: RR 0.42 [95% confidence interval (CI) 0.34, 0.53]; p< .0001). RR of all relapses (Week 96; CT3.5 vs PBO) was 0.43 [95%CI 0.37, 0.51]; p< .0001. Annualised relapse rates for PBO and CT3.5 were 0.35 and 0.15, (qualifying) and 0.63 and 0.27 (all relapses), respectively. Compared to PBO, the CT3.5 group had a significantly reduced risk of qualifying relapses leading to hospitalisation at all timepoints (Week 96 RR 0.41 [95%CI 0.29, 0.57]; p< .0001) and qualifying relapses leading to steroid treatment (Week 96 RR 0.41 [95%CI 0.32, 0.53]; p< .0001). Risk reduction of all relapses for hospitalisation and steroid use were 63% and 62%, respectively (Week 96). Both age at time of diagnosis (p=0.0011) and prior use of disease modifying drugs (p=0.0002) had a significant effect on qualifying relapse rate by Week 96 when added separately to the model. Gender had a marginal effect (p=0.0783) while disease duration had no effect (p=0.8770). None of the covariates influenced the RR of qualifying relapse for CT3.5 vs PBO at Week 96.
Conclusions: The RR of qualifying relapse (and all relapses) was consistently and significantly lower in the CT3.5 group, vs. PBO, for every timepoint (Weeks 24, 48 and 96), including severe relapses requiring hospitalisation or steroid treatment. After adjusting for covariates, the treatment benefit of CT3.5 vs PBO was not diminished by any of these model adjustments.

Disclosure
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Poly I: C-mediated TLR3 agonism re-establishes CNS immune surveillance in the setting of α4-integrin deficiency - implications for natalizumab-associated PML

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Objective: Natalizumab blocks α4-integrin-mediate leukocyte migration into the central nervous system (CNS). It diminishes disease activity in multiple sclerosis (MS), carries a high risk of progressive multifocal encephalopathy (PML), an opportunistic infection with JV virus that may be prompted by diminished CNS immune surveillance. The initial host response to viral infections entails the synthesis of type I interferons (IFN) upon engagement of TLR3 receptors. We hypothesized that TLR3 agonism re-establishes CNS immune competence in the setting of α4-integrin deficiency.

Method: We generated the conditional knock out mouse strain Mx1.Cre^{+}α4-integrin$^{fl/fl}$, in which the α4-integrin gene is ablated upon treatment with the TLR3 agonist poly I:C. Adoptive transfer of purified lymphocytes from poly I:C-treated Mx1.Cre^{+}α4-integrin$^{fl/fl}$ donors into naive recipients recapitulates immunosuppression under natalizumab. Active experimental autoimmune encephalomyelitis (EAE) in Mx1.Cre^{+}α4-integrin$^{fl/fl}$ mice treated with poly I:C represents immune-reconstitution.

Results: Adoptive transfer of T cells from poly I:C treated Mx1.Cre^{+}α4-integrin$^{fl/fl}$ mice causes minimal EAE. The *in vitro* migratory capability of CD45^{+} splenocytes from these mice is reduced. In contrast, actively-induced EAE after poly I:C treatment results in full disease susceptibility of Mx1.Cre^{+} α4-integrin$^{fl/fl}$ mice, and the number and composition of CNS leukocytes is similar to controls. Extravasation of Evans Blue indicates a compromised blood-brain barrier. Poly I:C treatment results in a 2-fold increase in IFNβ transcription in the spinal cord.

Interpretation: Our data indicate that TLR3 agonism in the setting of relative α4-integrin deficiency can re-establish CNS immune surveillance and may present a feasible treatment strategy to treat and prevent PML under natalizumab therapy.

Disclosure

Dr. Olaf Stuve serves on the editorial boards of the Multiple Sclerosis Journal, and Therapeutic Advances in Neurological Disorders.

Dr. Stuve has served on data monitoring committees for Pfizer and TG Therapeutics without monetary compensation.

Dr. Stuve has advised EMD Serono, Genzyme and Novartis.

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Safety, tolerability, pharmacokinetics and concentration-QT analysis of the novel BTK inhibitor evobrutinib (M2951) in healthy volunteers

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Background: Evobrutinib (M2951) is a highly selective, irreversible Bruton's tyrosine kinase (BTK) inhibitor that demonstrated efficacy in preclinical models of autoimmune disease. This first-in-human study investigated the safety, tolerability, and pharmacokinetics (PK) of evobrutinib in healthy subjects, and examined the relationship between evobrutinib exposure and changes in QT interval.

Methods: This was a single-centre, Phase I, double-blind, placebo-controlled trial. In Part 1, 48 healthy participants in six successive dose cohorts (20-fold difference between highest and lowest doses) were randomised to a single oral dose of evobrutinib or placebo (6:2). In Part 2, 36 participants in three ascending dose cohorts were randomised to evobrutinib or placebo (9:3) once daily for 14 days. Safety and tolerability were assessed following single and multiple dosing and PK parameters determined by non-compartmental methods. Change from baseline in QT interval, corrected for heart rate by Fridericia's method (QTcF), in the 24 hours following the first dose was determined by electrocardiography.

Results: Treatment-emergent adverse events (TEAEs) with evobrutinib were mostly mild, occurring in 25% of participants after

single, and 48.1% after multiple dosing. Nature and incidence of TEAEs were similar among evobrutinib and placebo groups, with no apparent dose relationship regarding frequency or type of TEAEs among evobrutinib-treated subjects. Absorption of evobrutinib was rapid (t_{max} ~0.5 h), half-life was short (~2 h), and PK were dose-proportional following single and multiple dosing, with no accumulation or time dependency on repeat dosing. Concentration-QTcF analyses revealed no significant exposure-effect relationship. Based on a linear mixed-effects model for change from baseline in QTcF (ΔQTcF), the slope of the relationship between mean placebo-adjusted ΔQTcF (ΔΔQTcF) and concentration was negative and close to zero (-0.00027 ms/ng per mL; p=0.86). The predicted ΔΔQTcF effect at geometric mean C_{max} for the highest dose (1512 ng/mL) was -1.16 ms with an upper limit of 3.26 ms for the 90% two-sided bootstrapped confidence interval, which is well below the 10 ms threshold of regulatory concern (ICH-E14 guidance).

Conclusions: Evobrutinib was well tolerated, with predictable PK and no prolongation of QT interval (ΔΔQTcF) in healthy volunteers, and is suitable for further investigation in patients with autoimmune disease.

Disclosure

Andreas Becker: Employee of Merck KGaA, holds shares in Merck; Emily Martin: Employee of EMD Serono; David Y Mitchell: Clinical pharmacology consultant working with Merck KGaA; Victor Ona: Employee of EMD Serono; Jonathan Willmer: Employee of EMD Serono; Andreas Johne: Employee of Merck KGaA

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ADA genetic variants influence central inflammation and clinical characteristics in MS: implications for cladribine treatment

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Background: Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) characterized by demyelination and neurodegeneration. A number of proinflammatory molecules released by activated T and B lymphocytes and local immune cells negatively influence MS disease course. Lymphocytes are very sensitive to impaired nucleotide metabolism. The activity of the enzyme adenosine deaminase (ADA) is critically involved in the regulation of the immune response homeostasis, as shown in ADA genetically deficient patients and in response to cladribine treatment.

Objective: To explore in a large cohort of MS patients the association between single nucleotide polymorphisms (SNP) of ADA gene, and both CSF inflammation and disease characteristics.

Methods: A number of ADA SNPs (rs244072, rs452159, rs181828191, rs73598374, rs244076, rs1799880) were determined in a group of 590 MS patients. CSF proinflammatory and anti-inflammatory molecules were measured at the time of diagnosis in a subgroup of 234 MS patients. Clinical and radiological disease characteristics were assessed at baseline, and during median follow-up period of 44 months.

Results: A significant association emerged between ADA rs244072 SNP and the levels of central inflammation. In particular, in patients presenting the C allele, significantly higher CSF levels of TNFα (TT patients median =0.68, IQR = 0 - 1.15; CT/CC median = 1.42, IQR = 0.31 - 3.45; p = 0.023), IL-5 (TT patients median = 0, IQR = 0 - 0.63; CT/CC median = 0.39, IQR = 0 - 17.8; p = 0.0274) and RANTES (TT patients median = 4.49, IQR = 0 - 99.9; CT/CC median = 157.3, IQR = 0.99 - 1129.5; p = 0.0403) have been observed. In addition, patients with the C allele showed lower CSF levels of IL-10 (TT patients median = 2.64, IQR = 1.14-4.07; CT/CC median = 1.91, IQR = 0 - 2.94; p = 0.044). Finally, a significant association emerged between the presence of the C allele and higher expanded disability status score (EDSS) at the time of diagnosis (TT patients median = 2, IQR = 1 - 3; CT/CC median = 2.5, IQR = 2 - 3.5; p = 0.0158).

Discussion: ADA SNP rs244072 influences central inflammation and disease characteristics in MS patients. These results suggest that pharmacological modulation of ADA pathway with cladribine could be effective in MS by targeting a pathogenetically relevant biological mechanism.

Disclosure

Dr. Buttari acted as Advisory Board member of Teva.

Dr. Centonze is an Advisory Board member of Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva. He is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Teva. His preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi-Genzyme e Teva.

Dr. Furlan has nothing to declare.

Dr. Marfia is an Advisory Board member of Biogen Idec, Genzyme, Merck-Serono, Novartis, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Teva. She is the principal investigator in clinical trials for Actelion,

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Dr. Matarese has nothing to declare.
Dr. Salvetti is an Advisory Board member of Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva. He is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Teva. His preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi- Genzyme e Teva.
Dr. Sica has nothing to declare.
Dr. Simonelli has nothing to declare.
Dr. Stampanoni Bassi has nothing to declare.
Dr. Uccelli is an Advisory Board member of Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva. He is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Teva. His preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi- Genzyme e Teva.
Dr. Visconti has nothing to declare.

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No correlation between lymphocyte repopulation kinetics and MS disease activity following alemtuzumab treatment in patients with relapsing-remitting multiple sclerosis

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Introduction: Alemtuzumab 12 mg showed significantly improved clinical and MRI outcomes versus SC IFNB-1a over 2 years in patients with active RRMS in two phase 3 clinical trials (CARE-MS I and II; NCT00530348; NCT00548405). Alemtuzumab remained efficacious in a 4-year extension (NCT00930553), wherein patients could receive as-needed alemtuzumab retreatment or other disease-modifying therapy (DMT); 56% of patients received no additional alemtuzumab or other DMT. The selective depletion and distinct pattern of repopulation of circulating CD52-expressing T and B lymphocytes that occur after alemtuzumab treatment may account for its effect in MS.
Aims: To examine the association between lymphocyte repopulation patterns during the CARE-MS studies and clinical/MRI disease activity through 6 years.
Methods: Blood cell counts in the CARE-MS studies were carried out monthly. Lymphocytes were phenotyped by flow cytometry quarterly and at Months 1 and 13 (ie, 1 month after receiving Courses 1 and 2 of alemtuzumab, respectively), and lymphocyte counts from the CARE-MS I and II studies were pooled for analysis. Pharmacodynamic assessments included total cell counts for the following cell types: lymphocytes, $CD3^+/CD4^+/CD8^+$ T cells, and $CD19^+$ B cells, as well as subset analyses for $CD4^+/CD8^+$ T cells (naïve/memory/regulatory [T_{reg}]) and $CD19^+$ B cells (immature/mature/memory). Further analyses examined ratios of $CD19^+$ (total/immature/memory) to T_{reg} ($CD4^+/CD8^+$) cells. The relationship between lymphocyte repopulation patterns over the 2-year core studies and efficacy over 6 years (core and extension studies combined) was assessed in patients who did or did not experience relapses, 6-month confirmed disability worsening (CDW; ≥1.0-point EDSS score increase [≥1.5 points if baseline EDSS=0]), or MRI disease activity (new gadolinium-enhancing lesions or new/enlarging T2 lesions).
Results: Lymphocyte subset repopulation kinetics over 2 years did not differ in patients with or without relapses, 6-month CDW, or MRI disease activity through 6 years. No correlation was observed between any $CD19^+/T_{reg}$ cell count ratio and relapse, CDW, or MRI disease activity.
Conclusions: Based on these analyses, lymphocyte repopulation kinetics were not associated with return of disease activity and likely cannot be used to predict need for treatment beyond Course 2.

Disclosure

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Impact of rituximab on Treg lymphocytes in MS patients

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Introduction: Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody (Ab), shares similar mechanism of action with ocrelizumab, a humanized anti-CD20 monoclonal Ab, recently approved by the EMA and FDA for the treatment of multiple sclerosis (MS). RTX is sometimes used off-label in MS. RTX treatment results in circulating B cell, but also T cell depletion. Regulatory T cells (Treg) play an immune-regulatory role and were recently identified to promote oligodendrocyte differentiation and remyelination. Specific impact of RTX on Treg in MS remains unknown.
Objectives: To define the impact of RTX on T and B lymphocytes in MS patients.
Methods: RTX-treated MS patients from the Pitié-Salpêtrière center were consecutively included in a prospective observational study during RTX treatment: 1000 mg IV, followed by a maintenance dose of 1000 mg every 6 months. Main outcome was circulating lymphocytes kinetics (B CD19/B CD20/B CD27/T CD4/T CD8/Treg/NK cells) before the first infusion and 6 months later. Secondary outcomes were the annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) and MRI activity.
Results: 43 patients (55.8% women, 19 relapsing-remitting (RR) MS, 24 progressive MS) were analyzed after 6 months (M6) of follow-up. Mean (SD) EDSS at baseline was 5.2 (1.4) and 5.3 (1.5) at M6 respectively. ARR significantly decreased at M6 from a mean 1.18 (1.2) to 0.18 (0.6) (p=0.00094). MRI activity was reported in 11% of patients compared with 56% at baseline. Levels of CD19+ and CD27+ memory B cell lymphocytes were significantly depleted at M6 (both $p < 0.0001$). While CD8+ lymphocytes percentage remained unchanged, we found a significant increase in CD4+ lymphocytes levels at M6 (M0: 44,7% (10.8) to M6 52.6% (8.8); p=0.0008). Among CD4+ T cells, activated Treg percentage remained unchanged (M0: 2.24% (1.65) to M6: 1.9% (1.2); p=0.36), but quiescent Treg significantly increased (M0: 1.56% (1.36) to M6: 2.3% (2.2); p=0.036). No change in NK ant NKT cell populations was observed.
Conclusion: Our findings highlight that RTX treatment is associated with an unexpected up-regulation of circulating CD4+ lymphocytes and quiescent Treg levels in MS patients. We postulate that quiescent Treg increase could reflect their reduced conversion into activated Treg, in RTX responders. A larger cohort and a longer follow-up are requested in order to establish a potential link between RTX clinical efficacy and T cell parameters at the individual level.

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Comparison of high-dose intravenous corticosteroids and therapeutic plasma exchange in acute relapsing multiple sclerosis

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Objective: Relapses and incomplete remission thereof significantly contribute to disability in relapsing-remitting multiple sclerosis (RRMS). Thus, optimal relapse therapy is essential for long-term outcomes besides immunomodulatory treatment.

Standard treatment for acute relapses is high-dose intravenous (methyl-) prednisolone (IVMPS). Usually, up to 1000mg per day is given for 3-5 days. Unfortunately, one quarter of patients shows unsatisfactory resolution and requires escalation treatment.
Single studies have demonstrated further dose-dependency of IVMPS and international guidelines include a second course with up to 2000mg per day for further 3-5 days. Therapeutic plasma exchange (TPE) is also an accepted alternative since it was first evaluated 20 years ago. Unfortunately, data on comparison of both regimens are still missing.
Methods: We set up a retrospective analysis including patients being treated between January, 2013 and December, 2016. In-depth medical chart review was performed regarding neurological status at discharge and after three months.
Results: 99 Patients were identified. 69 received a second course of IVMPS as first escalation treatment and 30 directly were subjected to five courses of TPE. 40 Patients received TPE after their second course of IVMPS.
Baseline characteristics between different treatment groups were evenly balanced (sex, age, number of previous relapses, baseline EDSS, relapse EDSS, proportion on DMT, proportion with first event). Overall, patients were young and early in their disease (median age: 32 years; median disease duration: 1 year).
Primary analysis included patients having received only a single course of escalation treatment. After second course of IVMPS, 10/29 (34.5%) experienced marked or even full response compared to 27/30 (90.0%) patients after TPE ($p < 0.001$). Contrasting, rescue therapy with TPE after two courses of IVMPS resulted in weaker response compared to early TPE. Remarkably, differences remained significant at follow-up.
Conclusion: Our findings indicate that early TPE has particular advantages compared to a second course of IVMPS. However, data from prospective, randomized trial in a well-defined cohort are desirable.
L. Lammerding and S. Pfeuffer contributed equally to this study. This study was financially supported by the Northrine-Whestphalian Section of the German Multiple Sclerosis Society (DMSG-NRW to S. Pfeuffer and Sven G. Meuth).

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Ozanimod-treated patients exhibited improvements in cognitive processing speed in the phase 3 SUNBEAM trial of relapsing multiple sclerosis (RMS)

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Introduction: Slowed processing speed, common in MS, is associated with impaired quality of life. Ozanimod, an oral, once-daily immunomodulator selectively targeting sphingosine 1-phosphate 1 and 5 receptors, is in clinical development for RMS. In the phase 3 SUNBEAM study, ozanimod demonstrated significant reductions in clinical and MRI disease activity vs interferon β-1a (IFN), with no clinically significant bradycardia or second-degree or higher atrioventricular block following first dose or serious infections. We report on the effect of ozanimod on Symbol Digit Modalities Test (SDMT) performance in SUNBEAM.
Methods: In total, 1346 patients with RMS were randomized to ≥12 months of once-daily oral ozanimod HCl 1 or 0.5 mg (equivalent to ozanimod 0.92 and 0.46 mg, respectively) or once-weekly intramuscular IFN. SDMT (Smith 1982) was a secondary endpoint in SUNBEAM. In post-hoc analyses, least-squares mean (LSM) changes from baseline to month 12 in SDMT score were

determined using a mixed model for repeated measures adjusted for baseline SDMT score and stratification factors, with the interaction between treatment and time point as fixed effects. For longitudinal binary data, an adjusted generalized estimating equation model was used (interaction between treatment and time point assumed an unstructured within-subject covariate structure). For simple binary data, an adjusted generalized model with log transformation was used.

Results: LSM changes in SDMT score demonstrated improvements for ozanimod HCl 1 mg (difference: 1.6, p=0.0013) and 0.5 mg (1.2, p=0.0188) vs IFN. Rate ratios (RR) for ozanimod HCl 1 and 0.5 mg vs IFN on the proportions of patients with clinically meaningful improvements in processing speed (≥4-point increase in SDMT score) at month 12 were 1.3 (95% confidence interval [CI]: 1.05, 1.55; p=0.0156) and 1.2 (0.94, 1.40; p=0.1689), respectively. More patients had ≥4-point increase in SDMT score at months 6 and 12 with ozanimod HCl 1 mg (RR, 1.7; 95% CI: 1.25, 2.32; p=0.0007) and 0.5 mg (1.5; 1.09, 2.05; p=0.0130) vs IFN.

Conclusion: Significantly greater mean increases in SDMT score at month 12 were seen in the ozanimod vs IFN group. Significantly more ozanimod HCl 1 mg-treated vs IFN-treated patients exhibited clinically meaningful (≥4 points) improvements in processing speed.

Disclosure

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BTK inhibition prevents inflammatory macrophage differentiation: a potential role in MS

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Bruton's tyrosine kinase (BTK) mediates B cell receptor (BCR) and Fc receptor (FcR) signaling. BTK inhibitors thus silence B cells and prevent innate immune activation via FcR, suggesting they may be beneficial for treating autoimmune diseases with B cell involvement. Furthermore, BTK has been implicated in mediating signaling of certain chemokine and cytokine receptors. The highly selective and irreversible BTK inhibitor evobrutinib inhibits disease development in an experimental autoimmune encephalomyelitis (EAE) model that is not amenable to B cell inhibition by anti-CD20 antibody, indicating that efficacy is mediated by effects beyond BCR. We therefore investigated the effect of BTK inhibition on the differentiation and activation of monocytes and macrophages, which may contribute to MS disease activity and progression.

GM-CSF has been shown to drive neuroinflammation in preclinical models for MS, and is crucial for the differentiation of pro-inflammatory M1 macrophages. In the studies reported herein we found that BTK is activated downstream of the GM-CSF receptor. In line with this finding, the *in vitro* GM-CSF differentiated M1 cells undergo apoptosis upon BTK inhibition. Monocytes treated with GM-CSF in the presence of BTK inhibitor secrete less TNF-α and express less IL-1ß, in addition to upregulating the expression of anti-inflammatory genes, such as IL-10. Furthermore, BTKi treatment increases the rate of phagocytosis by anti-inflammatory M2 Macrophages *in vitro*.

Our findings show that BTK inhibition hinders M1 macrophage differentiation and skews monocytes towards an anti-inflammatory M2 phenotype, while enhancing apoptotic cell uptake by the M2 cells. We therefore conclude that inhibiting BTK could have additional benefit in the treatment of MS and other autoimmune diseases, by targeting both B cells and myeloid cells simultaneously.

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Effects of natalizumab on work ability in patients with relapsing-remitting multiple sclerosis: results from the WANT observational study

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Background: Multiple sclerosis (MS) is a chronic, progressive neurologic disease that impairs daily activities and ability to work. Although previous research has shown that natalizumab (NTZ) treatment may improve work ability (WA), further data are needed to fully characterize this impact.
Objectives: The Work Ability in Natalizumab-Treated MS Patients (WANT) study assessed the association of NTZ with WA improvement and evaluated its effects on disease activity, quality of life, and cognitive function.
Methods: WANT was a 1-year, prospective, multicentre observational study conducted in Italy. Inclusion criteria included relapsing-remitting MS, NTZ treatment, full-time worker status, and loss of working hours due to MS as measured by the Work Productivity and Activity Impairment Questionnaire for MS (WPAI:MS). The primary endpoint was change in WPAI:MS domain scores (absenteeism, presenteeism, work productivity loss, and activity impairment) after 1 year on NTZ. Secondary endpoints included change in annualised relapse rate (ARR), MRI lesion load, and Expanded Disability Status Scale (EDSS), Multiple Sclerosis Impact Scale (MSIS-29), and Symbol Digit Modalities Test (SDMT) scores.
Results: At baseline, the 91 patients enrolled had a mean age of 38.3 (standard deviation [SD], 9.0) years, mean ARR of 1.5 (SD, 0.8), and mean EDSS score of 2.8 (SD, 1.5). After 1 year, improvements in all domains of WPAI:MS were observed, though only reductions in absenteeism and work productivity loss domains reached significance (−4.2 [SD, 26.0] and −7.2 [SD, 28.6], respectively; $P< 0.05$). These changes were accompanied by reduction in disease activity: ARR decreased by 1.3 (SD, 0.8; $P< 0.0001$) and 87.9% of patients were relapse free; mean EDSS score decreased by 0.2 (SD, 0.6; $P=0.0068$); and the gadolinium-enhanced lesion count decreased by 0.7 (SD, 2.0; $P=0.0078$). Significant improvement was also observed in MSIS-29 physical and psychological domains (reductions of 2.8 [SD, 11.6] and 6.3 [SD, 15.6], respectively; $P< 0.05$) and the SDMT (increase of 2.4 [SD, 7.9]; $P=0.0006$). Finally, an association between decrease in absenteeism and improvement in EDSS and ARR after 1 year was observed ($P< 0.05$).
Conclusions: NTZ was associated with significant reductions in absenteeism and work productivity loss, as well as improved physical and psychological functioning. The results extend our understanding of the effects of NTZ on important patient-centric and health economics outcomes.

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Mechanism of action of teriflunomide in multiple sclerosis

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Introduction: Teriflunomide is a disease modifying treatment approved for multiple sclerosis (MS). It inhibits reversibly dihydro-orotate dehydrogenase, a mitochondrial enzyme involved in de-novo pyrimidine biosynthesis, and down-regulates proliferation of activated lymphocytes.
Objectives: We further studied the impact of this drug on the lymphocyte profile of MS patients.
Methods: 55 patients with relapsing-remitting MS who initiated teriflunomide treatment were included in the study. We studied peripheral blood mononuclear cells obtained before and six months after treatment initiation and explored effector, memory and regulatory cells by flow cytometry. Wilcoxon matched pair tests were used to assess differences. p values below 0.05 after correction by Bonferroni test were considered as significant.
Results: When explored effector T and B cell subsets, we observed a decrease in the percentages of terminally differentiated CD4+ T cells ($p=0.001$) and plasmablasts ($p< 0.0001$) after 6 months of treatment. These results were confirmed with the total cell numbers ($p< 0.0001$ in both cases). When studied regulatory cells, we observed a clear increase of monocytes expressing programmed death-ligand 1 (PDL-1) ($p=0.005$), that was also confirmed with total cell numbers ($p=0.01$). It correlated negatively with all effector CD8+ T cell subsets. We also observed an increase in the percentage of CD8+ T cells ($p=0.028$) and monocytes ($p=0.04$) producing IL-10.
Conclusions: Teriflunomide induces a change in the abnormal immune response taking place in MS, with a specific reduction in effector T and B cells and an increase in regulatory cells. Particularly, this drug can produce a switch in the innate immune response to a tolerogenic profile.

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Comparative effectiveness and discontinuation of dimethyl fumarate and fingolimod in clinical practice at 36-month follow-up

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Objective: To assess real-world comparative effectiveness and discontinuation of dimethyl fumarate (DMF) and fingolimod (FTY) over 36 months in patients with multiple sclerosis (MS).
Background: DMF and FTY are approved oral disease modifying therapies (DMT) for relapsing MS. Previous randomized controlled trials (RCTs) and large observational studies, including our 12- and 24-month investigations, showed comparable effectiveness, but the rate of early discontinuation of DMF exceeded that of FTY.
Methods: From 659 patients in a large academic MS Center in the original 24-month cohort, 238 patients prescribed DMF and 177 prescribed FTY were identified with 36-month follow-up. Discontinuation and disease activity were assessed using propensity score (PS) weighting. Covariates used in the PS model included demographics and baseline disease characteristics. Outcomes of interest included proportion of patients discontinuing DMT, annualized relapse rate (ARR), proportions with MRI disease activity [gadolinium-enhancing (GdE) and new T2 lesions] and absence of disease activity (freedom from clinical relapses and GdE/new T2 lesions), and time to discontinuation and first relapse. After PS adjustment odds and hazards ratio estimates were calculated as DMF versus FTY.
Results: PS weighting demonstrated excellent covariate balance. We found that a similar proportion discontinued DMF (50.9%) and FTY (43.9%) over 36 months due to any reason [OR=1.36, 95% CI (0.88, 2.10)]. The leading cause for discontinuation was intolerability for both DMF (32.4%) and FTY (22.0%), with increased likelihood in DMF [OR=1.46, 95% CI (1.15, 2.74)]. Of patients who discontinued DMT, a small proportion discontinued therapy between 24 and 36 months (DMF, 11.1%; FTY 11.0%; p=0.76). Proportion with relapses was low in both groups (DMF, 16.7%; FTY, 15.5%; p=0.77). There was no difference in ARR [OR=1.08, 95% CI (0.75, 1.54)], GdE lesions [OR=1.44, 95% CI (0.80, 2.60)], or new T2 lesions [OR=1.00, 95% CI (0.56, 1.79)]. Proportion with absence of disease activity was also comparable [OR = 1.03, 95% CI (0.62, 1.07)]. Time to discontinuation [HR=1.19, 95% CI (0.96, 1.46)] and first relapse [HR=1.43, 95% CI (0.98, 2.09)] were similar across both DMTs by 36 months.
Conclusions: This analysis suggests similar effectiveness for DMF and FTY over 36 months. Discontinuation of both DMTs due to intolerability was common and more frequent with DMF, though persistence rates improved with longer DMT treatment.

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Cardiac safety profile of ozanimod in pooled phase 3 studies in relapsing multiple sclerosis (SUNBEAM and RADIANCE)

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Introduction: Ozanimod, an orally-active, selective sphingosine 1-phosphate (S1P) receptor subtype 1 ($S1P_1$) and 5 ($S1P_5$) immunomodulator, has shown therapeutic benefit in clinical trials of relapsing multiple sclerosis (RMS). Ozanimod HCl is initiated

with a low dose of 0.25 mg on days 1 to 4, followed by 0.5 mg on days 5 to 7 and 1 mg from day 8, if assigned to 1 mg (doses are equivalent to ozanimod 0.23 mg, 0.46 mg, and 0.92 mg, respectively). The S1P receptor selectivity of ozanimod, pharmaceutical properties, and initial dosing regimen may help to decrease the risk of clinically meaningful heart rate (HR) reduction and atrioventricular (AV) conduction effects. The results of the pooled cardiac safety data from two phase 3 pivotal studies in RMS are presented below.

Methods: In the phase 3 studies (n=1774 ozanimod-treated patients [Pts]), day 1 cardiac monitoring included collection of vital signs (VS) prior to dosing and hourly for the first 6 hours after dosing with ozanimod HCl 0.25 mg (supine and standing HR) and electrocardiogram (ECG) prior to dosing and at hour 6. ECGs also were collected at week 2, and annually thereafter. VS were collected at each visit.

Results: Six-hour post-dose monitoring on day 1 demonstrated that the nadir supine HR (mean change from baseline -1.2 bpm) with ozanimod occurred at hour 5, with values returning towards baseline at hour 6 (mean reduction -0.2 bpm). Asymptomatic, transient supine HR reduction below 45 bpm (but not lower than 40 bpm) was observed in 4 Pts, was not associated with AV block, and did not require treatment, with resolution toward >45 bpm within 1–2 hours and all Pts continuing on study drug uneventfully. Asymptomatic bradycardia adverse events (AEs) were reported in 0.6% of Pts on ozanimod versus 0% on interferon β-1a (IFN) on the day of treatment initiation. After day 1, asymptomatic bradycardia was reported for 0.8% of Pts on ozanimod HCl (0.5 mg and 1 mg) versus 0.7% on IFN. Incidence of serious AEs in the cardiac system organ class was low and similar across the treatment groups. There were no reported occurrences of second-degree or higher AV block.

Conclusions: Ozanimod is a novel oral S1P agent with a favourable cardiac safety profile for RMS Pts. There were no cases of ozanimod-related symptomatic reduction in HR and no occurrences of second-degree or higher AV block observed at the time of first dose, during dose escalation, or reported during dose escalation and during chronic dosing.

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Comparison of rituximab vs fingolimod, dimethyl fumarate and natalizumab in the treatment of multiple sclerosis: two year experience

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Introduction: Rituximab (RTX) has been used for the off-label treatment of multiple sclerosis (MS). Limited comparative effectiveness data exists comparing RTX to other highly effective therapies. **Objective:** Compare discontinuation rates and efficacy of rituximab (RTX) to fingolimod (FTY), dimethyl fumarate (DMF), natalizumab (NTZ) over two years in MS patients.

Methods: Patients prescribed FTY, DMF, NTZ or RTX at the Rocky Mountain MS Center at the University of Colorado between January, 2010 and October, 2013 were identified. Clinician-reported data including relapse history, adverse events, MRI outcomes, disease history and patient characteristics were retrospectively collected. Primary outcome was the probability of discontinuing drug by the end of year two. Simple and adjusted logistic regression were used for pairwise data analysis controlling for age, disease duration, type of MS, gender, and enhancing lesion at baseline.

Results: A total of 182, 271, 342, and 451 patients initiated RTX, FTY, DMF and NTZ and were included in this study. Patients had a mean age of 43.9(RTX), 42.5(FTY), 45.8(DMF) and 39.8(NTZ) years at the index date; were predominantly female (65.9% RTX; 72.0% FTY; 69.6% DMF; 76.7% NTZ); and were largely relapsing-remitting MS (62.1% RTX; 90.0% FTY; 77.5% DMF; 84.7% NTZ). At ≤24 months, 46(25.3%), 93(34.3%), 161(47.1%) and 147(32.6%) discontinued RTX, FTY, DMF, and NTZ, respectively. FTY versus RTX had an adjusted odds ratio(aOR) of 1.96 (95%CI:1.23-3.13,p=0.005) for discontinuation at ≤24 months. DMF versus RTX had an aOR of 3.32 (95%CI:2.15-5.13,p< 0.001). NTZ versus RTX had an aOR of 1.50 (95%CI:0.99-2.28,p=0.109). The leading cause of discontinuation RTX and NTZ were issues with insurance (9.9%) and being JCV positive (12.6%), respectively. Adverse events were the leading cause for discontinuation for FTY (17%) and DMF (24.0%). Fewer RTX patients (14.8%) experienced disease activity including a contrast enhancing lesion, a new T2 lesion and/or a clinical relapse during follow up compared to FTY (34.7%, p=< 0.001), DMF (33.6%, p=< 0.001) and NTZ (22.2%, p=0.037).

Conclusions: The odds of discontinuing ≤24 months was lower for RTX versus FTY and DMF. RTX demonstrated the lowest unadjusted disease activity outcomes. Given the differences in baseline characteristics, additional methods of adjustment will be presented.

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Influences upon healthcare professionals' prescribing of disease modifying treatments for multiple sclerosis in the United Kingdom: a National Survey

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Introduction: Prescribing rates of Disease Modifying Treatments (DMTs) for MS in the UK are lower than many European countries, with wide variation between home nations. A qualitative interview study of 36 MS Neurologists and MS Specialist Nurses from 15 UK sites, was presented previously (ECTRIMS 2017 EP1797) and identified 5 themes that influence prescribing.

Objectives: To quantify the proportion of UK prescribers experiencing factors identified in the interview study on their choice of MS DMTs. To explore differences between UK nations and types of DMT prescribers.

Methods: Based upon the survey themes, we designed an online questionnaire, for independent UK DMT prescribers, identified through snowball sampling of the authors'clinical networks, previous interviewees and by invitation of the Association of British Neurologists (ABN).

Results: 46 consultant neurologists (35 from England, 5 Wales, 2 Northern Ireland (NI) and 4 Scotland) completed the online questionnaire between June and August 2017, 36 MS specialists, 9 with an MS interest and 1 general neurologist (35% of known UK DMT prescribing population); 26 had >10 years of DMT prescribing experience, 3 were single-handed DMT prescribers. 61% suggested that MRI scans contributed to DMT decisions >50% of the time, 63% held dedicated relapse assessment clinics. Commonest factors for determining DMT eligibility were; time since previous relapse (33%), MRI disease activity (26%) and impact on patient's daily functioning (22%). For "borderline" DMT patients ie 2 sensory relapses 23 months apart, rapid and full recovery and no new MRI lesions in preceeding 2 years, 69% of England-based neurologists were "Somewhat" or "Extremely likely" to recommend a DMT, 25% in Scotland, 40% in Wales and 1 of 2 in NI. England based neurologists viewed National Institute for Health and Care Excellence (NICE) as being most impactful upon treatment decisions**,** in Wales ABN guidelines and in Scotland the Scottish Medicines Consortium's were most impactful. Multidisciplinary team meetings to discuss DMTs occur weekly in 30% to "rarely or never" in 17% >90% of respondents discuss DMTs with patients within 12 weeks of diagnosis, with 57% offering a guided choice. Country or UK-wide prescribing peer networks were practice benchmarks in > 2/3 of cases.

Conclusions: Variation in UK DMT prescribing is accounted for by national factors, eg guidelines, as well as individual variation in use of MRI and relapse assessment.

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P564

Sustained efficacy in relapsing remitting multiple sclerosis following switch to placebo treatment from cladribine tablets in patients with high disease activity at baseline

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Introduction: In CLARITY, Cladribine Tablets 3.5 mg/kg (CT3.5) showed strong efficacy vs placebo (PBO) over 2 years in patients with relapsing multiple sclerosis (RMS); efficacy was sustained in Years 3 and 4 without further treatment (CLARITY

Ext). In CLARITY, patients with high disease activity (HDA) showed clinical and magnetic resonance imaging (MRI) responses to CT3.5 that were better than, or comparable to, those seen in the overall CLARITY population.

Objectives: *Post hoc* analysis to determine if the efficacy in patients with HDA treated with CT3.5 in CLARITY (Years 1 and 2) was sustained for the long term in patients receiving PBO in CLARITY Ext (Years 3 and 4).

Methods: This analysis used 2 sets of HDA criteria based on relapse history, prior treatment, and MRI characteristics: 1. High relapse activity (HRA), defined as ≥2 relapses during the year before study entry whether on disease modifying drug (DMD) treatment or not; 2. HRA plus disease activity on treatment (DAT), defined as ≥1 relapse during the year before study entry while on therapy with other DMDs AND ≥1 T1 gadoliniumenhancing (Gd+) or ≥9 T2 lesions. Clinical and MRI outcomes were analysed for patients (N=806) randomised to CLARITY Ext who fulfilled HRA and HRA+DAT criteria at CLARITY baseline and who received CT3.5 in CLARITY and PBO in CLARITY Ext.

Results: The annualised relapse rate (ARR) for qualifying relapses in CLARITY Ext for the population who switched to placebo in Ext from CT3.5 in CLARITY (N=98) was 0.15 (95% confidence interval [CI]; 0.11, 0.21). ARRs for HRA (N=29) and non-HRA (N=69) were 0.15 (95%CI; 0.08, 0.28) and 0.15 (95%CI; 0.10, 0.22), respectively. For HRA+DAT (N=31) and non-HRA+DAT (N=67), ARRs were 0.14 (95%CI; 0.08, 0.26) and 0.15 (95%CI; 0.10, 0.22). The ARRs in this analysis were similar to those seen for the HDA subgroups in CLARITY. In this study, fewer patients in the HDA subgroups had confirmed 3-month Expanded Disability Status Scale (EDSS) progression relative to non-HDA and overall groups (overall population: 18%; HRA and non-HRA: 14% and 20%, respectively; HRA+DAT and non-HRA+DAT: 13% and 21%, respectively). The proportion of patients with confirmed 3- and 6-month EDSS progression was lower in HDA subgroups in CLARITY Ext compared to corresponding subgroups in CLARITY.

Conclusions: In CLARITY Ext, long-term sustainability of the clinical effect was observed in HDA patients who were treated with CT3.5 in CLARITY.

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Double-blind controlled randomised trial of plasma exchanges compared to sham-plasma exchanges in moderate to severe relapses of multiple sclerosis

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Introduction: Plasma exchanges have been proposed for treating severe relapses in inflammatory diseases of the central nervous system. No randomised controlled clinical trial has been performed so far in moderate to severe relapses in multiple sclerosis (MS)

Objective: To compare plasma exchanges (PE) to sham plasma exchanges (Sham-PE) in patients with a recent steroid resistant moderate to severe MS relapse.

Methods: Patients with relapsing-remitting MS presenting with a relapse since less than 2 months, without improvement 30 days after a course of at least 3 days of 1g methylprednisolone were randomized. Relapse type included optic neuritis, motor deficits, ataxia or oculomotor deficits. Specific criteria were used for each relapse type for defining moderate to severe disability. The primary endpoint was an assessment by investigators of improvement from 0 to 3 established after one month based on different objective criteria according to relapse type.

Results: 38 patients were randomised but 7 patients were not included in the analysis (6 no peripheral venous access, one patient in which the relapse was not confirmed). The ITT analysis included 14 patients in the PE group and 17 in the Sham-EP group. The relapse type was optic neuritis in 45.2% and motor deficit in lower limbs in 25.8%. Seven patients had a polysymptomatic relapse. 57.1% of patients in the PE group had moderate (level 2) to complete (level 3) improvement versus 47.1% in the Sham-PE group (p=0.57). Changes in objective assessments were described: in patients with optic neuritis, 83.3% of patients in the PE group had moderate (level 2) to complete (level 3) improvement versus 77.8% in the Sham-PE group (NS). No major side effect was observed.

Conclusions: No significant difference was observed between PE and Sham-PE in patients with moderate to severe relapses. An unexpected rate of improvement in the sham group may contribute to these results.

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Fingolimod therapy increases serum interleukin 7 levels without altering peripheral homeostatic proliferation in multiple sclerosis patients

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Introduction: The sphingosine-1-phosphate (S1P) receptor modulator fingolimod (FTY) induces a steady peripheral lymphopenia by sequestering lymphocytes, particularly T cells, into secondary lymphoid organs.

Objectives: The influence of FTY-induced lymphopenia on peripheral T cell homeostatic regulations is largely unknown.
Aims: We aimed to analyze the influence of FTY and FTY-induced lymphopenia in the regulation of the homeostatic cytokine interleukin 7 (IL-7) and its effects on homeostatic proliferation of peripheral T cells.
Methods: Therefore, we assessed recent thymic emigrants (RTE), serum levels of IL-7 and its receptor CD127 (IL-7Rα) and homeostatic T cell proliferation *ex vivo* in peripheral blood of multiple sclerosis (MS) patients before and during FTY therapy.
Results: We observed a decrease in the proportion and number of RTE as well as of surface expression of CD127 (IL-7Rα) on T cells and an increase in serum IL-7 levels in FTY-treated MS patients. Serum IL-7 levels inversely correlated with the degree of lymphopenia and T cell surface CD127 (IL-7Rα) expression, whereas unexpectedly no change in homeostatic proliferation of T cells was observed during FTY therapy.
Conclusions: In consequence, FTY-treated T cell compartments might be less responsive to IL-7 stimulation and FTY might therefore interfere with regulation of homeostatic proliferation and homeostatic replenishment of T cell numbers, thereby fostering a steady peripheral lymphopenia in FTY-treated MS patients.

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Autologous stem cell transplantation in multiple sclerosis: the London experience

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Introduction: There is accumulating evidence for the efficacy of autologous haematopoietic stem cell transplantation (AHSCT) in multiple sclerosis (MS). Here we describe findings from the Pan-London AHSCT group audit.
Methods: Retrospective audit of AHSCT performed as treatment for MS in 3 London centres during 2012-2017 of all cases with >6 months follow-up. Patient selection has evolved but eligibility criteria emphasised evidence of recent MRI inflammatory lesion activity and, in patients with relapsing MS (RMS), prior failure of treatment with a high-efficacy disease modifying treatment (HEDMT).
Results: Of 54 patients, 55.6% had RMS, 33.3% had secondary progressive MS and 11.1% primary progressive MS. Median age at AHSCT was 41.4 (22-58). 75% of the RMS group had failed a HEDMT. Median number of previous DMTs was 2 (0-5). Median baseline EDSS was 6 (2.0-8.0); median time from diagnosis to AHSCT was 8 years (1-19). Median inpatient stay for transplant was 22 days (17-81). Common complications were bacterial infection (53.8%), fluid overload (61.5%) and EBV reactivation (65.4%). 12 patients (22.2%) required re-admission following the procedure with a median length of stay of 9 days (3-119). 88% of patients were free from disability worsening 36 months post-transplant. 5 patients (9.3%) developed MRI lesions post AHSCT with a median time to development of 21 months (6-78). Of the RMS patients, 5 (16.7%) experienced symptoms consistent with a clinical relapse post AHSCT at a median time of 11 months (6-12); however only one of these patients demonstrated concomitant new lesions on MRI. There was no treatment-related mortality in this cohort.
Conclusion: In this non-trial setting with a varied patient population the results are consistent with previously reported cohorts. AHSCT requires further investigation as treatment in highly active/progressive MS.

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P568

The POINT study: a randomized, double-blind, parallel-group, add-on, superiority phase 3 study to compare the efficacy and safety of ponesimod to placebo in subjects with active relapsing multiple sclerosis who are treated with dimethyl fumarate

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Objectives: The POINT study aims to evaluate the safety and efficacy of ponesimod as add-on treatment to dimethyl fumarate (DMF) in patients with relapsing multiple sclerosis (RMS).
Introduction: Despite recent advances in the treatment of RMS, an unmet medical need remains to improve long-term disease control without compromising patient safety. Targeting RMS treatment with a combination of compounds that have different mechanisms of action may reduce disease activity to a level not achieved by any agent alone. Ponesimod, a novel, selective and rapidly reversible sphingosine-1-phosphate receptor modulator, has shown beneficial effects in a Phase 2 study and is currently in Phase 3 clinical development for RMS. Ponesimod acts by sequestering lymphocytes in lymphoid organs, thus reducing their circulation to the brain. DMF exhibits anti-inflammatory and potentially neuroprotective, anti-oxidative effects via inhibition of NF-κB and activation of Nrf-2. In preclinical studies, the combination of ponesimod with DMF showed improved efficacy versus each agent alone without increased toxicity. POINT is the first ever Phase 3 study in RMS where an oral investigational compound is added to oral background therapy approved for RMS.
Methods: Approximately 600 subjects with RMS who have signs of disease activity under ongoing treatment with DMF will be randomized 1:1 to ponesimod 20 mg or placebo as add-on treatment to DMF. Double-blind treatment will continue until the last subject enrolled has been treated for 60 weeks. Key eligibility criteria include a diagnosis of RMS, at least 6 months of ongoing treatment with DMF, stable lymphocyte counts above 800 cells/mm^3, and documented clinical and/or MRI disease activity within 12-15 months of screening. The primary efficacy endpoint is the annualized relapse rate, defined as the number of confirmed relapses from randomization to the end of study. Other outcome measures include clinical and MRI disease activity, fatigue, as well as safety and tolerability. Details of the study design and study status will be presented.
Results: Enrolment began in February 2017 and is ongoing.
Conclusion: POINT, as the first Phase 3 study investigating the combination of two oral compounds with different modes of action addressing relevant targets in the pathogenesis of MS, will provide valuable information about possible additive or even synergistic efficacy and the safety of this new treatment concept for RMS.

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Hypothesis: chronic progression of MS results from activity of LLPCs even after aggressive B-cell depletion therapy

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Evidence suggests LLPCs in the CNS of patients with MS contribute to the propagation and perpetuation of disease.
The plasmablasts that origínate in the secondary lymphoid nodules have the ability to migrate to the bone marrow or to inflamed tissue, where they compete for niches that provide a suitable environment for subsequent survival as long lived plasma cells (LLPCs). LLPCs are not cycling cells and they are responsible for antibody secretion. LLPCs identified in the niches of the bone marrow are $CD19^{-}CD38^{high}CD138^{+}CD28^{+}HLA\text{-}DR^{low}CD56^{+/-}CD95^{low}$ ↑BCL2 ↓Ki67. Non-proliferating CD 138+ (Ki67-) plasma cells have been found in the cerebral parenchyma, meninges and perivascular spaces of patients with MS, suggestive of LLPCs. Survival of LLPCs depend on the presence of APRIL, IL-6 and CXCL12 in specialized niches.
Reviewed medical literature related to the role of LLPCs in oligoclonal bands production and to the different outcomes of determination of oligoclonal bands in CSF from patients with MS after exposure to different immunotherapy.
Remarkable findings were reported in 1) a patient with RRMS with a clinical course refractory to therapy with beta interferon, subsequently found to be responsive to rituximab but ultimately developing SPMS with significant lesion load in the spinal cord. Oligoclonal bands were positive in CSF during the whole course of disease. 2) Negative oligoclonal bands in CSF among 55% of 24 MS patients who were treated with natalizumab for 24 months. 3) The persistence of CSF oligoclonal bands among 88% of SPMS patients treated with autologous stem cell transplant that included immunoablative conditioning regime with antithymocyte globulin (ATG), cyclophosphamide and total body irradiation.
LLPCs in the CNS compartment have the ability to produce antibodies for very long periods of time, resulting in perpetuation of oligoclonal bands production, and they are resistant to the any therapeutic attempt (systemic or intrathecal) with B-cell depleting therapy. Potential therapeutic strategies to ameliorate presence and effect of LLPCs in MS could include lenanidomide, a potent anti-inflammatory thalidomide analog that has been able to inhibit LLPCs in vitro. Additional therapeutic alternatives may include the use of ATG, proteasome inhibitors, targeting survival factors, targeting plasma cell homing, and targeting cell surface molecules.

Disclosure

Dr. Mora is a member of the Data & Safety Monitoring Board for the NINDS/NIH study NS003055-08/NS003056-08. He received no compensation for his participation in that study. ACL does not report any competing interests.

P570

Effects of real life use of oral disease modifying treatments for relapsing-remitting multiple sclerosis in Austria over one year

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Data Management, [7]Hermesoft, Statistics, Graz, [8]Clinical Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Objectives: To compare the efficacy, frequencies and reasons for treatment interruption of fingolimod (FTY), dimethyl fumarate (DMF) or teriflunomide (TERI) in a nationwide observational cohort using prospectively collected data.
Materials and methods: Two cohorts of patients with relapsing-remitting multiple sclerosis (RRMS) starting treatment with fingolimod, dimethyl fumarate or teriflunomide documented in the Austrian MS Treatment Registry (AMSTR) since 2014 and either staying on therapy for at least 12 months (12m cohort) or having at least one follow-up visit (total cohort). The 12m cohort included 664 RRMS patients: 315 in the fingolimod, 232 in the DMF and 117 in the teriflunomide group. Multinomial propensity scores were used for inverse probability weighting to correct for the bias of this non-randomised registry study.
Results: Estimated mean annualized relapse rates (ARR) over 12 months were 0.21 for fingolimod, 0.20 for DMF and 0.19 for teriflunomide treatment, causing an Incidence Rate Ratio (IRR) of 1.01 for fingolimod versus DMF (p=0.96) and 0.92 for teriflunomide versus DMF (p=0.84). No differences were found regarding the probability for experiencing a relapse, EDSS change, EDSS progression and EDSS regression, except regarding less sustained EDSS progression for 12 weeks concerning DMF versus fingolimod (p=0.02). The hazard ratio for treatment interruption comparing fingolimod versus DMF was 1.03 (p=0.86) and 1.07 comparing teriflunomide versus DMF (p=0.77).
Conclusions: In the AMSTR, there was no difference concerning ARR, probability for a relapse, EDSS change, treatment interruption, EDSS progression or regression between oral DMTs, except regarding less sustained EDSS progression for 12 weeks concerning DMF versus fingolimod.

Disclosure

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Stefan Kalcher declares that there is no conflict of interest.
Erich Kvas declares that there is no conflict of interest.
Thomas Berger has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Almirall, Bayer, Biogen, Biologix, Bionorica, Genzyme, MedDay, Merck, Novartis, Octapharma, Roche, Sanofi/Genzyme, TG Pharmaceuticals, TEVA-ratiopharm and UCB. His institution has received financial support in the last 12 months by unrestricted research grants (Biogen, Bayer, Merck, Novartis, Sanofi/Genzyme, and TEVA ratiopharm) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Bayer, Biogen, Merck, Novartis, Octapharma, Roche, Sanofi/Genzyme, and TEVA.

P571

Clinical trials of disease-modifying agents in pediatric MS: opportunities, challenges and recommendations from the International Pediatric MS Study Group (IPMSSG)

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Background: Biological processes involved in MS are largely shared across the age span. Despite a high relapse frequency in pediatric MS, very few drugs have been tested in that age group limiting the availability of safety and efficacy data. A randomized controlled phase 3 trial was completed in 2017 and 2 other phase 3 trials are ongoing. However, phase 3 trials for every newly approved DMT for adult MS are simply not feasible in children. Consideration should be given as to the best means to confirm efficacy and optimize safety for pediatric use.
Objective: To develop consensus recommendations for clinical trial designs that can deliver high quality data in pediatric MS patients.
Methods: The IPMSSG Steering Committee convened a meeting of experts in January 2018 to review the advances over the past six years in the understanding of pediatric-onset MS and issues faced in completed or ongoing clinical trials in that population.
Results: Challenges with recruitment, retention, study visits and choice of a control arm were identified that were specific to clinical trials in pediatric MS. The group considered how to improve study design and conduct based on specificities in this age group. Appropriate trial options for various categories of drug to be studied in pediatric MS were identified to address recruitment issues and avoid "ghost trials". The group agreed that clinical trials in

children with MS must consider pediatric-specific safety concerns both during the trial and in longer term open-label observation. IPMSSG Steering Committee recommendations will be presented regarding strategies for achieving these objectives, as well as endorsement of these recommendations by the IPMSSG membership.

Conclusions: These recommendations aim to ensure high quality evidence-based treatment for children and adolescents with MS to reduce reliance on off-label use, increase safety data and remove regulatory or insurance-based limitations in access to treatment.

Disclosure

Emmanuel Waubant has not received any pharmaceutical company honorarium. She is site PI for a Novartis and Roche trial and has volunteered on an advisory board for a Novartis trial. She is a non-remunerated advisor for clinical trial design to Novartis, Biogen-IDEC, Sanofi, Genentech, Serono and Celgene. She has funding from the NMSS, PCORI and the Race to Erase MS. She is the section editor for Annals of Clinical and Translational Neurology, and co-Chief editor for MSARD.

Brenda Banwell has served as a central MRI reviewer for Novartis. Dr. Banwell serves as a non-remunerated advisor on clinical trial design for Novartis, Biogen-IDEC, Sanofi and Teva Neuroscience.

Evangeline Wassmer has served as a consultant for Novartis and Biogen, She is an investigator in trials with Biogen Idec, Sanofi and Novartis. Her MS research projects have been funded by the UK MS Society, Action Medical Research and Birmingham Children's Hospital Research Foundation Maria Pia Sormani has received consulting fees from Biogen, TEVA, Merck, Novartis, Genzyme, Roche, Medday, GeNeuro, Actelion, Celgene

Maria Pia Amato has served on advisory boards for Biogen, Byer, Novartis, Merk, Teva, Sanofi- Genzyme, Roche and has received financial support for research activities from Biogen, Merk, Teva, Sanofi- Genzyme. She has received research grants from the Italian MS Society.

Rogier Hintzen has received honoraria for serving on advisory boards for Biogen Idec, Roche, Sanofi. He participated in trials with BiogenIdec, Merck-Serono, Roche, Genzyme and Novartis

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Silvia Tenembaum serves as a non-remunerated editorial board member of *Neurology: Neuroimmunology & Neuroinflammation*. She has received speaker honoraria from Biogen-Idec Argentina, Merck Serono LATAM, Genzyme, Novartis, and Teva Neuroscience. Tanuja Chitnis has served on the advisory boards for clinical trials for Novartis and Sanofi-Genzyme. She has received compensation for advisory/consulting boards for Biogen, Novartis and Sanofi-Genzyme. She has received financial support for research activities from Merck-Serono and Verily.

P572

Treatment with alemtuzumab after fingolimod in relapsing-remitting multiple sclerosis is effective and safe

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Background: It has been described that treating relapsing-remitting multiple sclerosis (RRMS) patients with alemtuzumab following fingolimod could be less effective due to the different dynamics of lymphocyte repopulation. Effectiveness and safety of alemtuzumab compared to a cohort of RRMS patients treated with rituximab after fingolimod withdrawal were analysed.

Patients and methods: A prospective follow-up of a cohort of RRMS patients of two MS Units in Valencia (Spain) treated with alemtuzumab or rituximab after fingolimod withdrawal was accomplished. Effectiveness, measured by the percentage of patients with no evidence of disease activity (NEDA), and the presence of side effects were registered.

Results: A total of 55 patients, 28 with alemtuzumab and 27 with rituximab were analysed. No differences in the washout period (median (interquantile range); alemtuzumab: 42 days (21.3-59.5); rituximab: 34 days (17.3-61.3); p=0,49) or in the number or lymphocytes before starting the new treatment (median (interquantile range); alemtuzumab: 1310 (815-1670); rituximab: 1100 (665-1580); p=0,44) were observed. After a mean follow-up period of 28.8 months (SD: 18), the annualized relapsing rate was significantly reduced in the alemtuzumab group from 1.29 to 0.004 ($p< 0.001$) and in the rituximab group from 1.24 to 0.02 ($p< 0.001$), without differences between groups. After one year of follow-up, a significant reduction of the median EDSS (interquartile range) from 2.8 (2-3) to 2.0 (1.5-2.5) (p=0.03) in the alemtuzumab group and from 3.5 (2-4) to 2.5 (2-4) ($p< 0.01$) in the rituximab group were observed; these reductions remained stable after the second year, without statistical differences between both groups. Eighty-two per cent (n=28) of patients in alemtuzumab group and 70% (n=27) in rituximab group achieved NEDA criteria, without differences (p=0.3). Symptoms related to the infusion were the most frequent side effect in both groups. No serious side effects were registered in any group.

Conclusion: Treating RRMS patients with alemtuzumab or rituximab after fingolimod withdrawal is effective and safe, without significantly differences between both groups. Previous treatment with fingolimod did not negatively influence response to alemtuzumab in our series.

Disclosure

We declare not conflict of interest

P573

Patient initiation of fingolimod treatment in clinics and in the Gilenya@Home Program: baseline heart rate data for the first-dose adverse cardiac effects subgroup

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Introduction: Largely asymptomatic, decreased transient heart rate (HR) is an expected pharmacodynamic effect of fingolimod (Gilenya®) initiation; heart block may also rarely occur. US prescribing information requires first-dose observation (FDO) of HR and blood pressure for ≥6 hours in patients initiating fingolimod. FDO can be conducted in clinics; with the Gilenya@Home program, most US patients initiate fingolimod at home.
Objectives: Assess if low baseline HR before initiating fingolimod was an indicator of adverse events (AEs), such as second-degree atrioventricular (2°AV) block, emergency room (ER) monitoring or documented bradycardia.
Methods: Retrospective, anonymized patient FDO data were collated from Gilenya@Home (Oct 2014-Jul 2017) and Gilenya assessment network clinics (Jul 2010-Dec 2016). Extended monitoring was conducted per product label or if HR was ≤45 beats per minute (bpm) at 6 hours. Patients attended the ER for overnight monitoring, if required. Pre-dose baseline HR was assessed retrospectively for patients initiating fingolimod in-home or in-clinic who had new-onset 2°AV block, ER monitoring or documented bradycardia.
Results: Data were collated for 5572 in-home visits and 15,025 in-clinic FDO procedures. Baseline HR (mean±standard deviation) was similar for the overall groups of patients initiating fingolimod in-home and in-clinic (74.8±12.2 bpm vs 74.2±11.4 bpm). Baseline HRs for in-home patients with 2°AV block (74.3±13.7 bpm; n=4 [0.1%]) or who attended the ER (70.4±13.4 bpm; n=15 [0.3%]) were similar to the HR for the overall in-home group. Baseline HRs for in-clinic patients with 2°AV block (76.8±8.4 bpm; n=9 [0.1%]) or who attended the ER (73.4±12.8 bpm; n=129 [0.9%]) were similar to the HR for the overall in-clinic group. Baseline HRs for in-home and in-clinic patients with documented bradycardia (64.4±8.1 bpm; n=20 [0.4%] and 65.3±12.4 bpm; n=10 [0.1%], respectively) were lower than the HRs for the respective overall groups.
Conclusions: Pre-first dose baseline HR for patients who had 2°AV block or attended the ER fell within the overall population range, but were lower for those with bradycardia, whether in-home or in-clinic. These data provide further evidence that first-dose AEs with fingolimod occur in a low percentage of patients, regardless of clinical setting. Analysis of individual-level data may determine whether there is a pre-dose HR threshold below which first-dose adverse cardiac effects are more likely.

Disclosure

John Osborne, medical director of the Gilenya@Home program, has received honoraria for educational programs that he has provided on behalf of Novartis as well as consultation fees for Gilenya@Home. Brandon Brown, Xiangyi Meng, Nina Jaitly, Wendy Su and Jamie Weiss are employees of Novartis Pharmaceuticals Corporation.

P574

Establish tolerence in MS with myelin-peptide coupled red blood cells - ETIMS^{red}trial

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Background: Induction of antigen-specific tolerance can be viewed as the most direct and specific means of correcting an altered and pathogenic immune response, which underlies many organ-specific autoimmune diseases. Compared to unspecific immunomodulatory or immunosuppressive interventions, which are currently used in all autoimmune diseases, antigen-specific therapies have the advantage to solely affect the aspects of the immune system responsible for the pathologic effects, without altering physiological immune responsiveness. We have developed a therapeutic regimen employing autologous blood cells chemically coupled with myelin peptides to induce antigen-specific tolerance in MS. The myelin peptides from three different myelin proteins myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) and proteolipid protein (PLP) were previously identified as important target antigens in MS. Following a successful first-in-man trial with myelin peptide coupled PBMC in MS patients (1) we have optimized the approach further using red blood cells (RBCs) as tolerogenic carrier cells.
Objective: We test the safety and tolerability of autologous RBCs coupled with 7 myelin peptides (MBP_{83-99}, MBP_{13-32}, $MBP_{111-129}$, $MBP_{146-170}$, $PLP_{139-154}$, MOG_{1-20} and $_{MOG35-55}$) in a phase Ib clinical trial in MS patients.
Result: Overall, ten relapsing-remitting and secondary-progressive MS patients will be treated in a dose escalation study to receive up to $3x10^{11}$autologous myelin-peptide coupled RBCs. All patients have shown T cell reactivity against one or several of these peptides prior to the treatment. The trial is accompanied by mechanistic studies to assess *in-vivo*immunological effects of the therapy.
Conclusion: In summary we report the safety and tolerability of a novel therapeutic approach in MS aiming at antigen specific immune tolerance.
Bielekova et al. J Immunol 2004, Lutterotti et al. Sci Transl Med 2013

Disclosure

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A. Lutterotti
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Co-inventor on a patent held by the University of Zurich on the use of peptide-coupled cells for treatment of MS.
R. Martin
Received unrestricted grants from Biogen and Novartis. Received financial compensation for lectures and advisory tasks from Biogen, Merck, Novartis, Roche, Teva, Genzyme, Neuway and CellProtect. R. Martin is a co-founder/-owner of Cellerys. R. Martin has received royalties for an NIH-held patent on the use of daclizumab in MS.
All other authors have nothing to disclose

P575

Inhibition of Bruton's tyrosine kinase selectively prevents antigen-activation of B cells and ameliorates B cell-mediated experimental autoimmune encephalomyelitis

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Background: The role of B cells as key mediators of inflammatory processes in multiple sclerosis (MS) has been increasingly recognized in the recent years. This notion was substantiated by the recent success of pan B cell depletion by anti-CD20 monoclonal antibodies. This however, not only targets pathogenic B cells but can also affect regulatory B cell properties. An alternative strategy may be the therapeutic abrogation of pro-inflammatory B cell functions by Bruton´s tyrosine kinase (BTK) inhibition. BTK is centrally involved in B cell receptor signaling and subsequent activation and differentiation of B cells. BTK inhibition (BTKi) could thereby be a promising strategy to control pathogenic function, such as antigen presentation and release of pro-inflammatory cytokines, while leaving regulatory B cell properties unaffected.
Methods: Daily oral treatment in C57Bl/6 mice with the BTK inhibitor evobrutinib (M2951) at three doses or vehicle control started 7 days prior to immunization. Mice were immunized with conformational MOG 1-117 protein, a model of experimental autoimmune encephalomyelitis (EAE) in which B cells can directly recognize the immunogen. EAE severity was assessed daily using a standard scale (0-5). Histopathology was performed at day 60 after immunization. Flow cytometry of activation markers on B cells, T cells and myeloid cells as well as analysis of the B cell phenotype was performed at day 12 after immunization. Intra-cellular calcium flux analysis was performed *in vitro* or after 3 days of BTKi treatment *ex vivo* using Fluo-3 and Fura Red calcium-sensitive dyes and anti-IgM B cell receptor (BCR) stimulation.
Results: The intermediate and highest dose of BTKi showed an amelioration of EAE severity throughout the 60-day observation period. Supporting these findings, BTKi reduced CNS inflammation and demyelination. BTKi treatment led to an accumulation of naïve B cells with a corresponding reduction of antigen-activated B cells. The expression of activation markers CD80, CD86, CD69 and MHCII was significantly reduced on B cells treated with evobrutinib. B cell receptor stimulation lead to reduced calcium influx in BTKi treated B cells *in vitro* and *ex vivo*.
Conclusion: BTKi reduces the influx of excitatory calcium in B cells upon BCR stimulation preventing their activation and conversion from naïve to antigen-activated B cells. This translates into reduced CNS inflammation and clinical amelioration in a B cell-mediated EAE model.

Disclosure

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P576

Real-world experience of the effectiveness, safety and tolerability of dimethyl fumarate in Barts Health MS cohort

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Introduction: Dimethyl fumarate (DMF) is a licensed oral disease modifying therapy (DMT) approved by the National Institute for Health and Care Excellence (NICE) for relapsing multiple sclerosis (RMS), with a favourable efficacy and safety profile established in phase III clinical trials.
Objectives: To evaluate real-world data and prevalence of lymphopenia in people with multiple sclerosis (pwMS) treated with DMF in a specialist London multiple sclerosis centre.
Methods: Retrospective analysis of 280 pwRMS treated with DMF at the Royal London Hospital with a minimum of three month follow-up data. Demographic, laboratory and clinical information, regarding MS history and follow-up, was extracted from the BartsMS database and patient's medical records.
Results: 280 pwMS were included (67% female; mean age: 39.8±10.2 years). Mean disease duration was 8.9±6.2 years. 55% pwMS were treatment naïve. 42% and 3% switched from first and second line DMTs respectively. The mean duration of DMF exposure was 21.5±11.5 months. The discontinuation rate was 36%. 38 pwMS (14%) discontinued due to adverse events. Most frequent adverse events were lymphopenia (n = 18), mild gastrointestinal side-effects and flushing (n = 8), proteinuria (n = 2) and alopecia (n = 2). 31 pwMS (11%) discontinued due to disease activity and 30 (11%) due to patient's own wish. In 192 pwMS (69%), absolute lymphocyte counts (ALC) were within normal limits at all post-baseline visits (CTCAE/ Common Terminology Criteria for Adverse Events grade 0). 88 pwMS (31%)

experienced lymphopenia, which was sustained for ≥3 months in 47 pwMS (53%). Mean duration of lymphopenia was 281.4±185.2 days. The incidence of grade I and II post-baseline CTCAE grade I and II lymphopenia was 41 (15%) and 40 (14%) respectively. 7 pwMS (2.5%) had CTCAE grade 3 lymphopenia. CTCAE grade 4 lymphopenia was not experienced by any pwMS. Persistent (>3months) lymphopenia (post-cessation of DMF) was experienced by 15 pwMS (5%). ALCs recovered over time following discontinuation of DMF. Mean baseline EDSS was 2.3±1.5 (range = 0 - 6.5 in 118 pwMS). At one year of follow-up, 86% of pwMS were relapse free and 9 pwMS (3%) had MRI activity. No new safety signals were identified.

Conclusions: Our real world observational data confirms the low discontinuation rate due to adverse events from the pivotal clinical trials, however lymphopenia was more frequent than in these original studies.

Disclosure

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Klaus Schmierer has been a PI of trials sponsored by Medday, Roche and Teva and involved in trials sponsored by Biogen, Sanofi-Genzyme, Novartis and Canbex.

Ben Turner has received travel bursaries, grants and advisory boards fees from Biogen, Roche, Sanofi-Aventis, Novartis and Merck.

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Evidence-based patient information handbooks on immunotherapies - a nationwide German project

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Background: With an availability of 17 different treatment options, people with multiple sclerosis (PwMS) face complex decisions on immunotherapies. Their right on evidence-based patient information as a decisional base is legally and ethically justified and PwMS prefer an active role in the decision-making process. The objective of this joint project of the German competence network MS (KKNMS) and the MS society (DMSG) is to develop handbooks on all immune-therapeutic treatment options for PwMS.

Methods: The development follows the criteria of evidence-based health information and the first handbook on Tecfidera® serves as a blueprint respective structure, layout, content and graphics. Every handbook consists of an introduction to the drug, information on risk reduction of relapses and progression, MRI, side-effects and monitoring, Information is summarized by a drug fact box and there is an overview on all treatment options. The development goes along in close collaboration with consumer representatives, authors of the corresponding physician handbook, the management boards of the KKNMS and DMSG, the national board of PwMS and the respective pharmaceutical company. Previously developed figures on absolute risk reduction (ARR) were modified and tested with PwMS as well as newly developed figures on relative risk reduction (RRR) and side effects. Two focus groups, one with neurologists and one with PwMS were conducted to explore the handbooks' feasibility. Currently, 4 handbooks are in print (each run 10,000) and will be handed out together with an evaluation sheet to PwMS in June 2018.

Results: Patient (n=29) feedback led to a change in colour of the ARR-figure and figures on RRR and side-effects were revised multiple times. Feedback of the boards was generally positive. Members of the neurologist focus group (n=5) were rather critical, as they expressed, that it was too much and too complex information. On the other hand, participants of the PwMS-focus group (n=3) found it comprehensive and considered it a viable decision making-aid. The ongoing quantitative survey evaluation of the first 4 Germanwide disseminated handbooks will provide data on the acceptability and understandability.

Conclusions: The handbook might support PwMS in making informed decisions in accordance with personal preferences. Further evaluation data will be presented at the conference.

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Neuroprotection and Repair

P578

An increase in chemokine, CXCL1 with ERβ ligand treatment potentially stimulates axon myelination in a mouse model of multiple sclerosis

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Current therapeutics reduce relapse rates in multiple sclerosis (MS) patients but fail to reverse or prevent neurodegeneration or initiate repair/remyelination. Different ERβ ligands diarylpropionitrile (DPN), WAY 202041 (WAY), chloroindazole (IndCl) all

demonstrate remyelination but with differential immune effects on experimental autoimmune encephalomyelitis (EAE). The superior role of IndCl as an immunomodulatory, pro-myelinating, and neuroprotective agent in MS models prompted the development and screening of several novel IndCl analogues. Two analogues, STW-1 and STW-2 displayed similar efficacy to IndCl and were selected for their impact on clinical disease course, and disease pathology. These compounds ameliorated disease severity, increased oligodendrocyte (OL) numbers and enhanced myelination in the corpus callosum. To investigate a potential common immune mechanism for ERβ ligand-mediated remyelination, leukocyte populations and secreted cytokines/chemokines were analyzed from mice treated with one of several ERβ ligands from EAE onset to peak disease. Nearly all ERβ ligands tested, reduced peripheral levels of OL toxic IFNγ and C-X-C motif ligand 10 (CXCL10) and enhanced chemokine CXCL1 intensity on astrocytes in spinal cord of EAE mice. CXCL1 has been shown to stimulate OL progenitor cell (OPC) migration, proliferation, and differentiation, and has been shown to be upregulated during pro-inflammatory conditions by IL-1β and TNFα. CXCR2 receptor, the primary receptor for CXCL1, is critical for developmental OPC positioning and differentiation in the CNS. Supernatant collected from primary astrocyte cultures stimulated with IL-1β contained increased levels of CXCL1. The same supernatant was added to OL cultures and induced an accelerated cell differentiation. OL primary cultures, in the presence of CXCR2 antagonist, SB 225002 and IL-1β astrocyte conditioned media, showed decreased OL differentiation and enhanced OL apoptosis. The present study indicates an interplay between the peripheral and central immune systems that involves ERβ ligands modulation of the cytokine and chemokine milieu to promote repair/remyelination. The results presented here offer new possibilities for promising and selective MS treatment options to achieve functional recovery from MS disease.

Disclosure

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P579

Clean-surfaced, faceted gold nanocrystals stimulate the differentiation of oligodendrocyte precursor cells by up-regulating genes involved in oligodendrocyte myelination

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Chronic multiple sclerosis (MS) lesions contain significant numbers of quiescent oligodendrocyte precursors cells (OPCs). The failure of these OPCs to differentiate into mature oligodendrocytes and subsequently remyelinate neurons within MS lesions is believed to contribute to the progression of the disease. Therefore, one therapeutic strategy to address demyelination, and ultimately axonal loss, in multiple sclerosis is to stimulate OPC differentiation into mature OLs to enable remyelination.
We have developed a novel electro-crystallization method that produces clean-surfaced, faceted gold nanocrystals in aqueous suspension. Our previous work demonstrated the therapeutic value of oral administration of these gold nanocrystals (CNM-Au8) in the *in vivo* cuprizone and lysolecithin demyelination animal models. To further characterize the effect of CNM-Au8 on OPC differentiation, we conducted an *in vitro* RNAseq expression study using isolated, purified OPC cultures, with each treatment condition performed in triplicate. Here we show that 1 μg/mL and 10 μg/mL CNM-Au8 treatment of mouse OPCs in primary culture for 72 hours results in differential expression (DE) of genes involved in myelination. Markers of oligodendrocyte (OL) maturation such as *MAG*, *MBP, GJC2*, *NKX6.2*, and *SOX10* mRNAs were elevated at least 2-fold over untreated vehicle controls. We conducted Multidimensional Scaling Analyses to examine distances between samples according to their gene expression profiles. These analyses demonstrated that CNM-Au8-treated OPC expression profiles were more similar to the expression profile of differentiated OLs treated with a promoter of OPC differentiation, triiodothyronine (T3), than to the profile of proliferating OPCs treated with platelet derived growth factor (PDGF). Furthermore, there was an enrichment of mRNA transcripts with gene ontology terms related to lipid metabolism uniquely present in the DE gene profile for CNM-Au8-treated OPCs. These included a panel of genes encoding proteins involved in long chain fatty acid synthesis, which is essential to the generation of lipids that comprise ~70% of myelin. In contrast, the DE gene profiles for the T3 and PDGF controls did not demonstrate enrichment in long chain fatty acid synthesis mRNAs. Taken together, these data demonstrate that treatment with CNM-Au8 promotes OPC differentiation and OL maturation. CNM-Au8 represents a promising potential remyelinating treatment for demyelinating disorders such as MS.

Disclosure

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P580

Efficacy of dimethyl-fumarate in preventing grey matter pathology in multiple sclerosis

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Introduction: Despite the evidence of the efficacy of dimethyl-fumarate (DMF) as disease modifying drug in multiple sclerosis (MS), no data are so far available about its effect on focal and diffuse gret matter (GM) pathology.
Objective: In this study we evaluate in a large population of relapsing remitting MS (RRMS) patients, the safety and efficacy of DMF having particular attention to GM parameters
Methods: We conducted a longitudinal 2-year, prospective, single blind study including 199 patients with relapsing-remitting MS treated with DMF. Each subject underwent a neurological examination with EDSS evaluation every 6 months and a 3T-MRI at baseline and after 12 and 24 months. The images were processed by MIPAV-software to detect the cortical lesion load and by FreeSurfer-software to establish the regional cortical thickness. We also evaluated the percentage brain volume change (PBVC) by means of SIENAX. The annualized relapse rate, the appearance of new white matter and new Gad+ lesions, the occurrence of severe adverse events including severe lymphopenia and the quality of life were also recorded. In addition, 40 untreated patients were enrolled in the study as reference population.
Results: Number of relapses and new T2 lesions observed in the treated patients were in line with literature data. New or enlarged CLs were observed in 22.0% treated and 48.7% untreated patients ($p=0.009$). The number of new CLs was lower ($p< 0.001$) in the treated group (0.2±0.3; 0.0-2.0) compared to untreated group (2.9±1.8; 2.3-3.5). At T24 the PBVC was significantly ($p< 0.001$) lower in the DMF treated group (0.36±0.08%,). The regional analysis revealed, in the untreated group, a more pronounced cortical thinning in several regions including hippocampus, cingulate, insula and superior frontal gyrus. The EDSS change was significantly higher (one tail $p< 0.01$) in the untreated (mean= 1.4±0.7; 0.0-2.5) compared to the treated group (mean= 0.2±0.3; 0.0-1.0). Eleven treated patients dropped out for disease activity (new or enlarging lesions, relapses or disability progression), 3 patients for persisting severe side effects, 4 patients for persisting severe lymphopenia and finally 4 dropped out wishing a pregnancy. No severe adverse events were observed.
Conclusion: Aside the high safety and tolerance, these results suggest a robust effect of DMF on both WM and GM pathology, possibly by delaying and/or halt progression of focal and diffuse GM damage.

Disclosure
Zuco Carmela: nothing to disclose

P581

Circulating T cells of fingolimod treated patients with MS secrete an increased BDNF levels

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Background: Albeit the detrimental effect of CNS infiltrating immune cells in MS, they may also possess a neuroprotective activity through secretion of neurotrophins such as brainderived neurotrophic factor (BDNF). The human cellular source of the BDNF include immune cells, such as T cells, B cells and monocytes, beside the CNS cells. Fingolimod is an immunomodulator of the sphingosine 1-phosphate receptor, approved in RR-MS and able to slow disability progression and brain volume loss. We explored whether the selective effect of fingolimod on T cells egress from the lymph nodes, creates a favorable neuroprotective immune activity.
Methods: A longitudinal one-year follow up of 25 RR-MS patients initiating treatment with fingolimod was performed. EDSS=1.0-3.5. Disease duration= 1-9 years. Blood samples were collected at baseline (prior to fingolimod initiation), at 6 months and at 1 year. Due to the lymphopenic effect of fingolimod, PBMCs were separated into T cells and monocytes using MACS system (purity > 95%), in order to ensure that the same number of cells were cultured at all time-points. The levels of BDNF in the 24 hrs-supernatants were measured by ELISA and presented by mean±SEM. The differences between groups were tested by student´s t-test.
Results: BDNF levels were increased during treatment with fingolimod (average of 6 and 12 months) vs. baseline, both for the total PBMC (990.4± 160.4 pg/ml vs. 659.0±87.2 pg/ml, respectively, $p=0.048$) and the separated T cells (46.2 ±15.6 pg/ml vs. 6.3±3.8 pg/ml, respectively, $p=0.008$). No significant differences were found in the supernatant´s BDNF levels of monocytes between those that were taken during treatment vs. baseline 68.9±23.7 pg/ml vs. 96.8±49.1 pg/ml. At baseline monocyte secreted higher BDNF levels than T cells ($p=0.049$). This difference disappeared during therapy ($p=0.44$). No differences were found in BDNF levels between unstimulated cells and stimulation with antiCD3/CD28 for T cells and LPS for monocytes and between levels at 6 and 12 months after fingolimod installation.
Discussion: Treatment with fingolimod significantly increases BDNF secretion from immune cells and especially from T cells. This effect was independent of the signal I and II stimulation of T cells. This effect may contribute for the neuroprotective effect of this therapy as manifested by slowing down brain atrophy. Our results discover an unreported aspect of the mechanism of fingolimod in RR-MS.

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P582

Sigma 1 receptor and melanocortin receptor agonists protect oligodendroglia from death induced by products of B cells from multiple sclerosis patients

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Objective: Determine if melanocortin receptor (MCR) and sigma-1 receptor (s-1R) agonists protect oligodendrocytes (OL) from cytotoxic factors released by B cells from patients with multiple sclerosis (MS).
Background: No disease modifying therapy for relapsing MS has been shown to directly protect OL/myelin. OL express MCRs *in vitro* that mediate the ability of adrenal cortical stimulating hormone (ACTH 1-39), a melanocortin, to protect OL and OL precursors (OPC) from mechanisms likely important in MS: excitotoxicity, reactive oxygen species, inflammation and apoptosis. Dextromethorphan (DM) and Anavex®2-73, s-1R agonists and weak NMDAR antagonists, protect OL and OPC from these same toxic stimuli. B cells from blood of MS patients, but not normals, release toxic factors/s that kill OL *in vitro* involving apoptosis. We sought to determine if ACTH, DM and Anavex2®-73 also inhibit OL death induced by products of MS B cells.
Methods: B cells were isolated by positive selection with anti-CD19 MACS beads. B cells were cultured without any *in vitro* stimulation, supernatants (Sup) harvested and frozen until testing. Glial cell cultures prepared from brains of neonatal rats contained OL, OPC, astrocytes and microglia. ACTH, DM, Anavex®2-73 or additional medium was added to glial cultures prior to adding B cell Sup. OL death was determined by trypan blue uptake.
Results: Sup from MS B cells were toxic to OL, those from normals were not. ACTH, DM and Anavex®2-73 all markedly inhibit OL death induced by MS B cell Sup. Antagonists of MCR or s-1R added prior to Anavex®2-73 reverse the ability to block B cell Sup mediated cytotoxicity.
Conclusions: ACTH, DM and Anavex®2-73 are able to inhibit B cell Sup mediated death of OL *in vitro.* Since there is progression and degeneration in many treated MS patients, development of agonists for MCR and s-1R are potential protective treatments for patients with MS.

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P583

Mir-219 enriched exosomes decrease experimental autoimmune encephalomyelitis symptoms after intranasal administration

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Introduction: Multiple sclerosis (MS) is a central nervous system (CNS) disease in which myelin is damage by an autoimmune attack. Although there are several treatments to modulate the immune system, remyelination promotors are not available. The use of microRNAs and more concretely hsa-miR-219, has been proposed as oligodendrocyte precursor cell differentiation mediator and therefore as a remyelination inductor. Nevertheless, the administration of the microRNA to the CNS is a tricky question and delivery systems, such as the use of exosomes are under study. Exosomes are 100 nm particles released by cells and implicated in the intercellular communication which carry proteins and genetic material.
Aims: The goal of this work is to address the ability of miR-219 enriched exosomes (Ex-219) to promote OPC differentiation in vitro and to induce remyelination in an animal model of MS, the experimental autoimmune encephalomyelitis (EAE).
Methods: Exosomes were isolated from HEK 293T cells which were previously infected with the pLKO1-miR219 plasmid. Exosomes were isolated with tangential flow filtration system and sequential centrifugation steps. Exosomes were characterized by Nanotrack Particle Analysis and Cryo-TEM. Droplet Digital PCR was used to quantify the cargo of miR-219 in the exosomes. Uptake and differentiation studies were performed in OPC primary cultures obtained from P2 C57BL/6 mice and analysed by confocal microscopy and qPCR respectively. MOG_{35-55} EAE induced model was used to determine the ability of exosomes to decrease clinical symptoms after intranasal administration of Ex-219. T11 Nuclear Magnetic Resonance was performed to characterize the EAE lesions. Animal procedures were approved by the pertinent ethical committee.
Results: Ex-219 overexpressed miR-219 with a FC=108 when compared to non-enriched exosomes (NE-Ex). OPC were able to up-take exosomes with a 63% of efficiency. Ex-219 increased the expression of myelin related genes in OPCs (MBP, PLP1, MOG and CNPase; FC>2) and decrease the EAE score after intranasal administration (AUC $p< 0.05$) when compared to NE-Ex and non-treated animals.
Conclusions: To conclude, Ex-219 are able to induce OPC differentiation in vitro and to decrease EAE score after intranasal administration. In addition, exosomes have shown to be a proper microRNA delivery system for CNS diseases. These results open

a promising and feasible remyelination therapy for MS and other neurodegenerative diseases.

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P584

Early treatment with Natalizumab prevents cortical gray matter atrophy: a two-year prospective study in relapsing-remitting multiple sclerosis patients

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Background: Natalizumab (Tysabri), a humanized monoclonal antibody directed against a4-b1 integrin, is a leading immunomodulatory drug for the treatment of relapsing-remitting multiple sclerosis (RRMS) and is currently evaluated in in patients with secondary-progressive disease course.
Objectives: To assess longitudinal effects of Natalizumab, a humanized monoclonal antibody directed against a4-b1 integrin, on cortical gray matter thickness and cognitive performance in relapsing-remitting multiple sclerosis (RRMS) patients.
Methods: A longitudinal prospective study. RRMS patients underwent 3.0T 3D high resolution brain MRI (Signa, GE) examination and comprehensive computerized cognitive assessment before initiation of Natalizumab and at 2 years of treatment, along with neurological assessments once every 3 months. FreeSurfer 5.3 was applied to obtain brain morphometrics and to perform paired, longitudinal, cortical thickness analyses.
Results: Sixty RRMS patients, 44 Females, 16 Males, age 36.3 ± 9.3 years, disease duration 8.4 ± 6.0 years, expanded disability status scale (EDSS) score 2.6 ± 1.5, were included. Following 2 years of Natalizumab treatment, cortical thickness of the left hemisphere was stable (-0.7%, p=0.15), while the right hemisphere cortical thickness significantly decreased (-1.3% p=0.006). Surface based analysis demonstrated focal clusters of cortical gray matter atrophy (CGMA) at the parietal and frontal regions bilaterally with cluster wise probability p< 0.01. Patients who started Natalizumab treatment early (≤7.5 years from onset) exhibited no CGMA while those who initiated the treatment late (>7.5 years from onset) exhibited significant CGMA in five focal clusters on the right hemisphere and in one cluster in the left hemisphere, p< 0.02. Under 2 years of Natalizumab treatment cognitive performance was stable with significant improvement in information processing speed score (+3.7%, p=0.011).
Conclusions: We identified an early therapeutic window that is important to prevent CGMA in Natalizumab treated RRMS patients.

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P585

Real-world effectiveness of MD1003 (high dose pharmaceutical grade biotin) in patients with progressive MS

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Background: The efficacy and safety of MD1003 (high dose Pharmaceutical grade Biotin) for the treatment of progressive MS (PMS) was recently examined in the MS-SPI study (Tourbah et al., 2016). MD1003 led to a reversal of disability in 12.6% of patients (pts) with PMS (vs. 0% of pts receiving placebo) and was well tolerated. MD1003 is available in France through an expanded access programme.
Objective: To evaluate the effectiveness and safety of MD1003 for the treatment of PMS in real-world clinical practice.
Methods: This is a prospective, observational, single-centre (CHU de Reims, France) study of MD1003. Pts with primary or secondary PMS (PPMS; SPMS), any baseline Expanded Disability Status Score (EDSS), and without clinical or radiological evidence of inflammatory activity within the previous year ("not active") were treated with MD1003 300 mg/day. Disease progression was assessed using EDSS, timed 25-foot walk (TW25), walking distance, and Clinical Global Impression (CGI). Safety outcomes, including the occurrence of relapses, were also recorded.
Results: As of May 2018, 71 pts have been treated with MD1003, of which 36 were followed up to 1 year. Of these 36 pts, 53% were

female, 53% were diagnosed with SPMS, mean age was 54 years (SD=9.4), and mean disease duration since diagnosis was 17.3 years (SD=8.4). At month (M) 12, 25 (69.5%) pts improved in at least one of the 3 parameters measuring disease progression (EDSS, TW25 ≤20%, or walking distance ≥20%). Conversely, 3 (8.3%) pts worsened at M12. Prior to initiating MD1003 treatment, mean EDSS change from baseline showed worsening of the disease (-0.22); this worsening was reversed from M0 to M12 (0 to -0.22) under MD1003 treatment. In addition, between M0 and M12, mean TW25 and mean walking distance improved with a decrease in TW25 (-14.1%) and an increase in mean walking distance of 167.4 meters. CGI confirmed the effectiveness of MD1003 in PMS, with 25 (69.4%) pts demonstrating improvement. Adverse events were in line with results from previous studies. Additional data at M12 in a larger cohort of pts and complementary sub-group analysis will be presented.

Conclusions: MD1003 was effective in a real-world clinical setting in France, with > 2/3 of pts with PMS experiencing improvement in at least one of 3 commonly used disease activity measures (EDSS, TW25, and walking distance) at M12. MD1003 was also well-tolerated, with safety outcomes in line with previous studies.

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P586

Effect of teriflunomide on oxidative stress-mediated alterations of CNS mitochondria

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In Multiple sclerosis (MS), immune cell- derived reactive oxygen and nitrogen species are involved in both neuronal and mitochondrial damage. Mitochondrial alterations resulting from oxidative stress are hypothesized to contribute to neuroaxonal damage in inflammatory neurodegenerative diseases including MS.

The immunomodulatory drug teriflunomide (TFN) is approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). TFN acts by inhibiting cell proliferation through reversible inhibition of the mitochondria associated enzyme, dihydroorotate dehydrogenase (DHODH), which is required in the rate-limiting step of *de novo* synthesis of pyrimidine. However, how medication may affect mitochondrial function during neuroinflammation and concomitant oxidative stress is unclear.

Here, we have investigated the consequences of DHODH inhibition on oxidative stress-mediated mitochondrial alterations inside the CNS. For that, we established an *ex vivo* model to investigate motility, morphology and bioenergetics of neuronal mitochondria in acute hippocampal slices. We demonstrated that TFN treatment (50µM) prevents morphological alterations of H_2O_2-treated mitochondria, but has no effect on motility. During oxidative stress, TFN seems to reduce the production of reactive oxygen species (ROS) and prevents partial depletion of ATP.

Since dihydroorotate oxidation by DHODH is coupled to the proximal electron acceptor ubiquinone/coenzyme Q, inhibition of DHODH attenuates mitochondrial respiratory chain at complex III. Thus, apart from its anti-proliferative effects, TFN treatment has an effect on mitochondrial bioenergetics affecting mitochondrial dynamics.

Disclosure

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Long-term treatment monitoring

P587

Extended interval dosing of natalizumab: is efficacy preserved?

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Introduction: Some clinicians in Italy extended the dose of natalizumab infusions after 24 doses,with the hypothesis of reducing PML risk; this idea was supported by recent reports.
Objective:To make this strategy feasible, it is necessary to ascertain the therapeutic durability of the extended dosing strategy.
Aim: To evaluate the non-inferiority in controlling disease activity of an extended interval dosing (EID) of natalizumab.
Methods: Patients who received natalizumab for at least 24 weeks in 14 Italian centers were included in the analysis. Patients were grouped in 2 categories according to the mean number of weeks between doses (< =5.5 weeks, standard interval dosing (SID);>5.5 weeks, EID). Only the dose intervals before the first relapse was used to estimate the mean intervals between doses, to minimize the bias associated to a possible return to SID in patients under EID after they experienced a relapse. The non-inferiority of EID vs SID was a priori defined as satisfied if the upper limit of the 95%CI of the annualized relapse rate (ARR) in the EID group did not exceed the mean ARR of the SID group by 0.02 relapse/year. Baseline characteristics were comparedbetween groups by aMann Whitney U test. ARR during follow up was estimated and compared between groups by a multivariate Poisson regression model.
Results: 341 patientswere included in this analysis. The median interval between doses was 4.9 weeks (range 3.7-8.4), with a clear bimodal distribution (modes at 4 and 6 weeks) associated with individual centers strategies (the median was 4.5 weeks in 220 patients from 12 centers and 6.2 in 121 patients from 2 centers). 221 patients were in the SID (median dose interval=4.5 weeks) and 120 in the EID group (median dose interval=6.3 weeks). The ARRduring follow up adjusting for all the baseline variables (age, disease duration, relapses in 2 years pre-natalizumab start, EDSS, number of previous treatments) was 0.042 (95%CI=0.026-0.067) in the SID group, and it was 0.007 (95%CI=0.002-0.028) in the EID group. The non-inferiority of EID vs SID was satisfied.
Conclusions: In this cohort there is no evidence of a reduced efficacy of natalizumab by extending the intervals between doses from a median of 4.5 to a median of 6.3 weeks. This observation confirms previous results and together with the emerging evidence of a reduced risk of PML associated to an EID supports the need of a randomized study to change the standard of the natalizumab dosing schedule.

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Long-term reduction in brain MRI disease activity and atrophy after 5 years of ocrelizumab treatment in patients with relapsing multiple sclerosis

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Background: The efficacy and safety of ocrelizumab (OCR) in relapsing multiple sclerosis (RMS) were demonstrated in the 96-week double-blind control period (DBP) of OPERA I and OPERA II (NCT01247324; NCT01412333). Long-term brain tissue preservation is a critical objective in the treatment of multiple sclerosis (MS).

Objective: To assess brain MRI measures of disease activity and atrophy after earlier vs delayed initiation of OCR at 5 years from core study baseline in Phase III trials in RMS.

Methods: At end of DBP (Year 2), patients entered the open-label extension (OLE) and continued OCR (OCR-OCR) or were switched from interferon (IFN) β1a to OCR (IFN-OCR) and were analysed until Year 5. Brain MRI lesion activity (T1 gadolinium-enhancing [T1Gd+] lesions, new/enlarging T2 [N/ET2] lesions) and percentage change in whole brain volume (WBV), cortical grey matter volume (cGMV) and white matter volume (WMV) were analysed.

Results: Among IFN-OCR patients, the adjusted number of T1Gd+ lesions was 0.48 lesions/scan at Week 96 (DBP Year 2), and decreased to an unadjusted rate of 0.007, 0.004 and 0.004 at Week 144 (Year 3/OCR Year 1), Week 192 (Year 4/OCR Year 2) and Week 240 (Year 5/OCR Year 3), respectively. Similarly, the number of N/ET2 lesions decreased from an adjusted rate of 2.16 lesions/scan in Year 2 pre-switch to 0.33 in Year 3 (OCR Year 1) and decreased further to unadjusted rates of 0.063 and 0.038 in Years 4 and 5 (OCR Years 2 and 3). OCR-OCR continuers maintained low numbers of T1Gd+ and N/ET2 lesions at Years 3, 4 and 5 of OCR treatment. Earlier OCR-treated patients (5 years of OCR) vs delayed IFN-OCR switchers (3 years of OCR) had lower brain atrophy from core study baseline to the end of Years 3, 4 and 5 measured by WBV change (-1.31%/-1.51%, -1.58%/-1.87% and -1.87%/-2.15%; $p< 0.01$ for all); cGMV change (-1.47%/-1.56%, -1.73%/-1.91% and -2.02%/-2.25%; $p=0.16$, $p< 0.01$ and $p< 0.01$) and WMV change (-0.94%/-1.23%, -1.11%/-1.45% and -1.33%/-1.62%; $p< 0.01$ for all).

Conclusions: Patients with RMS switching at Year 2 from IFN to OCR had an almost complete and sustained suppression of MRI disease activity as measured by T1Gd+ lesions and N/ET2 lesions from Year 2 to 5. At 5 years from core study baseline, patients with 5-years' continuous OCR treatment from randomisation experienced a lower brain atrophy as measured by change from baseline in whole brain, white matter and cortical grey matter volume compared with patients with a 2-year delayed OCR treatment start.

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L. Kappos' institution (University Hospital Basel) received in the last 3 years and used exclusively for research support at the Department: steering committee, advisory board and consultancy fees from Actelion, Alkermes, Almirall, Bayer, Biogen, Celgene/Receptos, df-mp, Excemed, GeNeuro SA, Genzyme, Japan Tobacco, Merck, Minoryx, Mitsubishi Pharma, Novartis, Roche, sanofi-aventis, Santhera, Teva, Vianex and royalties for Neurostatus-UHB products; the Research of the MS Center in Basel has been supported by grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, the European Union and Roche Research Foundations.

S. L. Hauser serves on the board of trustees for Neurona and on scientific advisory boards for Annexon, Bionure and Symbiotix and has received travel reimbursement and writing assistance from F. Hoffmann-La Roche Ltd for CD20-related meetings and presentations.

X. Montalban has received speaker honoraria and travel expense reimbursement for participation in scientific meetings, been a steering committee member of clinical trials or served on advisory boards of clinical trials for Actelion, Biogen, Celgene, Merck, Novartis, Oryzon, Roche, Sanofi Genzyme and Teva Pharmaceutical.

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V. Levesque is an employee of Genentech, Inc.

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Twenty-five years of continuous treatment of multiple sclerosis with glatiramer acetate: long-term clinical results of the US open-label extension study

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Introduction: Glatiramer acetate (GA) is the only treatment for relapsing forms of multiple sclerosis (RMS) to be prospectively studied for more than a decade in a continuously monitored, long-term study. Beginning in 1991, 251 relapsing MS (RMS) patients enrolled in the multi-center, placebo-controlled, double-blind US pivotal trial of GA. At the end of the pivotal study, placebo patients were crossed over to GA and the prospective open-label study was begun. The clinical effectiveness and safety of GA in this study have been reported at 2 and 3 years compared to placebo and at 6, 8, 10, 15, and 20 years in the open-label study. We now report the final 25-year results of the long-term extension of the original US pivotal trial.

Objectives: To assess the long-term neurological disease course, and the safety and effectiveness of GA 20 mg daily and later, 40 mg three times weekly, in patients with RMS.

Methods: Patients participating in the original 36-month, randomized, placebo-controlled US Glatiramer Acetate Trial were eligible to proceed to an open-label extension phase, now in its 25th year, in which patients receiving GA continued treatment, while those receiving placebo switched to GA.

Results: This study is now complete. Database lock was March 29, 2018. Analyses of this final data set are underway and will be presented.

Conclusions: We will report clinical results for patients remaining on continuous long-term GA. These findings should be considered within the context of the disease course of these patients, now approaching 35 years with their illnesses.

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Jessica Alexander is an employee of Teva Pharmaceuticals.

Yafit Stark is an employee of Teva Pharmaceuticals.

Ofra Barnett is an employee of Teva Pharmaceuticals.

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Long-term reduction of relapse rate and confirmed disability progression after 5 years of ocrelizumab treatment in patients with relapsing multiple sclerosis

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Background: The efficacy and safety of ocrelizumab (OCR) in relapsing multiple sclerosis (RMS) were demonstrated in the 96-week double-blind control period of OPERA I and OPERA II (NCT01247324; NCT01412333), and results for the 2-year follow-up of the pooled OPERA I and OPERA II open-label extension (OLE) period have previously been reported (Hauser SL, *et al*. AAN 2018; Abstract P1.366).
Objective: To assess the efficacy of switching to or maintaining OCR therapy on clinical measures of disease activity and progression after 3 years of follow-up in the OLE period of the OPERA I and OPERA II Phase III trials in RMS.
Methods: At the start of the OLE period, patients continued OCR (OCR-OCR) or were switched from interferon (IFN) β-1a to OCR (IFN-OCR). Adjusted annualised relapse rate (ARR), time to onset of 24-week confirmed disability progression (CDP24) and change in adjusted mean Expanded Disability Status Scale (EDSS) score from baseline were analysed.
Results: Overall, 88.6% of patients who entered the OLE completed OLE Year 3. Among IFN-OCR patients, ARR decreased from 0.20 in the year pre-switch to 0.10, 0.08 and 0.07 at Years 1, 2 and 3 post-switch ($p< 0.001$, Year 1 vs pre-switch; $p=0.31$, Year 1 vs Year 2; $p=0.56$, Year 2 vs Year 3). OCR-OCR continuers maintained the low ARR through the year pre-OLE and the 3 years of the OLE period (0.13, 0.11, 0.08 and 0.07). OCR-OCR continuers versus IFN-OCR switchers had lower proportions of patients with CDP24 in the year pre-switch and Years 1, 2 and 3 of the OLE period (7.7%/12.0%, 10.1%/15.6%, 13.9%/18.1% and 16.1%/21.3%; $p< 0.05$, all difference comparisons). Changes in mean EDSS scores from baseline in OCR-OCR continuers versus IFN-OCR switchers will also be presented.
Conclusions: Switching from IFN to ocrelizumab after 2 years at the start of the OLE period was associated with a rapid reduction in ARR. Both OCR-OCR as well as IFN-OCR patients maintained their robust reduction in ARR through the 3-year follow-up of the OLE period. After 5 years of follow-up, the proportion of patients with disability progression was lower in patients who initiated ocrelizumab treatment earlier (OCR-OCR), compared to patients who received initial IFN treatment (IFN-OCR switchers), showing that patients who initiated ocrelizumab 2 years earlier accrued significant and sustained reductions in disability progression compared to patients switching from IFN.

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B. Brochet has received research support from Bayer, Merck, Genzyme, Biogen, Novartis, Roche, Actelion, MedDay and Teva, and has consulting agreements with Novartis and Biogen.
X. Montalban has received speaker honoraria and travel expense reimbursement for participation in scientific meetings, been a steering committee member of clinical trials or served on advisory boards of clinical trials for Actelion, Biogen, Celgene, Merck, Novartis, Oryzon, Roche, Sanofi-Genzyme and Teva Pharmaceutical.
R. T. Naismith reports financial relationships with Acorda, Alkermes, Bayer, Biogen, EMD Serono, Genentech Inc., Genzyme, Novartis and Teva.
J. S. Wolinsky has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with AbbVie, Acetilon, Alkermes, Biogen, Bionest, Celgene, Clene Nanomedicine, EMD Serono, Forward Pharma A/S, GeNeuro, MedDay Pharmaceuticals, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech, Sanofi Genzyme.; royalties are received for out-licensed monoclonal antibodies through UTHealth from Millipore Corporation.
M. Manfrini is an employee of F. Hoffmann-La Roche Ltd.
M. Garas is an employee and shareholder of F. Hoffmann-La Roche Ltd.
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F. Model is an employee of F. Hoffmann-La Roche Ltd.
S. Hubeaux is an employee and shareholder of F. Hoffmann-La Roche Ltd.
L. Kappos' institution (University Hospital Basel) received in the last 3 years and used exclusively for research support at the Department: steering committee, advisory board and consultancy fees from Actelion, Alkermes, Almirall, Bayer, Biogen, Celgene/Receptos, df-mp, Excemed, GeNeuro SA, Genzyme, Japan Tobacco, Merck, Minoryx, Mitsubishi Pharma, Novartis, Roche, sanofi-aventis, Santhera, Teva, Vianex and royalties for Neurostatus-UHB products; the Research of the MS Center in Basel has been supported by grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, the European Union and Roche Research Foundations.

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Treatment effectiveness in relapsing remitting multiple sclerosis patients treated for 5 years with fingolimod in clinical practice: interim results from the observational study PANGAEA

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Background: Once-daily fingolimod (Gilenya®, Novartis Pharma AG) is a sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing remitting multiple sclerosis (RRMS). As of February 2018 more than 231.000 patients have been treated with fingolimod; total patient exposure exceeds 536.000 patient-years. PANGAEA is a non-interventional study (NIS), conducted in Germany, to investigate long-term safety, effectiveness and patient reported outcomes in daily clinical practice.
Objective: Here we present interim results on the effectiveness of fingolimod in RRMS patients treated for 5 years in daily clinical practice.
Methods: Recruitment into the study finished in December 2013. 4229 patients from 374 centers were enrolled. By Jan 2018, 726 patients finished the 5 years documentation period of fingolimod treatment, of which 433 (59.6%) were treated for the first time with fingolimod.
Results: Within the analyzed subgroup of 5 years completers, the mean age at baseline was 40.6 (±9.0 SD) years and the proportion of female patients was 69.0%. With an annual relapse rate of 1.2 (±0.08 95%CI) at baseline, the annualized relapse rate over the entire 5 years observational period improved by approximately 84.2% to 0.19 (±0.02 95%CI). The mean baseline EDSS was 3.1 (±1.7 SD) and remained stable over 5 years. In the fifth year of treatment, 82.0% of the patients showed a stable EDSS or experienced a 6 months confirmed improvement. The documentation period of 5 years allows calculating a 6 months confirmed disability progression up to year 4 of treatment. The proportion of patients free of relapses and 6 months confirmed disability progression increased from 60.4% in year 1 to 70.3% in year 4 of treatment. 46.9% of the patients neither had a relapse nor a 6 months confirmed disability progression over the observational period. After 5 years, 94.8% of physicians and 95.7% of patients rated treatment effectiveness under fingolimod as "good" or "very good". After 5 years, total score of the symbol digital modalities test (SDMT; baseline 45.7 (±3.49 95%CI)) as a measure of cognitive processing speed improved by 10.0 points (±3.48).
Conclusion: The results of the 5 year interim analysis of PANGAEA support the positive efficacy profile of fingolimod demonstrated in phase III clinical trials with long-term real world evidence data.

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Effect of MD1003 (high dose pharmaceutical grade biotin) for the treatment of progressive MS: 48-month follow-up data

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Background: MS-SPI was a 12-month (M) double-blind study where 154 patients (pts) with nonactive progressive multiple sclerosis (PMS) were randomised to MD1003 (n=103) or placebo (n=51). As reported previously, expanded disability status scale (EDSS) or timed 25-foot walk (TW25) improvement, mean EDSS (mEDSS) score, and clinical global impression (CGI) score were all significantly ($P< 0.05$) in favour of MD1003 relative to placebo (Tourbah et al., 2016). In the open-label extension phase, all pts received MD1003 after M12. Here, we present the 48M results (shown as MD1003>MD1003 [MM] vs placebo>MD1003 [PM]).
Objective: To evaluate the effects of MD1003 in pts with PMS during the open-label extension phase of the pivotal MS-SPI study.
Methods: A total of 133 pts (MM: 91; PM: 42) entered the extension phase. At M18, M24, M30, M36, M42 and M48 we assessed EDSS or TW25 improvement, mEDSS change from baseline, CGI, and adverse events (AEs).
Results: In the extension phase, where both groups received MD1003, EDSS or TW25 improvement remained higher for MM vs PM pts at M18 (13% vs 7%), M24 (8% vs 5%), M30 (10% vs 2%), M36 (13% vs 0%), and M42 (13% vs 3%) (each confirmed after 6M). The difference in mEDSS score between the MM and PM groups was significant at M30 (0.10 vs 0.23, P=0.041) but not at M24 (0.04 vs 0.15, P=0.13), M36 (0.09 vs 0.18, P=0.35), and M48 (0.16 vs 0.4, P=0.17). The 2 mEDSS evolution curves remained parallel, suggesting that earlier treatment leads to a lower disability at M48. CGI scores remained stable for MM pts and improved for PM pts upon switching to MD1003; the CGI scores were no longer significantly different at M24 (4.17 vs 4.24,

P=0.75), M36 (4.11 vs 4.09, *P*=0.88), or M48 (4.40 vs 4.35, *P*=0.80). Between M42 and M48, AEs were experienced by 38% vs 34% of pts in MM and PM groups, respectively. The main reasons for treatment withdrawal throughout the study (n=86 pts) were consent withdrawal (30 pts), lack of efficacy (30 pts), and AEs (14 pts).

Conclusions: Results from the long-term extension phase of MS-SPI at 4 years of follow-up indicate that 1) the effects of MD1003 observed in the 12-month double-blind phase are sustained over time, 2) pts show improvement when switching from placebo to MD1003, 3) delayed treatment in PM pts results in higher disability over time, and 4) MD1003 is well tolerated over 48M. These data confirm previous observations made after 3 years of follow up.

Disclosure

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Utilization, safety and tolerability of ocrelizumab: year 1 data from the Providence Ocrelizumab Registry

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Background: Ocrelizumab (OCR), a CD20 antibody, was approved in the US in March 2017 for the treatment of relapsing MS (RMS) and primary progressive MS (PPMS). Given the favorable efficacy and safety results from OPERA I and II in RMS and ORATORIO in PPMS, we anticipated a strong interest in OCR among our MS patients.

Objective: To establish a registry to monitor utilization, safety and treatment outcomes of OCR.

Methods: Adult MS patients who have been prescribed OCR were eligible. A trained RN collects clinical data from medical records at the time of starting OCR and then every 6 months. Expanded Disability Status Scale (EDSS) scores are determined by the treating provider at baseline and then yearly.

Results: Of the 223 patients enrolled from March 2017 to April 2018 (76% are female; mean [SD] age, 51[11.6] years), 73.4% RMS, 17% SPMS, and 9.6% PPMS. Forty percent of the patients are older than 55. Mean EDSS at the time of the first dose of OCR was 3.59 (±1.8), 6.27 (±1.5), and 5.93 (±1.6) respectively. In the RMS cohort, annualized relapse rate prior to starting OCR was 0.349 (±0.50). Six (2.7%) patients were previously treated with interferon beta, 13 (5.9%) with glatiramer acetate, 33 (15.1%) with dimethyl fumarate, 40 (18.3%) with fingolimod, 12 (5.5%) with teriflunomide, 39 (17.8%) with natalizumab, 23 (10.5%) with other agents, and 53 (24.2%) were treatment naïve. Infusion reactions occurred in 65 (29.3%) patients during the first dose but reduced to 5.8% (5/84) after the second dose. 45 patients (20.2%) have had at least one infection, with upper respiratory infections (URIs) and urinary tract infections (UTIs) being the most common. Four patients have been hospitalized secondary to possible adverse events; sepsis, urinary tract infection, bilateral leg edema, and urosepsis. One patient died secondary to suicide. Seven patients have had a relapse since starting OCR which occurred on average 69 days after starting OCR (26 to 124 days), and two patients have stopped OCR; secondary to a relapse and dermatologic changes respectively.

Conclusion: Despite an older patient cohort, the tolerability and safety outcomes observed at our center appear to be consistent with the earlier Phase III clinical trials.

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TS, CC, LG have no disclosures.

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Radiological findings suggest long-term treatment with delayed-release dimethyl fumarate is associated with tissue and axonal preservation

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Introduction: Delayed-release dimethyl fumarate (DMF) has demonstrated a favourable benefit-risk profile in clinical trials and real-world analyses. Radiological measures such as T1 black hole conversion and annual changes in brain atrophy may be used as a marker for improved clinical outcomes for patients. ENDORSE, an ongoing extension study of the original pivotal trials, allows assessment of the impact of long-term DMF treatment.

Objectives: Report radiological outcomes in patients with relapsing remitting multiple sclerosis (RRMS) treated long-term with DMF in ENDORSE.
Methods: Patients from the MRI cohort of DEFINE/CONFIRM who continued DMF treatment in ENDORSE were included (BID-BID, PBO-DMF, GA-DMF). MRI scans were obtained yearly. The first ENDORSE MRI was performed at the end of year 1; therefore, only data from year 1 forward were analysed. For analysis of new hypointense T1 and hyperintense T2 lesions, only patients with a yearly scan for 5 years were included (completer analysis); data are reported by year of exposure to DMF. For the percent brain volume change (PBVC) analysis, all patients regardless of number of scans were included due to sample size restrictions; data are reported by year of ENDORSE.
Results: Of the 530 ENDORSE MRI cohort patients, 209 were included in the completer analysis; 116 patients newly initiated treatment with DMF in ENDORSE and 93 were previously treated with DMF. When analysed annually, most patients revealed no new hypointense lesions on T1: Year 1-2: 83/116 (72%); Year 2-3: 79/116 (68%); Year 3-4: 145/209 (69%); Year 4-5: 146/209 (70%); Year 5-6: 65/93 (70%); Year 6-7: 67/93 (72%). The annual rate of new/newly enlarging T2 lesions was also positively affected by DMF treatment. For the PBVC analysis, 134 BID-BID patients were included. After 2 prior years of DMF treatment, the adjusted mean yearly PBVC at end of ENDORSE year 2 was -0.22 (n=134); year 3: -0.28 (n=116); year 4: -0.37 (n=114); year 5: -0.22 (n=108); year 6: -0.19 (n=89).
Conclusions: The data suggest that long-term DMF treatment translates into meaningful benefits of tissue protection on MRI: a low frequency of new T1 hypointense lesions, suggesting axonal preservation; annual changes in brain volume approaching that of healthy individuals; and, a low annual rate of new/newly enlarging T2 lesions consistent with maintained anti-inflammatory effects. These findings indicate that DMF provides long-term efficacy for RRMS patients.
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Disclosure

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Lili Yang: employee of and holds stock/stock options in Biogen.
Catherine Miller: employee of and holds stock/stock options in Biogen..

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Real-world efficacy of delayed-release dimethyl fumarate in early multiple sclerosis: interim results from ESTEEM

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Introduction: Delayed-release dimethyl fumarate (DMF) demonstrated strong efficacy and a favourable benefit-risk profile in patients with relapsing-remitting multiple sclerosis (RRMS) in clinical studies. ESTEEM (NCT02047097) is an ongoing, 5-year, observational study to characterise the long-term safety and effectiveness of DMF in patients treated in clinical practice.
Objectives: To evaluate the real-world effectiveness of DMF in patients who are treatment naïve, or have been treated within 3 years of diagnosis, or treated with only one prior interferon-beta (IFN)/glatiramer acetate (GA).
Methods: This post-hoc interim analysis of ESTEEM includes patients newly prescribed DMF in routine practice at ~380 sites globally. Annualised relapse rate (ARR) was evaluated in the overall population, as well as newly diagnosed (no prior disease-modifying therapy [DMT] and initiated DMF ≤1 year of diagnosis), early MS (≤1 prior DMT and initiated DMF ≤3 years of diagnosis), and IFN/GA switch (received prior IFN/GA at any time from diagnosis) patients. ARRs were obtained via a repeated-measure negative binomial model.
Results: Enrolled in ESTEEM were 3075 patients; 73% were on-treatment at the time of the interim analysis; median (min-max) follow-up was 13 (0-40) months. The unadjusted ARRs for the 12 months before DMF vs. the 24 months post DMF initiation were as follows: overall population (n=3075), 0.80 (95% confidence interval [CI]: 0.78-0.83) vs. 0.15 (95% CI: 0.14-0.16), representing a 81% lower ARR ($P< 0.0001$); newly diagnosed patients (n=770), 1.12 (95% CI: 1.07-1.17) vs. 0.17 (95% CI: 0.14-0.21), representing an 85% lower ARR ($P< 0.0001$); early MS patients (n=1291), 1.03 (95% CI: 0.99-1.08) vs. 0.17 (95% CI: 0.14-0.19), representing an 84% lower ARR ($P< 0.0001$); and IFN/GA switch patients (n=1915), 0.69 (95% CI: 0.65-0.73) vs. 0.16 (95% CI: 0.14-0.17), representing a 77% lower ARR ($P< 0.0001$). For reference, in pooled data from the DEFINE/CONFIRM trials, the ARR after 2 years among patients who received placebo (n=771) was 0.37 (95% CI: 0.33-0.42).

Conclusions: After treatment with DMF, ARR at 2 years was significantly reduced compared to the year prior to DMF initiation in patients who were treated with DMF in the real-world setting. These data provide further evidence of real-world effectiveness of DMF in patients who are early in their MS disease course.
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German real-world data from over 10 years in the TYSABRI® Observational Program: long-term effectiveness of natalizumab treatment in German patients with relapsing-remitting MS

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Introduction: The TYSABRI Observational Program (TOP) is an ongoing, global, open-label study in patients with relapsing-remitting multiple sclerosis (RRMS) treated with natalizumab in the real world. Country-specific data from TOP can provide information on the effectiveness of natalizumab in local clinical practice. The German cohort is the largest country-specific population in TOP.
Objectives: To evaluate the effectiveness of natalizumab in patients with RRMS in the German cohort in TOP.
Methods: Data from study initiation in July 2007 to November 2017 were included in this analysis. Annualized relapse rates (ARRs) before and on natalizumab were compared using a repeated Poisson model. The cumulative probabilities of 24-week-confirmed Expanded Disability Status Scale (EDSS) worsening (increase of ≥1.5 from a score of 0.0, ≥1.0 from a score of 1.0-5.5, or ≥0.5 from a score ≥6.0) and 24-week-confirmed EDSS improvement (decrease of ≥1.0 from a score ≥2.0) were estimated using the Kaplan-Meier method.
Results: As of November 2017, 6149 patients were enrolled in TOP globally; 1707 TOP patients (27.8%) were German. At baseline, German TOP patients had a median (range) disease duration of 6.7 (0-37.2) years and mean (standard deviation) EDSS scores of 3.2 (1.65). Most patients (92.1%) had used a disease-modifying therapy prior to natalizumab initiation. On study, German patients received a median (range) of 35 (1-135) doses of natalizumab. ARR decreased from 2.21 pre-natalizumab to 0.25 on treatment (an 88.7% decrease; $P< 0.0001$). At 10 years, the cumulative probability of confirmed EDSS worsening was 37.5%, and the cumulative probability of confirmed EDSS improvement was 37.7%.
Conclusions: Over 10 years of treatment with natalizumab, ARRs remained low in German patients with RRMS. The probabilities of EDSS worsening and improvement were similar. Overall, these results are consistent with outcomes observed in the global TOP population and support the long-term effectiveness of natalizumab in real-world settings.

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HS-F: nothing to disclose.
KR, SL: employees of and/or hold stock and/or stock options in Biogen.
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Natalizumab is associated with a reduction in relapse-related hospitalisations and steroid treatment in relapsing-remitting multiple sclerosis patients enrolled in the TYSABRI® Observational Program

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Introduction: Relapsing-remitting multiple sclerosis (RRMS) patients who experience relapses may require hospitalisation and/or treatment with steroids; such relapses contribute to both disability accumulation and overall disease management costs. Natalizumab (NTZ) has reduced relapse rates and severity in the clinical trial setting; published data have confirmed this in the real world. In the phase 3 AFFIRM trial, annualised relapse rates (ARRs) for relapses resulting in hospitalisations or steroid use were 0.04 and 0.15, respectively. Here, we evaluate relapses resulting in hospitalisations or steroid use in the TYSABRI Observational Program (TOP), an ongoing, global, open-label study of NTZ-treated RRMS patients in clinical practice.
Objectives: Examine the impact of NTZ on relapses resulting in hospitalisations or steroid use in RRMS patients in TOP.
Methods: In TOP, data on relapses (overall, requiring hospitalisation, or requiring steroid use) were collected at enrolment (for the previous year) and at clinical visits. ARRs for the year prior to starting NTZ and on NTZ were compared using a repeated Poisson model.
Results: As of November 2017, 6149 patients were enrolled in TOP. Median exposure was 38 (range, 1-135) doses; 3210 patients (52.2%) discontinued NTZ and 2118 patients (34.4%) withdrew from the study. Overall ARR was reduced by 89.4% (from 1.99 pre-NTZ to 0.21 post NTZ initiation; $P < .0001$). ARR was reduced by 91.1% (from 0.56 to 0.05; $P < .0001$) and by 89.2% (from 1.67 to 0.18; $P < .0001$) for relapses resulting in hospitalisations or steroid use, respectively. During NTZ treatment, the proportion of patients with any relapse-related hospitalisation or steroid use decreased from baseline (36.6% [2221 of 6073] to 11.1% [681 of 6149] and 89.1% [5438 of 6104] to 33.0% [2031 of 6149], respectively), despite longer follow-up in the on-NTZ than the pre-NTZ period (22,103 vs 6073 person-years). Overall, 88.9% and 67.0% of NTZ-treated patients remained free of relapses resulting in hospitalisation and steroid use, respectively, after NTZ initiation.
Conclusions: In TOP, NTZ initiation was associated with a significant decrease in relapses resulting in hospitalisation or steroid treatment, and ARRs for both are consistent with those observed in AFFIRM. These results support the long-term, real-world effectiveness of NTZ and may reflect reductions in healthcare resource utilisation associated with NTZ treatment.

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LK: Ludwig Kappos' Institution (University Hospital Basel) received in the last 3 years and used exclusively for research support at the Department: steering committee, advisory board and consultancy fees from Actelion, Alkermes, Almirall, Bayer, Biogen, Celgene/Receptos, df-mp, Excemed, GeNeuro SA, Genzyme, Japan Tobacco, Merck, Minoryx, Mitsubishi Pharma, Novartis, Roche, sanofi-aventis, Santhera, Teva, Vianex and royalties for Neurostatus-UHB products. The Research of the MS Center in Basel has been supported by grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, the European Union and Roche Research Foundations.
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IC, SN, P-RH, SL: employees of and may hold stock and/or stock options in Biogen.

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Providence Dimethyl Fumarate Registry: year five results on discontinuation and treatment outcomes

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Objective: To report our experience of dimethyl fumarate (DMF) since the medication's approval in March 2013.
Background: This registry was established in 2013 to monitor long-term utilization of DMF and the treatment outcomes. Three years after the approval of DMF our results indicated a large portion of patients stopped DMF, 38%, with the vast majority stopping secondary to side effects
Methods: This is a chart review study of patients who were prescribed DMF 240mg twice a day for relapsing MS between March 2013 and April 2018 at the Providence MS Center.
Results: Of the 419 adult patients (77.1% female; mean (SD) age, 51.6 (12.1) years) with a diagnosis of relapsing MS, 385 (91.9%) were enrolled from March 2013 to December 2014. Median disease duration was 11.0 years [interquartile range (IQR): 6.9, 15.9], and median duration of DMF treatment was 1.78 years [IQR: 0.6, 3.5]. Sixty-five (15.5%) of the 419 patients were not on therapy prior to starting DMF and 141 (33.7%) were previously treated with interferon beta. Within five years of follow up, 216 (51.6%) patients discontinued DMF and of those, 85 (39.4%) stopped within the first 6 months of starting DMF. Median time to DMF discontinuation was 311 days [IQR: 64, 729]. The main reason for discontinuing was due to side effects (n=146, 60.6%). Clinical relapse occurred in 84 (20.1%) patients. The annualized relapse rate (ARR) was 0.123. Patients transitioning from glatiramer acetate had the lowest ARR of 0.068, and patients from fingolimod had the highest ARR of 0.182. Of the 311 (74.2%) patients who had an MRI, 246 (79.1%) were stable. To date, 83 (34.5%) patients have stopped DMF secondary to clinical or radiographic progression. Grade III lymphopenia developed in 44 (12.2%) patients. Mean age was 60.5 (11.3) years compared to 50.2 (11.6) years.

Discussion: Five years after the approval of DMF, a little over half of the patients have discontinued DMF. Tolerability of DMF has been the main reason for discontinuing the medication. Our rate of discontinuation is higher compared to other reported data possibly due to the majority of our patients starting shortly after DMF's approval. In addition, the incidence of grade III lymphopenia is higher due to likely an older patient cohort.

Disclosure

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KS has received research support from Biogen, medDay, and IMS Health and consulting fees from Acorda, Biogen, EMDSerono, Genzyme, Novartis, and Teva.
EL has received either consulting fees from EMD Serono, Genentech, Teva, Novartis, Biogen, and Genzyme.
MR, CC, TS, LL &LG have no disclosures.

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Initiation of the first disease-modifying treatment for multiple sclerosis patients in the Czech Republic - data from the national registry ReMuS

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Background: The Czech national registry ReMuS has been collecting data on more than 13,000 multiple sclerosis (MS) patients since 2013. Among others, the data indicates the influence of reimbursement criteria on the accessibility and utilization of various first disease-modifying drugs (DMD).
Objective: To describe the temporal evolution of treatment commencement in the Czech Republic and estimate factors influencing treatment effect.
Methods: The study included patients starting with first-line therapy (glatiramer acetate, interferon beta, teriflunomide) or starting directly with more effective but costlier escalation therapy (alemtuzumab, dimethyl fumarate, fingolimod, natalizumab). MS patients initiating DMD between 2013-2016 were identified from the respective DMD start date. We explored the relationship between the type of DMD treatment and the severity of MS before and shortly after DMD start. Probability of having relapse within 1 year after DMD initiation was modelled using logistic regression to access the effect of Expanded Disability Status Scale (EDSS) one year before DMD and the effect of number of previous relapses with regards to other characteristics (age, sex, disease duration). Differences in covariates between patients starting therapy in years 2013-2016 were explored using ANOVA.
Results: Out of 3,328 patients, 3,203 started on first-line therapy and 125 started directly on escalation therapy. The proportion of patients starting on escalation therapy increased in time (1.8% in 2013 and 4.7% in 2016). The occurrence of a relapse one year after DMD initiation is significantly connected with the EDSS one year before DMD ($p< 0.001$, higher EDSS is associated with higher probability of a relapse) and the number of previous relapses ($p< 0.001$, patients with ≥ 2 prior relapses were more likely to have further relapse). Both the average EDSS and the number of relapses prior to DMD are significantly lower ($p=0.002$ and 0.018) in patients starting the first DMD in later years of the explored interval.
Conclusions: The data from the national registry ReMuS showing decreasing EDSS and number of relapses prior to the first DMD treatment over time evidences the improving management of MS in the Czech Republic. Despite these trends, the rate of patients starting directly on escalation drugs is still low and does not correspond to the estimated number of patients with highly-active disease nor treatment trends in countries with no economic restrictions.

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P600

Pregnancy outcomes in patients with multiple sclerosis and other autoimmune diseases treated with ocrelizumab in clinical trials and post-marketing studies

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Background: Ocrelizumab (OCR), a humanised monoclonal antibody that selectively targets $CD20^+$ B cells, is approved for the treatment of relapsing and primary progressive forms of multiple sclerosis (MS), and has also been studied in clinical trials for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). As a large proportion of patients with MS are women of reproductive age, pregnancy outcomes in patients exposed to OCR is of importance. B-cell levels in neonates following maternal exposure to OCR have not been studied in clinical trials and the effect of OCR on the immune system of the newborn is unknown.
Objective: To provide an update of pregnancy outcomes in women treated with OCR during clinical trials and post marketing.
Methods: This analysis includes pregnancies in women with MS, RA and SLE in OCR clinical trials and from post-marketing sources (dose range 20 to 2000 mg) up to 31/03/2018. In the EU, women of childbearing potential are recommended to use contraception while receiving and for 12 months after last OCR infusion, while across trials, women of childbearing potential were required to use two methods of contraception and continue contraception for 48 weeks after the last OCR infusion or until B cells repleted, whichever was longer. An embryo/foetus was considered exposed to OCR *in utero* if the last infusion occurred within 3 months of conception or during pregnancy or if the date was unknown.
Results: As previously reported, between 2008 and 31/01/2017, 56 women randomised to OCR in clinical trials reported 58 pregnancies (25 MS, 11 SLE, 22 RA). This cumulative update provides approximately 14 months' additional data on pregnancies reported in clinical trials and from post-marketing sources up to 31/03/2018, and will review 108 pregnancies reported in 106 women (68 patients with MS, 7 patients in whom the OCR indication was not reported, and 31 patients with RA or SLE). Among the 68 pregnancies in patients with MS, 38 were considered to have foetal OCR exposure, 17 had no foetal OCR exposure, and 13 were not assessable for foetal OCR exposure. Preliminary outcomes of the 68 pregnancies include 20 ongoing at cutoff and 14 electively terminated or ended in spontaneous abortion or stillbirth.
Conclusions: The current update on pregnancy outcomes remains in line with previous reports. As the number of pregnancies is too small to draw firm conclusions on the effect of OCR on pregnancy outcomes, data will continue to be collected and assessed.

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P601

Effect of age on clinical outcomes in patients treated with fingolimod: pooled analysis of real-world phase iv studies

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Introduction: Young patients with relapsing MS (RMS) have higher disease activity compared with the adult RMS population. In clinical settings, fingolimod (FTY) 0.5mg significantly improved clinical and radiological outcomes in young patients compared with placebo and interferon β-1a. However, real-world evidence of FTY in young patients with RMS is limited.
Objectives: To describe baseline (BL) characteristics and evaluate the effect of FTY 0.5mg on disease activity in young versus older patients with RMS from pooled global Phase IV studies: TRANSITION, PASSAGE US, PASSAGE Europe & Rest of the World, and Cardiac sub-study PASSAGE EU.
Methods: Patients with RMS from Phase IV studies treated with FTY 0.5mg were included in the analysis, stratified by age: 18−25 years (youngest), 26−30 years (younger) and >30 years (older). EDSS change from BL to Month (M) 12 and M24 was analysed. On study annualised relapse rate (ARR) reduction compared to estimated ARR in 2 years prior and time to 6-month confirmed disability progression (6m-CDP− defined as 6 months of confirmed EDSS worsening by ≥1.5/≥1/≥0.5 if BL EDSS=0/1−5/>5, respectively) were retrospectively analysed up to M36. Negative binomial (ARR) and Cox (6m-CDP) regression models were used and p-values derived using the Wilcoxon rank sum test.
Results: Of the 5240 patients included, 7.6% were youngest, 11.0% younger, and 81.3% older with a mean (±SD) age of 22.6 (±2.06), 28.1 (±1.41) and 43.8 (±8.49) years, respectively. At BL, youngest and younger patients (vs older patients) had significantly lower mean disease duration (4.1 and 5.7 years vs 11.5 years, p< 0.0001 for both), higher number of relapses in the previous 2 years (2.0 and 2.0 vs 1.7, p< 0.0001 for both) and lower median EDSS scores (1.5 and 2.0 vs 3.0, p< 0.0001 for both). The effect of FTY 0.5mg on ARR was observed across the age groups with 67%, 75% and 76% reductions in youngest, younger and older patients, respectively. Change in EDSS from BL to M24 was similar in the youngest (p=0.1785) but improved in the younger (p< 0.0001) patients versus older patients. No significant difference was observed in the proportion of patients with time to 6m-CDP in youngest and younger patients versus older patients.
Conclusions: At BL, young patients had shorter disease duration, a higher number of relapses in the previous 2 years and lower EDSS scores versus older patients. The beneficial effect of FTY on clinical outcomes was observed across the age groups.

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P602

Safety of fingolimod in RRMS patients treated for up to 5 years in real world: interim results from the non-interventional PANGAEA study

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Background: The sphingosine-1-phosphate receptor modulator fingolimod (Gilenya®, Novartis Pharma AG) is an once-daily capsule approved for the treatment of relapsing remitting multiple sclerosis (RRMS). As of February 2018, more than 231.000 patients have been treated with fingolimod; total patient exposure exceeds 536.000 patient-years.
Objective: Here we present interim results on the safety of fingolimod and persistency of patients treated with fingolimod for up to 5 years in daily clinical practice in Germany.
Methods: PANGAEA is a non-interventional study, conducted in Germany, to investigate long-term safety, effectiveness and patient reported outcomes in daily clinical practice. Recruitment into the study finished in December 2013. In total, 4229 patients were enrolled, of which 726 patients completed the 5 year documentation period by January 2018. The current mean observational period in PANGAEA is 3.02 (±1.83 SD) years representing approximately 12,771 patient years.
Results: Yearly study discontinuation ranged between 10.4% and 15.0% over the 5 years of observation. The rate of treatment discontinuation was between 12.3% (1st year) and 8.1% (4th year). 61.7% of patients who started fingolimod treatment between 2011 and 2013 in PANGAEA are still on drug. The most frequent reason for premature study discontinuation (multiple answers possible, 1st vs. 4th year of treatment) was adverse events (AEs; 34.1% vs. 12.9%) followed by patient's decision (23.4% vs. 25.9%) and disease progression (21.3% vs. 32.0%). 87.5% of the patients had no therapy interruption in the documentation period, while 10.6% interrupted treatment with fingolimod once (1.9% more than once). Over the 5 years of observation, the safety profile of fingolimod was comparable to that observed in phase III clinical trials. Commonly reported adverse events were lymphopenia (11.3%), increased liver enzyme levels (5.33%), upper respiratory tract infections (e.g. nasopharyngitis (9.9%)), and potentially MS related adverse events such as fatigue (3.4%) and depression

(2.6%). 5.0% of all adverse events were rated serious. 28.3% of the patients experienced no AEs so far.
Conclusions: This 5 year interim analysis of PANGAEA provides real world data supportive for the good safety profile of fingolimod demonstrated in phase III clinical trials. The nature of reported adverse events is consistent with previous findings from clinical trials.

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Risk management for disease modifying treatments

P603

Pregnancy outcomes from an international registry of patients treated with delayed-release dimethyl fumarate

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Introduction: Available data from clinical trials and post-marketing reports show no safety signals with delayed-release dimethyl fumarate (DMF) exposure during pregnancy; however, the product label recommends use during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Objective: To assess pregnancy outcomes in an ongoing international registry (NCT01911767) of women with multiple sclerosis (MS) exposed to DMF since the first day of their last menstrual period prior to conception or at any time during pregnancy.
Methods: In this interim analysis, DMF-exposed women were prospectively evaluated for live births and pregnancy loss. Ectopic and molar pregnancies, birth defects, congenital anomalies or infant death occurring at ≤52 weeks of age, and maternal death at ≤12 weeks postdelivery, were reported. Data were collected at baseline (enrollment), 6-7 months of gestation, 4 weeks after the estimated delivery date, and 4, 12, and 52 weeks after birth. Potential birth defects were adjudicated by an external expert. Gestational size was classified as small (< 10^{th} percentile), appropriate (10^{th}-90^{th}), or large (>90^{th}) based on WHO or country-specific growth charts.
Results: As of 15 December 2017, 199 patients were enrolled in the registry; mean (SD) age was 32 (4) years. Earliest DMF exposure occurred in the first (99%, 186/187), second (< 1%, 1/187), and third (0%) trimester in the 187 patients with a known exposure date. To date, 132 pregnancy outcomes have been reported, including 126 (95%) live births and 6 (5%) spontaneous abortions (< 22 weeks). Of the 126 live births, 115 (91%) were full term (delivered ≥37 weeks) and 8 (6%) premature. Four (3%) infants had adjudicator-confirmed birth defects: 1 with pyloric stenosis; 1 with transposition of the great vessels; and 2 infants had ventricular septal defect. No ectopic or molar pregnancies were reported. No maternal, neonatal, perinatal, infant deaths or still births were reported. Of the 105 infants with gestational size data, 9 (9%) were classified as small, 87 (83%) as appropriate, and 9 (9%) as large and median (min, max) gestational weight was 3300 (1450, 4660) grams.
Conclusions: Consistent with previous reports, there was no safety signal for DMF exposure on pregnancy outcomes based on data from this ongoing registry. This registry continues to provide essential information concerning exposure to DMF during pregnancy.
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Claudia Prada: employee of and holds stock/stock options in Biogen
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P604

Incidence of natalizumab-associated progressive multifocal leucoencephalopathy and its relationship with the pattern of natalizumab exposure over time

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Introduction: Since the 2012 identification of 3 risk factors for natalizumab-associated progressive multifocal leucoencephalopathy (PML)—presence of anti-JC virus (JCV) antibodies, prior immunosuppressant (IS) use, and longer treatment duration—changes in the PML incidence rate have been of interest.
Objective: Determine the natalizumab-associated PML incidence over time in the global postmarketing setting since introduction of the anti-JCV antibody assay and evaluate the relationship of PML incidence with natalizumab exposure over time.
Methods: The incidence of confirmed PML cases in Biogen's global safety database from November 2009 to November 2017 was evaluated retrospectively. Overall incidence in all exposed patients was determined by the estimated total number of patients ever exposed to natalizumab and the number of confirmed PML cases. Changes in natalizumab exposure patterns over time were evaluated by 12-infusion epochs. As individual-level data for anti-JCV antibody status and history of prior IS use are often not available in the postmarketing setting, this evaluation focused on overall PML incidence and exposure (based on postmarketing data).
Results: As of 30 November 2017, 180,656 patients worldwide had received ≥1 natalizumab dose (total exposure: 625,451 patient-years); overall natalizumab-associated PML incidence was 4.19/1000 patients. The increase in overall monthly incidence reported from 2012 onward appears to level off in mid-2016; overall incidence remained between 4.18-4.24/1000 over the last 21 months. PML incidence was greatest in the later, higher risk infusion epochs (37-48, 49-60, and 61-72); however, the number of patients in these higher risk epochs increased over time, with the most dramatic percentage increase between 2011 and 2013. This may have been a key factor in the increased overall PML incidence during that period. Increases in the proportion of patients in later exposure epochs (>24 infusions) declined from 2013-2015 and further from 2015-2017, coinciding with a slower increase in overall PML incidence from 2013 onward and the flattening observed since mid-2016.
Conclusions: Overall PML incidence has been stable since mid-2016. This stabilisation coincides with the introduction and publication of a new risk algorithm, suggesting that risk stratification factors are being incorporated into clinical practice and may continue to impact future PML incidence.

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P605

Diffuse necrotising leuko-encephalopathy after treatment with alemtuzumab and imiquimod

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Alemtuzumab is a highly effective treatment for relapsing-remitting multiple sclerosis (RRMS) used in>20000 people with multiple sclerosis (pwMS) worldwide. Clinical use is

complicated by infections and antibody mediated secondary autoimmune disease. CNS autoimmunity leading to severe neurological deterioration has been recently described. This may be a B-cell-mediated process causing either diffuse necrotizing leukencephalopathy (DNL) or acute disseminated encephalomyelitis (ADEM).

A 27 year old lady with aggressive RRMS for 8 years, initially treated with interferon and natalizumab, but untreated since 2014, had a 1st course of alemtuzumab in February 2017 without complication. In September 2017 she reported reactivation of genital warts and was treated with imiquimod.

In November 2017 she developed a significant deterioration in motor function, progressing to needing a wheelchair by 8/1/18, and became bedbound by 15/1/18. MRI showed >30 contrast enhancing tumefactive lesions across her brain and spinal cord. CSF protein was 1.48g/L, WCC 11/Cu.mm. CD19+B cell count was 152cells/cmm (within normal range (NR)) comprising 41% of total lymphocytes. CD3+T cell count was relatively low at 174cells/cmm (NR>700) comprising 46% of total lymphocytes. Infectious causes, including toxoplasmosis were excluded. She was treated with methylprednisolone (7g) and 5 sessions of plasma exchange (PLEX) providing transient stability. 6 days after PLEX she deteriorated, becoming anarthric and quadriparetic. A tracheostomy was needed due to impaired bulbar function. MRI appearances worsened, with even more enhancing lesions and widespread leukoencephalopathic changes. She was given rituximab (2.4g) and 5 more PLEX sessions. Repeat lymphocyte subsets after rituximab showed a CD19 B cell count of 1 and CD3+T cell count of 252 comprising 87% of total lymphocytes. She is recovering and can now talk, swallow and use her right arm.

B-cell mediated severe neurological deterioration (BCMND) is thought to occur as a result of rapid reproliferation of B cells without T cell regulation. Eight cases of BCMND after alemtuzumab have been reported and we think that similar mechanisms led to this presentation suggesting an overall risk of approximately 1/2000. The use of the immune stimulating treatment imiquimod may be relevant in this case, and doctors should avoid its use after alemtuzumab. Severe neurological disability and death from DNL is a risk without aggressive treatment

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P606

Influence of natalizumab extended interval dosing on the PML risk biomarker L-Selectin

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Low levels of L-selectin (CD62L) on CD4+ T cells have been introduced in 2013 as a risk biomarker for development of progressive multifocal leukoencephalopathy (PML) during natalizumab treatment or HIV infection. The biomarker has been reproduced internationally, but also been discussed with controversy concerning applicability/stability. In the current study, 1218 samples of 509 MS patients were collected alongside their natalizumab therapy in a prospective, observational study. Data were analyzed using a generalized linear mixed model (GLMM) with CD62L as the dependent, with sex, age, time point, season of blood draw, JCV serostatus, natalizumab treatment, treatment duration, development of PML, and fingolimod pre-exposure as covariates. Significant independent influences on CD62L were age (p=0.000264; effect size (ES)= -0.159%CD62L/year), treatment with natalizumab (p=0.00000012; ES= -10.285%CD62L in treated patients), season of blood draw (p=0.000654; ES= -1.938%CD62L in winter), pre-exposure to fingolimod (0.0202156; ES= -3.32%CD62L in patients with exposure), and development of PML (p=0.000091216; ES= -13.585%CD62L in (later) PML patients). The dataset, therefore, validated the reduced CD62L values by natalizumab treatment and by the condition of (later) PML. Subsequently, 779 samples of 247 patients were subjected to a subgroup analysis with available information for treatment intervals. The underlying hypothesis behind extended interval dosing (EID) is that patients with lower amounts of plasma are over-saturated by the standard monthly natalizumab infusion and, therefore, their immune-surveillance might be compromised. EID studies showed comparable clinical efficacy of the drug with suggested reduction of PML risk. In line with this hypothesis, the model showed that CD62L was influenced by the average days between infusions (p=0.000083). PML risk could not be evaluated in this subgroup analysis due to the low number of PML patients in the group, but the fact that EID was associated with higher CD62L values would be consistent with the working hypothesis: extended infusion intervals of natalizumab would lead to decrease of serum levels and receptor saturation and, subsequently, diminished natalizumab influence on CD62L. Taken together, the biomarker L-Selectin reflects validated PML risk factors: CD62L is lowered by natalizumab treatment, age, standard interval dosing, and in patients, who later develop PML or currently suffer from the disorder.

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Pancytopenia, evening fever and hepatosplenomegaly in a Fingolimod treated-woman

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Introduction: Fingolimod,the first oral immunomodulatory treatment for relapsing multiple sclerosis(MS),acts by blocking lymph-node egress of T cells expressing the CCR7-receptor,resulting lymphopenia by selective lymphocyte redistribution with preservation of immunological memory.

Objectives: To report a visceral Leishmaniasis in a patient treated with fingolimod for 62 months.

Case report: This 55-year-old Caucasian, Spanish woman presented with an evening fever of 37-39°C,night sweats,fatigue and mild pain in the left hypochondriac region for 2 weeks.Physical examination revealed hepatosplenomegaly.During fingolimod treatment regular blood tests had showed acceptable lymphopenia (over 500 /μl).Blood tests revealed normocytic,normochromic anaemia, leukocytopenia (1.980/μl), neutropenia, lymphocytopenia (200/μL), thrombocytopenia, elevated CRP(212.73mg/dl) and ESR(91 mm), increased GGT, liver function tests and serum gammaglobulins.Abdominal ultrasound and computerized tomography revealed marked hepatosplenomegaly.Bone marrow biopsy revealed no evidence of haematologic disease and scattered infiltration by *Leishmania* between cells and some within macrophages,later confirmed by serum PCR(*Leishmania infantum)*.The patient was treated with intravenous liposomal amphotericin B and made full recovery with normalization of blood tests.

Discussion: Visceral leishmaniasis,a disseminated disease, caused by *Leishmania spp.*, transmitted between vertebrate hosts by the bite of phlebotomine sandflies.In Spain there are about 110 annual cases of human leishmaniasis(18 declared in the Madrid community).In individuals with impaired cellular immunity, visceral leishmaniasis is characterized by increased humoral immune responses. More importantly,there is evidence that both CD4+ and CD8+ T central memory(CM) cells provide immunity to *Leishmania spp* acting as a reservoir of effector memory T-cells(TEM cells)upon secondary infection.In extended periods of antigen presentation the TEM cells decline and the integrity of TCM cells is a prerequisite for the replenishment of the TEM cells reservoir and the successful immune response.Th1 cells and TCM,mainly affected by fingolimod,are integral parts of an effective immune response to leishmaniasis infection.In patients with MS living in regions where leishmaniasis is endemic the administration of fingolimod should be done with caution,and in a patient with pancytopenia,fever,hepatosplenomegaly we should suspect visceral leishmaniasis.

Disclosure

No disclosures to report

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The results of a 24-month controlled, prospective study of relapsing MS patients at risk for PML who switched from long term natalizumab to teriflunomide

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Introduction: Natalizumab (NTZ) is a highly effective disease modifying treatment (DMT) for relapsing forms of MS but NTZ use carries the risk of progressive multifocal encephalopathy (PML) with prolonged use and detectable anti-JCV antibodies.

Objective: There is a need for a DMT that would be safe and effective to prevent recurrence of MS exacerbation upon discontinuation of NTZ without the risk of PML.

Aims: To explore the safety and efficacy of teriflunomide in patients switching from NTZ to teriflunomide.

Methods: Patients with MS who received 12 or more NTZ treatments and be anti-JCV-ab positive without prior immunosuppression. Patients had to be free of clinical relapses during prior 12 months of NTZ treatment. MS patients ages 21 to 65 began teriflunomide at 14mg daily, within 4 weeks after last dose of NTZ. Relapse assessment, EDSS, 3T brain MRI, laboratory tests were performed at baseline and monthly for 6 months. Assessments were done at 12, 18 and 24 months.
Results: There were 58 patients screened and 51 enrolled. Mean age was 48.. Seventy five percent were female. The mean EDSS at baseline was 2.94.; 47 patients completed 12 months with mean EDSS of 2.98. Twenty eight patients completed month 24, with mean EDSS of 2.86. The mean number of NTZ treatments prior to treatment with teriflunomide was 41.
MRI results showed 15 patients (29%) stable in all parameters from baseline to month 24. Of the 28 patients having completed month 24, 15 patients had new MRI activity . There were 15 patients with Gd+ enhancing lesions, 11 patients with new T2 hyperintensities and 4 patients with enlarging lesions. Most of the patients with new MRI lesions had no symptoms. Only six patients required change of DMT due to MRI progression. Fourteen patients dropped out of the study due to adverse events or lack of efficacy.
Conclusions: These results show that, in the majority of patients, teriflunomide may be a rational choice for long term safety and efficacy for patients at risk for PML. Early switch, in fewer than 4 weeks, from NTZ to teriflunomide, may be important to suppress ongoing ´rebound´ and recurrent MS activity after stopping NTZ. There were no cases of severe MS exacerbation and no cases of PML.

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Reduction of the risk of PML in natalizumab treated MS patients in Sweden: an effect of JCV ab index surveillance

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Background: Natalizumab (NTZ) was approved in 2006 for treatment of active relapsing-remitting MS (RRMS). Because of progressive multifocal leukoencephalopathy (PML) during NTZ treatment, a global risk management plan was introduced. Increased risk of PML is found in patients with previous immunosuppressive therapy, NTZ treatment >24 months and in patients with high titre JC virus (JCV) serology.
Aim: To investigate influence of the national PML risk management of NTZ for treatment of RRMS in Sweden.
Methods: Swedish MS registry data was retrospectively collected on NTZ treatment, other disease modifying treatments, and JCV serology from 2006 to March 2018. The risk management plan included JCV serology and index (introduced in late 2011). The data from Sweden was compared to the global number of PML cases diagnosed during NTZ treatment reported by Biogen.
Results: Since the introduction of NTZ 763 cases have been diagnosed with PML globally (March 2018). Eight of these PML cases have been diagnosed in Sweden between June 2008 and December 2012. Mean NTZ treatment duration at the time of PML diagnosis was 36 months (range 17-50 months) in Sweden compared with 50 months (range 8-144 months) globally. In February 2018, the incidence of PML in Sweden and globally was 0.7 and 4.2 per 1000 patient years, respectively. The number and proportion of RRMS treated patients in Sweden with an ongoing NTZ treatment increased from 113 (4%) in 2006 to 1139 (23%) in 2011. Although the number of NTZ treated patients was similar thereafter (n=1116, year 2018), the proportion of JCV + NTZ treated patients decreased to 13%. The main reasons for NTZ discontinuation were JCV+ (41%) and pregnancy/planning pregnancy (15%). Patients who discontinued NTZ treatment mainly switched to rituximab (33%) and fingolimod (19%). In 2011, available JCV serology showed that 55% were JCV+ and the corresponding value in 2018 was 13%. However, of the JCV+ patients 34% had an index >0.9, i.e. approximately 4.5% had increased PML risk according to JCV index, and 66% of these had been treated >24 months, indicating that the number of patients at risk was < 3%.
Conclusion: Since 2012, no new PML cases have been diagnosed during NTZ treatment in Sweden. This is probably due to improved nation-wide PML risk management. The proportion of JCV+ has been markedly reduced and second-line treatment alternatives to NTZ have been used more frequently. Similar development has not been seen globally.

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Sanofi Genzyme; has served on scientific advisory boards for Almirall, Teva, Biogen, Merck, Novartis and Sanofi Genzyme; serves on the editorial board of the Acta Neurologica Scandinavica; has received unconditional research grants from Biogen, Novartis and Teva.

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Determinants of MS re-activation after discontinuing therapies

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Introduction: A decision to discontinue MS immunotherapies is common in clinical practice - whether in order to switch to another therapy or at an advanced stage of progressive MS without relapses. The evidence regarding individual risk of MS re-activation after treatment discontinuation is limited.

Aims: To evaluate associations of demographic and clinical patient characteristics with the risk of relapses after discontinuing treatment. Both overall and treatment-specific associations are explored.

Methods: Using the global MSBase registry, we identified all patients who discontinued MS immunotherapy after ≥3 months on treatment, with the recorded disability score (EDSS) at the time of discontinuing treatment, and prospectively recorded follow-up of ≥6 months. The probability of experiencing a relapse after discontinuing treatment, conditional on patient characteristics, was analysed with Cox proportional hazards model. Differences in these associations among different therapies were studied with interaction terms.

Results: 24,989 episodes of treatment discontinuation were recorded from 17,871 patients (74% female, mean age at discontinuation 39 years, 88% relapsing-remitting MS, mean MS duration 10 years, median EDSS 2.5). The patient characteristics associated with a lower hazard of MS re-activation were male sex (b=0.87, p< 0.001), older age (b=0.98, p< 0.001), MS duration (b=1.01, p< 0.001), secondary progressive MS (b=0.73, p< 0.001), longer treatment duration (0.95, p< 0.001), greater number of prior treatments (1: b=0.62, p< 0.001; ≥2: b=0.39, p< 0.001) and greater number of relapses during the previous year (1: b=1.30, p< 0.001; ≥2: b=1.62, p< 0.001). The characteristics associated with a greater risk of MS re-activation were clinically isolated syndrome (b=1.87, p< 0.001) and greater EDSS (4-5.5: b=1.41, p< 0.001; ≥6: b=1.17, p=0.001). Therapies used more recently (dimethyl fumarate, fingolimod, natalizumab) tended to be associated with a lower hazard of MS re-activation compared to interferon β. These associations differed among therapies for MS and treatment duration and number of prior therapies.

Conclusions: Patient demographic and clinical characteristics help determine the risk of clinical MS re-activation after treatment discontinuation. These associations differ between immunotherapies. We will further characterise these associations in detail and will estimate time frames for disease re-activation specific to the individual therapies.

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Minimal impact of anti-alemtuzumab antibodies on the pharmacodynamics and efficacy of alemtuzumab in RRMS patients from the CARE-MS studies

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Introduction: MS patients (pts) on biologic therapies develop anti-drug antibodies (ADA) that may affect the treatment pharmacodynamic (PD) profile and/or efficacy. Alemtuzumab, a humanized, anti-CD52 monoclonal antibody approved for RRMS pts, is administered as 2 initial courses (12 mg/day; baseline: 5 consecutive days; 12 months later: 3 consecutive days) with up to 2 additional courses (3 consecutive days; ≥12 months apart) as needed for disease control. In the CARE-MS studies (NCT00530348, NCT00548405), 2 courses of alemtuzumab significantly improved clinical/MRI outcomes vs SC IFNB-1a; efficacy was maintained in a 4-year extension (NCT00930553), wherein pts could receive additional courses as needed.
Aims: To determine the effect of alemtuzumab ADA on PD and efficacy in CARE-MS pts.
Methods: Alemtuzumab-binding ADA status (ever positive or always negative) was evaluated in pts receiving Course 2 (C2; all pts) and Course 3 (at any time point; median interval from C2, 2.2 years). Other assessments for correlation: lymphocyte counts (total, CD4+ T cells), annualised relapse rates (ARR), and new Gd-enhancing lesions.
Results: Of 811 pts from the pooled CARE-MS studies, 87.8% were positive for binding ADA at any time point during the 2-year alemtuzumab treatment period; 292 (90.4%) pts who received C3 were ADA positive. Median ADA titres peaked 1 month after C2 and C3, and decreased 100-fold 12 months later (defined treatment interval); titres were higher post-C3 vs post-C2. No discernible difference was detected in total or CD4+ lymphocyte depletion and repopulation patterns or efficacy measures after C2 between pts who were ADA positive or negative. The mean total lymphocyte count nadir was lower post-C2 vs post-C3. The ADA effect was minimal on CD4+ T cell depletion after C3, with limited non-significant changes in pts in the highest titre quartile. ADA had no effect a year after C3 on ARR (ADA negative: 0.19; titre quartiles 1-4: 0.16, 0.15, 0.26, and 0.15) or the percentage of pts free of Gd-enhancing lesions (ADA negative: 89%; titre quartiles 1-4: 87%, 90%, 90%, and 82%). There was no consistent trend for an ADA impact on efficacy through Year 5 post-C3.
Conclusion: Although the incidence of ADA was high at mid-course determinations with marked reduction prior to each course, it had minimal impact on long-term alemtuzumab PD/efficacy in CARE-MS pts. Peak ADA titres dropped precipitously by 12 months, the required treatment interval post-alemtuzumab.

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P612
$CD4^+CD62L^+$cells could be a useful biomarker for monitoring intermittent drug holidays of fingolimod administration

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Background: Patients with multiple sclerosis (MS) treated by fingolimod (FTY) show lymphocytopenia. To prevent severe lymphocytopenia, we proposed intermittent drug holidays. However, we did not have a useful biomarker for monitoring FTY dosage to avoid an increase of MS disease activity or progressive multifocal leukoencephalopathy.
Methods: Twenty-nine Japanese MS patients (M/F: 11/18) treated by FTY (MS-FTY) were studied. The duration of FTY treatment was 47.2 ±18.2 months, in that, period of daily administration of FTY was 27.8 ± 21.0 months (median, 22 months).Fifteen Japanese MS patients (M/F: 9/20) treated by interferon beta or glatiramer acetate and untreated 14 patients were also included as control. We examined $CD4^+CD62L^+$cells (CD4/62L cells) in their peripheral blood by FACS (fluorescence activated cell sorting).
Results: The numbers of total lymphocytes and CD4/62L cells in control were 1680 ±587 (810 to 3257, median, 1500) and 396 ±148 (150 to 764, 378)/mm^3, respectively. On the other hand, MS-FTY patients (daily administration 14%, 5-6 times 52%, 3-4 times 29%, twice a week 5%)showed that 472 ±137 (250 to 710,

median, 489), and 12 ±13 (2 to 67, 8) /mm^3, respectively. After 8 months (gradually decreased todaily administration 4%, 5-6 times 30%,2-4 times per a week 26%, every 5 days 40%), the same MS-FTY patients showed total lymphocyte number 490 ±103 (290 to 690, median, 491), and CD4/62L cells 28 ±19 (6 to 80, 22)/mm^3, respectively. Lymphocyte counts were not changed (p= 0.485) but CD4/62L cells were increased significantly (p= 0.001) after further decrement dosage of intermittent drug holidays including every 5 days administration. We found no change of R-R intervals of ECG in 10 MS patients during every 5 days administration just before and 6 hours after FTY administration (p= 0.137), although they showed prolonged R-R intervals at the initiation (p< 0.00001). We found no relapses or no brain MRI (examined every 3-6 months) activity in the cases with less than 80/mm^{3}of CD4/62L cells, however, we found an exceptional female patient with a relapse of mild left leg weakness at 360/mm^{3}lymphocytes and 17/mm^{3}CD4/62L cells.

Conclusions: We found that number of CD4/62L cells are more suitable marker for monitoring FTY dosage than total lymphocyte count. And gradual decrement of FTY dosage to every 5 days administration may not influence on a cardiac conduction.

Disclosure

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P613

Evolution of anti-JCV index with natalizumab treatment for multiple sclerosis: a retrospective, longitudinal study

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Introduction: Among patients treated with natalizumab for multiple sclerosis, the presence of serum anti-JCV antibodies predicts development of progressive multifocal leukoencephalopathy (PML). However, the association between prolonged natalizumab therapy, rising antibody titres and their relevance to increased PML risk is poorly understood.

Objectives: A retrospective, longitudinal audit was undertaken to investigate effects of natalizumab on serum anti-JCV antibody titres over time.

Aims: To determine whether natalizumab treatment length increases risks of seroconversion.

Methods: Among 154 patients treated with natalizumab for MS, we evaluated sequential changes in anti-JCV antibody titres from baseline using the STRATIFY JCV™ DxSelect™ assay.

Results: No baseline differences in mean antibody titres were identified between patients seroconverting or remaining seronegative (0.178±0.0161 vs. 0.208±0.0157, p=0.417 respectively). However, seroconverting patients showed rising antibody titres early in the follow-up period, with mean antibody titres that were consistently and significantly higher than those remaining seronegative (p< 0.01). Antibody titres remained stable over time with prolonged natalizumab use among all baseline-seronegative patients and those that seroconverted. However, seroconverting patients were treated for significantly longer with natalizumab compared to those remaining seronegative (44.9±3.61 vs. 32.1±2.05 months, p=0.005). There were no gender differences in anti-JCV titres at baseline (0.503±0.0855 male vs. 0.555±0.214 female, p=0.97) or over time. No significant differences were observed in baseline antibody titres between age groups, with no age group more likely to seroconvert (p=0.445).

Conclusions: Contrary to previous publications, anti-JCV antibody titres remained stable among baseline-seronegative patients treated with natalizumab despite established associations between high antibody titres, treatment length, and PML development. Our results suggest certain patients demonstrate early changes in anti-JCV titres with natalizumab leading to seroconversion, indicating variability in the immune predisposition to seroconvert. This warrants further investigation to better understand the complex interplay which exists between viral, host and environmental factors that link seroconversion to PML development.

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P614

Two cases of atypical psychiatric presentations after ocrelizumab induction with near complete resolution

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Introduction: Ocrelizumab is a novel humanized CD-20 monoclonal antibody that has been deemed safe and effective for treatment in Multiple Sclerosis. Primary adverse events were

comparable to placebo, and less frequent than other non-humanized antibody infusions.
Objectives: We present two patients with unique psychiatric presentations occurring approximately two weeks after the second induction infusion. Both patients had a similar weakness, paranoid and somatic delusions, memory deficits, and delirium and both followed a similar natural time course.
Aims: We aim to describe a novel and ultimately benign clinical phenomenon associated with ocrelizumab infusions in two patients.
Methods: Patients self presented to local emergency departments at the urging of family who noticed an atypical confusion. They were monitored and evaluated for other causes of encephalopathy, and they were seen in follow up in a rehab setting, and then followed clinically by their neurologists. When the atypical nature of their syndrome became present, data was gathered retrospectively from documentation during their hospitalizations and follow up to determine similarities and differences in their clinical course and recovery.
Results: Case 1: 48 year old woman with a 20 year history of treatment for relapsing remitting multiple sclerosis (RRMS), anxiety, hypothyroidism, insomnia, and post-menopausal symptoms. She presented to a regional medical center in January of 2018 for weakness, fatigue, and confusion. She described three weeks of new episodic anterograde memory deficits, paranoia, and somatic delusions of her bones changing. Case 2: 54 year old woman with 6 year history of treatment for RRMS who presented in December of 2017 for falls, weakness, paranoia, anterograde memory loss, and a belief that her teeth were melting. For both patients, symptoms had begun two weeks after receiving her second induction dose of ocrelizumab. Workup was negative and both patients improved to near baseline within 2 months with minimal intervention.
Conclusions: Two separate cases of a unique psychiatric syndrome within six months of regular use of a monoclonal antibody is not enough to suggest causation. However, because patients with neuroinflammation and degeneration may have unique psychiatric reactions to immune modulating infusions, better and more focused analysis of the progression and phenomenology of post infusion syndromes should be monitored and analyzed.

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P615
Shared decision making; is it truly 'shared' in multiple sclerosis? The neurologist, nurse, & patient perspective

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Background: Navigating Multiple Sclerosis (MS) is a global initiative which aims to improve outcomes for people with MS through the global adoption of strategies that optimize therapeutic decision-making and improve the way that healthcare professionals, patients and care partners communicate around benefit and risk in the management and treatment of their disease. In order to better understand the potential barriers to effective communications and shared-decision making (SDM), the Navigating MS Steering Committee developed and disseminated a survey to MS healthcare professionals and people living with MS (PLwMS) to identify potential and perceived barriers to successful SDM in MS practice.
Method: Three barrier surveys were conducted to clarify perceptions of neurologists, nurses and patients with regard to SDM and treatment discussions. These surveys were disseminated amongst clinical networks and MS patient advocacy organisations. A total of 73 neurologists,104 nurses, and 1184 (PLwMS) have responded to date.
Findings: Discord in the perception of neurologists, nurses and PLwMS regarding the adequacy of resources required for successful SDM was demonstrated in the data received. Four main areas of contention were identified; lack of education, resources, time, and variable involvement of the interdisciplinary team.
Nurse respondents indicate a perceived proficiency with SDM and adequacy of education and training to fulfil this role. However, 73% of PLwMS respondents indicated a strong preference for engagement with the neurologist in discussing the benefits and risks of treatment options. There was no clear consensus regarding the degree to which decision-making is accurately a collaborative process within the interdisciplinary team. 50% of nurses stated the decisions were shared, although PLwMS reported a lot of ambiguity and variation in how actively involved they were in the decision-making process. Despite neurologists stating the main barrier to SDM was lack of time, 49% of PLwMS strongly disagreed that time was a barrier to SDM, with 60% of nurses reporting clinic timeframes as adequate.
Conclusion: The incongruency of perceptions amongst clinicians and PLwMS regarding the success of current models of care to deliver optimal outcomes demonstrates an ongoing need to educate both healthcare professionals and patients on best practices in adopting a SDM approach to discussions around treatment decisions.

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P616
A modified premedication protocol significantly reduces ocrelizumab-induced infusion reactions

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Introduction: Ocrelizumab is a monoclonal antibody directed against CD20+ B cells that is approved for RRMS and PPMS. One of the known side effects is infusion reactions, which was reported to be 34-40% in the clinical trials.
In an attempt to decrease the occurrence of infusion reactions, a modified premedication protocol was implemented at The University of Chicago MS Center in addition to what is recommended in the PI. The night and morning prior to infusion, patients were instructed to take cetirizine 10mg and ranitidine 75mg, as well as adequate hydration. Immediately prior to the infusion, they received diphenhydramine 50mg, methylprednisolone 125mg, and acetaminophen 650mg.
Objectives: The primary objective was to compare whether addition of cetirizine, ranitidine, and hydration to standard of care further decreases chances of ocrelizumab-related infusion reactions. The secondary objective was to examine predictors of infusion reactions.
Methods: A retrospective chart review was undertaken to record age, race, smoking status, body mass index (BMI), and whether an individual was instructed to take the modified premedications for patients who received ocrelizumab at The University of Chicago. Presence of infusion reactions were ascertained by examining documentation by infusion nurses.
Results: 207 patients received ocrelizumab from the time the drug entered the market through April 2018. 110 patients were instructed to take the modified premedication protocol. There was a significant decrease in odds of infusion reactions with our modified premedication protocol (OR 0.40, p=0.02).
Among the patient characteristics, we found that age and male sex decreased odds (OR 0.94, p=0.001; OR 0.34, p=0.034), and BMI increased odds (OR 1.07, p=0.029) for infusion reactions. Race and smoking status did not have a statistically significant odds ratio.
Conclusion: A modification in the premedication protocol for ocrelizumab showed significant reductions in infusion-related reactions. We suggest that this should be more widely implemented. Our study also found that male sex and increasing age were protective against infusion reactions whereas increasing BMI was a risk factor for infusion reactions.

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P617

A real-world comparison of infection rate and lymphocyte counts among relapsing-remitting multiple sclerosis patients 50 years or older treated with subcutaneous interferon beta-1a or dimethyl fumarate

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Background: In clinical trials of disease-modifying therapies (DMTs) in patients with relapsing-remitting multiple sclerosis (RRMS), therapies such as dimethyl fumarate (DMF) and interferon beta-1a (IFN-b1a) have decreased total lymphocyte count (TLC) levels which, in real-world settings, are potentially associated with increased risk of infections. Data on these outcomes in older patients are lacking. This study compared infection rates and lymphocyte counts in RRMS patients ≥50 years old receiving subcutaneous (sc) IFN-b1a 44 mcg 3 times a week or DMF 240 mg twice daily.
Methods: A total of 36 RRMS patients ≥50 years old treated with IFNβ-1a sc (n=15) or DMF (n=21) were identified as having laboratory and clinical follow-up over 1 year with index date (baseline) between 1 January and 31 December 2015, by retrospective chart review at The Neurology Center of New England.
Results: Patients treated with IFNβ-1a sc and DMF had similar baseline characteristics (mean [SD]) including: duration of disease (14.7 [8.07] and 14.0 [12.52] years, respectively), number of prior DMTs (1.5 [0.99] and 2.0 [1.79], respectively) and number of relapses in prior 2 years (0.9 [1.03] and 1.0 [1.36], respectively). Only 1 patient in each group had a prior history of infection; 1 patient in each group had lymphopenia grade II at baseline, all others had normal TLC. The proportion of patients with ≥1 infection over 1 year was significantly lower for patients receiving IFNβ-1a sc than for those receiving DMF (33% vs. 71%, respectively; p=0.0409 by Fisher's exact test). Infection reports were also significantly fewer for patients receiving IFNβ-1a sc: 5 of 15 IFNβ-1a sc-treated patients had 7 total infections compared with 15 of 21 DMF treated patients, who had 43 infections over 1 year (rate ratio for IFNβ-1a sc vs. DMF=0.23; 95% confidence internal: 0.09-0.59; p=0.0023 by negative binomial regression). TLC from baseline to 1 year in DMF-treated patients decreased significantly compared with IFNβ-1a sc-treated patients (mean [SD] change: -686.4 [577.64] vs. 336.9 [1179.89] cells/μL, respectively; p=0.0459 by t-test). Further results on changes in CD4 and CD8 counts and CD4:CD8 ratio will be presented.
Conclusions: Significantly higher infection rates and more severe TLC reductions were seen in older RRMS patients receiving DMF compared with those receiving IFNβ-1a sc. Further evaluation of the effect of DMTs on lymphocyte levels and infection rates is warranted in a larger study.

Disclosure

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P618

Safety liver profile of teriflunomide versus interferon β in multiple sclerosis: systematic review and indirect comparison meta-analysis

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Objectives: To compare the liver safety profile of interferon β (IFN β) and teriflunomide in patients with multiple sclerosis
Methods: A systematic review of literature and network meta-analysis was carried out following the Cochrane Collaboration methodology. All randomised, double-blind, single-blind, or open-label, as well as cross-over trials, comparing all types of IFN β with teriflunomide, or either drug with glatiramer acetate, natalizumab, alemtuzumab, fingolimod, daclizumab, or placebo in participants with RRMS were included. Studies involving patients with secondary progressive multiple sclerosis (SPMS) were excluded. An indirect comparison network meta-analysis within a Bayesian framework with STATA (version 13.0) was done for this study. We summarised the results of network meta-analysis with effect sizes (OR) and their confidence intervals (95% CI).
Results: The database searches yielded 284 titles, with 15 records as duplicates. One study was identified by manually searching. Thirteen articles were included in the systematic review. Twelve studies compared IFN β (4203 patients) vs another DMT. Four studies evaluated the effectiveness and safety of teriflunomide (906 patients) vs another DMT. Six studies reported drug-induced liver injury as per the Hy's Law. However, only one study had a direct comparison and reported no cases of liver toxicity in either group, so it was not possible to estimate the OR. The indirect comparisons metanalysis shows that there was no statistically-significant difference between teriflunomide and IFN β (OR 1.09, 95% CI 0.02-2.16).
Conclusions: There were no significant difference when comparing IFN β and teriflunomide in terms of liver failure or elevation of transaminases. Even though there was evidence that patients of with teriflunomide, compared to IFN β, had an increased risk of having a liver function test alteration, it is difficult to provide a meaningful interpretation given that the liver tests evaluated and cut-off points used varied widely from study to study

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Tools for detecting therapeutic response

P619

Ocrelizumab treatment effect on upper limb function in PPMS patients with disability: subgroup results of the ORATORIO study to inform the ORATORIO-HAND study design

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Background: It is critically important, for independent daily living, to preserve upper limb function in patients with primary progressive multiple sclerosis (PPMS), especially among those with advanced disability. In the Phase III ORATORIO study (NCT01194570), ocrelizumab (OCR) demonstrated efficacy vs placebo (PBO) in reducing upper limb dysfunction, assessed by 9-Hole Peg Test (9HPT) in PPMS patients with Expanded Disability Status Scale (EDSS) ≤6.5. An important unmet need would be addressed if OCR benefited upper limb function in more disabled PPMS patients ineligible for inclusion in ORATORIO who are more representative of real-world clinical settings.
Objective: To assess the effect of OCR on upper limb function in subgroups of more disabled/older patients in ORATORIO, and thereby to inform the design of ORATORIO-HAND, a Phase IIIb, randomised, double-blind, placebo-controlled study in PPMS.
Methods: In ORATORIO, PPMS patients (N=732) with EDSS 3.0-6.5, aged 18-55 years were randomised (2:1) to OCR or PBO for ≥120 weeks and until a pre-specified number of EDSS progression events (primary endpoint) occurred. Efficacy of OCR in preventing confirmed 20% worsening in 9HPT was investigated in pre-specified baseline (BL) subgroups of EDSS ≥6.0 and age >45 years, and in an additional subgroup with 9HPT times >25 seconds (s).
Results: Subgroup analyses indicate that OCR reduces progression of upper limb disability in more disabled/older PPMS patients: relative risk reduction with OCR vs PBO in 12-week confirmed 9HPT was similar in patients with BL EDSS < 6.0 and ≥6.0 (40% vs 38%, interaction p=0.9187). It was also similar in patients with BL 9HPT ≤25s and >25s (49% vs 44%, interaction p=0.8221); however, 9HPT progression events mainly occurred in patients with 9HPT >25s vs ≤25s (PBO: 34.3% vs 17.8%; OCR: 21.5% vs 9.9%). In patients ≤45 years, OCR showed a weak trend for greater risk reduction for 9HPT progression than those >45 years (52% vs 33%, interaction p=0.2854).
Conclusions: Based in part on the observed encouraging treatment effect of OCR on upper limb function, the ORATORIO-HAND study has been designed to further investigate the efficacy of OCR on upper limb function in a rigorous, controlled manner. Eligible patients will be randomised (1:1) to OCR or PBO for ≥120 weeks and until a pre-specified number of confirmed 9HPT progression events (primary endpoint) occur. Key entry criteria include EDSS 3.0-8.0, age 18-65 years, 9HPT >25s. Screening will begin Q4 2018.

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P620

Analysis of a biomarker signature (TLR2, TLR4 and CCR1) by flow cytometry in patients with relapsing-remitting multiple sclerosis treated with fingolimod

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Background and Objective: We previously identified a putative biomarker signature, consisting of toll-like receptor 2 (TLR2), TLR4 and chemokine receptor 1 (CCR1), which had higher expression on naïve CD4 T-cells from patients with multiple sclerosis (MS) having rapid vs. slow transition to progressive MS. Here, we questioned whether differences in expression of this biomarker signature on naïve, central memory (CM), effector memory (EM) or terminal memory re-expressing CD45RA (TEMRA) CD4+ T-subsets or on monocytes predict disease activity in patients with RRMS treated with fingolimod.

Methods: Patients beginning fingolimod for MS were followed clinically and with seral MRI for up to 24 months. We defined patients as 'active' (n=10) or 'stable' (n=9) based on clinical (relapse) and radiological (new T2 hyperintense lesions) evidence on treatment. Using flow cytometry, we analyzed baseline and on-treatment (On-TX) cryopreserved peripheral blood mononuclear cells for surface expression of our biomarker signature: we analyzed CD3+ T-cells and naïve (CD45RA+CCR7+), CM (CD45RA-CCR7+), EM (CD45RA-CCR7-), TEMRA
(CD45RA+CCR7-) CD4 T-cells plus CD14+CD3- monocytes.

Results: Absolute numbers of all CD4+ T-subsets decreased in both patient cohorts On-TX with proportional decreases in CCR7+ and increases in CCR7- T-subsets. 'Active' patients had higher

numbers of CCR1+CD3+ T-cells/µl at baseline than 'stable' patients (19.96±2.99; vs. 11.99±1.80, p=0.04). In On-TX samples, the frequencies of naïve and CM CD4+ T-cells expressing each biomarker increased in both groups. The number of TLR4+ monocytes increased from baseline to On-TX only in the stable group (14.26±2.62 cells/ml vs. 41.27±6.54 cells/ml, p=0.002).

Conclusion: The 'active' vs. 'stable' groups showed several differences in biomarker expression. The differences in baseline T-cell CCR1 expression between groups complement the results of our previous biomarker study on rapid MS progression, by suggesting that CCR1 may predict subsequent disease activity in patients treated with fingolimod. The monocyte findings were unexpected but suggest that increasing TLR4 expression On-TX correlates with a positive response to treatment with fingolimod. In conclusion, we suggest that further flow cytometry analyses of immune cells may facilitate the development of clinically useful biomarkers that predict treatment responses.

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Dr. Jack Antel: Serves on advisory /safety monitoring boards for Novartis, Sanofi-Genzyme, Biogen Idec, EMD Serono and Medday Pharmaceuticals, and is editor of the Americas, Mutiple Sclerosis Journal.

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P621

Measuring disease activity in multiple sclerosis: the essential role of spinal cord MRI monitoring

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Background: Magnetic Resonance Imaging (MRI) of the Spinal Cord (SC) is recommended during diagnostic process in suspected Multiple Sclerosis (MS), while its role in monitoring disease evolution or as a surrogate marker in clinical trials, is still controversial. We hypothesize that the use of brain MRI only can reduce the ability to detect inflammatory activity in a proportion of MS patients.

Objective: To study the frequency of SC activity in a large sample of MS patients and to investigate whether MRI activity of brain and SC occurs independently.

Methods: From MS registry of a single clinical center, we selected patients fulfilling the following criteria: 1) at least two different MRI scan (Brain and SC) at two time point (at least 30 days apart); 2) minimum MRI requirements protocol [1.5 T system; Brain: a) Axial dual-echo PD;b) Axial contrast-enhanced T1-weighted. SC: a) sagittal T2-weighted; b) Post-gadolinium (Gd) sagittal T1-weighted]. The presence of inflammatory activity was defined as the detection of at least one Gd enhancing lesion (Gd+). A descriptive statistic was applied.

Results: From an initial cohort of 1332 patients we enrolled 828 subjects [F: 572; medium age: 34.7 ± 9.7; median Expanded Disability Status Scale (EDSS): 2.0 (range: 0-8); medium disease duration: 5.8 ±6.3; Clinically Isolated Syndrome (CIS): 305; Relapsing Remitting (RR): 430; Primary Progressive (PP): 50; Secondary Progressive (SP): 43]. A total of 5717 scans were reviewed (medium scans for patient 7±2); 4537 scans (79,3%) did not present Gd+. Of the 1180 left, 651 scans (55,2%) showed brain Gd+ lesions only, 232 (19,7%) a concomitant presence of brain and SC Gd+ lesions, while 297 (25,2%) showed SC Gd+ lesions exclusively. 58% of the SC Gd+ scan were not associated with a clinical relapse. When considering inflammatory activity along follow up, 282 patients have never presented Gd+ lesions, 546 patients presented Gd+ in at least one scan. The majority of them were CIS/RR=501 vs SP/PP=45. SC Gd+ alone in at least one scan was observed in 223 (approximately 40%) of patients.

Conclusions: MRI activity can be detected frequently in SC and it occurs in approximately 25% scans independently from brain activity. High percentage of SC GD+ can be asymptomatic. Limiting MRI monitoring to brain only, underestimates inflammatory activity in clinical trials. Including MRI of SC in clinical practice will allow switching treatment to more powerful drugs in a larger number of patients.

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P622

Fingolimod may exert a neuroprotective role at retinal level in multiple sclerosis when compared to first-line injectable treatments

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

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P623

Detecting response to fampridine on motor functioning with activities of daily living and classical neurological examinations in multiple sclerosis patients

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Background: Patients' subjective improvement of motor functioning after treatment with fampridine in multiple sclerosis (MS) is not fully covered with objective measures of walking speed, such as the Timed 25-Foot Walk Test (T25FW). This results from the incomplete coverage of other aspects of ambulatory function, and omission of upper extremity function (UEF) assessment, including tasks of activities of daily living (ADL).
Objective: To examine changes in motor functioning in MS patients treated with fampridine using a wide range of clinical tests, including UEF and ADL.
Methods: Patients were derived from a cohort of MS patients treated with fampridine that also participated in the Assess MS study, a project to improve clinical disability assessment through automated quantification of motor function. Patients were assessed before and after a minimum of two weeks of treatment. Tests for ambulatory function were: the MS Walking Scale (MSWS), T25FW, 'sit-to-stand', 'Romberg's test', 'turning-on-the-spot', 'tightrope walking' and '25-foot walking'. Tests for UEF were: the Arm function in MS questionnaire (AMSQ), 9-hole peg test, 'finger-to-nose test', 'pronator drift test' and 'drinking from a cup'. Treatment responder groups were compared, which were defined as ≥20% improvement on the T25FW (i.e. objective responder) and ≥8-point decrease on the MSWS (subjective responder).
Results: A total of 47 patients were included. Preliminary results revealed 27.0% objective and 45.9% subjective responders. There were no significant differences in age, sex, MS phenotype and disease duration among responders and non-responders. Compared to the non-responder group, the objective responder group had significantly greater MSWS change (16.5 vs 6.9 pts; $p = 0.022$) and T25FW improvement (27.6 vs 4.4%; $p < 0.001$). Assessment of treatment effects of fampridine on other motor tasks and further subgroups analyses (including stratification of

objective responders into improvement of £10%, between 10 and 20%, and ≥20%) are pending.
Conclusion: These preliminary results confirm that a larger proportion of patients improve subjectively after treatment with fampridine than measured with walking speed. Therefore, assessment of other domains of motor function (including UEF and ADL) may be useful to capture the full range of treatment response to fampridine. These analyses are currently pending.

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P624

FLOODLIGHT: smartphone-based self-monitoring is accepted by patients and provides meaningful, continuous digital outcomes augmenting conventional in-clinic multiple sclerosis measures

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Background: Sensor-based, active and passive smartphone-based self-monitoring (SSM) may be more sensitive and specific than periodic in-clinic assessments to measure progression in multiple sclerosis (MS).
Objective: To report an analysis of adherence, results from a patient satisfaction questionnaire and correlations between in-clinic tests and FLOODLIGHT SSM measures (NCT02952911).
Methods: Patients with MS (18-55 years; Expanded Disability Status Scale score 0-5.5; n=76) and healthy controls (n=25) received a preconfigured smartphone and smartwatch that prompt the user to perform the FLOODLIGHT SSM, comprising 'active tests' and 'passive monitoring' for 24 weeks. The primary analysis assessed participants' adherence (proportion of study weeks with at least 3 days of completed testing and at least 4 hours/day of passive monitoring) and patient satisfaction with the FLOODLIGHT SSM solution. In-clinic tests and brain MRI assessments were performed. Secondary analyses compared FLOODLIGHT SSM outcomes 1) between patients with MS and healthy controls and 2) with in-clinic outcomes in patients with MS. The correlation between FLOODLIGHT SSM outcomes and in-clinic tests was reported using Spearman's correlation coefficient (SCC).
Results: As of 4 May 2018, the interim analysis of adherence of 61 patients who completed the study showed 76.5% adherence to active tests and 83.2% to passive monitoring. Satisfaction amongst patients with MS who completed the study (n=61) was good to excellent (73.33 average score out of a possible 100 at termination visit). Correlations between FLOODLIGHT SSM and conventional in-clinic assessments at baseline (Spearman's rank correlation) were as follows: Correct responses from smartphone-based Symbol Digit Modalities Test (SDMT) vs oral SDMT: SCC=0.635, $p< 0.001$, n=53; Time between two consecutive pinch attempts in the FLOODLIGHT Pinching Test vs 9-Hole Peg Test: SCC=0.508, $p< 0.001$, n=54; Turning speed measured with the FLOODLIGHT Five-U-Turn Test vs Timed 25-Foot Walk test: SCC=-0.524, $p< 0.001$, n=55. Further comparisons between baseline FLOODLIGHT SSM and in-clinic testing MS outcomes will be presented.
Conclusions: Patients' adherence and satisfaction combined with correlations observed between in-clinic assessments and digital outcomes show promising potential for the FLOODLIGHT SSM solution to capture meaningful and relevant outcomes augmenting the clinical picture in patients with MS.

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Searching for predictors of response to high-efficacy therapies in relapsing-remitting multiple sclerosis: results from a single centre cohort

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Background: The use of high-efficacy therapies in patients with multiple sclerosis (MS) is becoming more frequent. Unlike interferon treatment, the early identification of patients who do not respond to this second line of drugs is unknown. This is of crucial importance to adopt a timely therapeutic strategy change.
Objective: To investigate several criteria of clinical and radiological early response to high-efficacy treatment to evaluate which criteria best identifies patients with a poor response.
Methods: From a prospective on-going cohort including all patients starting natalizumab and alemtuzumab in our centre, patientsthat started treatment ≥ 12 months ago at the time of data collection were selected. Patients are followed every 3 months, and presences of relapses and EDSS score were collected. Besides, patients underwent MRI scans at baseline and yearly thereafter. Following the methodology of the Rio Score, different categories were assigned according to the degree of clinical (EDSS, relapses) and radiological (new and active lesions) activity during the first year. In this way 8 categories were obtained: 3 categories + (MRI+ EDSS+ R+), 2 categories + (MRI+ EDSS+ R- /MRI+ EDSS- R+/ MRI- EDSS+ R+), 1 category + (MRI+ EDSS- R-/MRI- EDSS- R+/MRI- EDSS+ R-) and 0 categories + (MRI- EDSS- R-). Statistical association between clinical or radiological activity during the first 12 months and EDSS worsening after 36 months of follow-up was calculated.
Results: Two hundred and four patients who received natalizumab and 33 patients under treatment with alemtuzumab for at least one year were analyzed. Data failed to demonstrate any significant association between clinical or MRI activity and EDSS worsening. Nonetheless, regarding natalizumab treatment, it seems to be an association between the relapses occurred in the first 12 months of treatment and the appearance of new lesions in MRI at the third year. The change of the EDSS at 12 months correlates with that occurred at 36 months. As for alemtuzumab, the presence of relapses and the appearance of new lesions in the first year of treatment correlate with the appearance of relapses at 36 months.
Conclusions: We have not identified predictors of response to high-efficacy therapies in relapsing-remitting MS in our cohort. A larger sample of patients is probably needed to reach conclusive data, taking into account the low persistence of disease activity with the use of these drugs.

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P626
Brain network response upon natalizumab versus dimetylfumarate in multiple sclerosis

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Introduction: Efficient personalized therapy paradigms are needed to modify the disease course and halt grey matter (GM) and white matter (WM) damage in patients with multiple sclerosis (MS). Presently, promising new disease-modifying drugs show impressive efficiency, however, tailored markers of therapy responses are needed. In this study, we aimed to detect in a real-world setting and at a short-term the patients with a favorable therapy response upon dimethyl fumarate (DMF) or natalizumab (NAT) treatment by analyzing disease activity, brain structural integrity and the individual blood immunocellular response.
Methods: We selected two equivalent patient cohorts, based on age, disease duration, disability status (EDSS) and lesion volume, receiving DMF (n = 42) or NAT (n = 36) and followed them over 16 months. In these patients, the rate of cortical atrophy and deep GM volumes were quantified. GM and WM network dynamics were characterized by brain modularization as a marker of structural alterations. Additionally, lymphocyte subsets were analyzed in the DMF group by flow cytometry and related to clinical and MRI parameters.
Results: Two clinically equivalent DMF and NAT patient groups showed similar disease activity and comparable GM and WM network dynamics with increased global disconnection over 16 months. The rate of cortical atrophy was higher in the DMF group (2.4%) compared to NAT (2.1%) treatment. Among DMF-treated patients, those free of disease activity (MRI and clinical) (n = 17 responders, DMF_R) and those with disease activity (n = 21, DMF_{NR}) differed in their CD8+ cell depletion rates (DMF_R: 298.4 ± 190.6 /µl; DMF_{NR}: 197.7 ± 97.1 /µl) but also in cortical atrophy (DMF_R: 1.7%; DMF_{NR}: 3.2%). DMF_R presented reduced longitudinal GM and WM disconnection, as a marker of preserved or even improved structural global network integrity, when compared not only to DMF_{NR} but also to NAT-treated patients.
Conclusions: In a real world data set of clinically and radiologically comparable patient cohorts, the rate of cortical atrophy over 16 months was less upon NAT vs. DMF treatment. However, patients under DMF treatment with a stronger CD8+ T cell depletion presented a more favorable response in terms of cortical integrity and GM and WM network modularization. Our findings support the development of personalized treatment paradigms.

Disclosure
Nothing to disclose

P627
Lymphocyte dynamics are not associated with disease activity in patients switching to alemtuzumab from fingolimod and injectable treatments

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Background: Previous case series have highlighted high rates of disease activity in patients switching from fingolimod to alemtuzumab, potentially due to prolonged sequestration of autoreactive lymphocytes in lymph nodes after fingolimod withdrawal.
Objective: To investigate the relationship between disease activity and lymphocyte dynamics in patients switching to alemtuzumab from fingolimod and injectable disease-modifying therapies (DMTs).
Methods: We retrospectively collected data on consecutive patients switching to alemtuzumab from fingolimod (n=20) or injectable DMTs (n=28). Demographic (age, sex), clinical (disease duration, previous DMTs, relapses), laboratory (lymphocyte counts on day 1 and 5, and monthly thereafter for year 1) and MRI data were collected. Disease activity in year 1 after starting alemtuzumab was defined as clinical relapses, new/enlarging T2 and/or gadolinium-enhancing lesions. The two groups were compared using ANOVA and cross tabulation, and logistic regression was used to identify predictors of disease activity at 12 months
Results: The fingolimod group tended to be older (42 vs 37 years, p=0.116) and had a longer disease duration (158 vs 96 months, p=0.01) than the injectable group. The baseline lymphocyte count on day 1 of alemtuzumab treatment was lower in the fingolimod group compared with the injectable group (1.36 vs 1.88, p=0.01), but the lymphocyte nadir on day 5 was similar (0.048 vs 0.056, p=0.64). The fingolimod group had a higher lymphocyte count at all time points during the first 11 months after alemtuzumab. 4/20 (20%) patients in the fingolimod group and 1/28 (4%) in the injectable group had disease activity in the first year after

switching to alemtuzumab (p=0.15). No association was seen between baseline lymphocyte count, lymphocyte count nadir or lymphocyte recovery with disease activity in the whole cohort, or in the subgroup of patients switching from fingolimod.
Conclusions: We observed a high rate of disease activity in patients switching from fingolimod to alemtuzumab that was not explained by lymphocyte counts at the time of starting treatment or the dynamics of lymphocyte recovery in year 1.

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Symptomatic treatment

P628

Additional courses of alemtuzumab improved clinical and MRI outcomes in pooled CARE-MS I and II patients with disease activity after three courses: analysis of patients who received ≥4 courses

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Introduction: Over 2 years (y) in the CARE-MS studies, 2 courses of alemtuzumab (12 mg/day; baseline: 5 days; 12 months [M] later: 3 days) significantly improved outcomes vs SC IFNB-1a in treatment-naive RRMS patients (CARE-MS I; NCT00530348) or those who had an inadequate response to prior therapy (CARE-MS II; NCT00548405). Alemtuzumab remained efficacious in a 4-y extension (NCT00930553), wherein patients could receive additional courses of alemtuzumab (12 mg/day on 3 days; ≥12M apart) as needed for disease activity, or receive another disease-modifying therapy (DMT; investigator discretion). After the 4-y extension, patients could continue in TOPAZ (NCT02255656), an additional 5-y extension study, in which patients can receive additional as-needed alemtuzumab (≥12M apart; no criteria), or receive another DMT (any time).
Aims: To evaluate efficacy and safety in pooled CARE-MS patients who received Course 4 (C4) of alemtuzumab over 7 y.
Methods: Inclusion criteria for this analysis: ≥4 courses by M72, to allow ≥12M follow-up post-C4; no other DMT. Data were censored at C5.
Results: 742/811 (91%) pooled CARE-MS patients entered the extension, with 129 (17%) receiving ≥4 courses. C4 was given in Y4 (6.0%), Y5 (4.6%), Y6 (3.5%), or Y7 (3.2%); mean time was 1.9 y after C3. 103 (14%) patients met the analysis inclusion criteria. Annualised relapse rate was 1.59 12M pre-study, 0.77 12M pre-C4, 0.24 12M post-C4 ($P< 0.0001$), and 0.27 36M post-C4. At 36M post-C4, mean EDSS score change was -0.37 from the time of C4 administration, 95% of patients were free of 6-M confirmed disability worsening, and 31% of patients had 6-M confirmed disability improvement. At 12M pre-C4, 12M post-C4, and 36M post-C4, patients were free of MRI disease activity (50%, 65% [$P< 0.01$], and 74%, respectively), new gadolinium-enhancing lesions (64%, 81% [$P< 0.01$], 88%), new/enlarging T2 hyperintense lesions (50%, 65% [$P< 0.01$], 74%), and new T1 hypointense lesions (66%, 75% [$P< 0.05$], 87%). Incidence of adverse events (AEs), including infections and autoimmune AEs, in patients receiving additional courses was similar to the overall CARE-MS population and those receiving 2 courses over 7 y.
Conclusion: In the small percentage of patients with disease activity after C3, a fourth course of alemtuzumab, given on average 1.9 years after C3, improved clinical and MRI outcomes up to 36M. Safety was similar to the overall CARE-MS population and those receiving 2 courses over 7 y.

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FLX-787 significantly reduces muscle cramp/spasm frequency and improves spasticity in a phase 2 study (Flex-201) in patients with multiple sclerosis

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Introduction: FLX-787 is believed to dampen α-motor neuron and reflex hyperexcitability by chemical neurostimulation. In this process, TRPA1/TRPV1 coactivation in the oropharynx and esophagus leads to excitatory sensory input to stimulate brainstem nuclei and subsequently descending spinal tracts to inhibit hyperexcitability. The Flex-201 study was initiated in patients with Multiple Sclerosis (MS) to evaluate the safety and efficacy of FLX-787 in a disease state where the symptoms of cramps, spasms and spasticity are prevalent.

Objectives: To assess in an exploratory Phase 2 study: 1.)the frequency of cramps/spasms and associated-pain in MS patients; 2.) the efficacy of FLX-787 in treating cramps/spasms, pain and spasticity; 3.)the safety and tolerability of FLX-787.

Methods: Flex-201 was a multicenter, randomized, blinded, cross-over study which investigated the effects of FLX-787 in 57 MS patients with symptoms of spasticity, spasms and cramps versus inactive control. A daily questionnaire capturing cramp/spasm events, pain, stiffness and spasticity was administered using an interactive voice response system (IVRS). IVRS data, as well as in-clinic end-of-period assessments of spasticity, were analyzed.

Results: Analysis of the parallel portion of the study in the per-protocol population (n=45) showed that FLX-787 treatment caused a 27.3% reduction (p=0.0010) in the total number of cramps/spasms relative to baseline and a 42.5% reduction in total pain intensity (p=0.0486). Patients experienced a median increase of 1.4 cramp free days over the course of treatment (p=0.0457). Importantly, FLX-787 treatment caused a 1-point decrease relative to inactive control of the CGI-C spasticity score rated as a total improvement being entirely due to drug treatment (p=0.0427). CGI-C spasticity responders comprised 25% of the population and demonstrated a 2-point improvement on total modified Ashworth scale (p=0.025) and a 1-point improvement by NRS (0-10 scale) for spasticity (p=0.053). FLX-787 was generally well tolerated and resulted in infrequent GI-related adverse events (diarrhea and nausea).

Conclusion: This is the first report of FLX-787 being well-tolerated, safe and effective in treating common MS symptoms including cramps/spasms, pain and spasticity. These findings are similar to FLX-787 mediated reductions in cramp frequency associated with ALS and nocturnal leg cramps and suggest a broad applicability of FLX-787 across many neurological disorders.

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P630

Efficacy of prolonged-release fampridine vs placebo on walking ability, dynamic and static balance and quality-of-life: an integrated analysis of MOBILE and ENHANCE

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Introduction: MOBILE, an exploratory study, evaluated prolonged-release fampridine (PR-FAM) 10mg twice daily (n=68) vs placebo (n=64) on self-reported walking and balance in people with multiple sclerosis (PwMS; Expanded Disability Status Scale score 4-7) over 24 weeks. MOBILE identified an 8-point change in the 12-item MS Walking Scale (MSWS-12) as clinically meaningful. ENHANCE was similarly designed (PR-FAM [n=315] vs placebo [n=318]) and used MOBILE's threshold to evaluate clinically meaningful responses in self-reported walking, mobility, balance, and changes in self-reported physical MS impact.
Objectives: A post hoc integrated efficacy analysis of PR-FAM vs placebo using MOBILE and ENHANCE data.
Methods: MOBILE and ENHANCE data were pooled. The main analysis was the proportion of PwMS with a mean improvement in MSWS-12 score exceeding a predetermined threshold (≥8-points) from Baseline (BL) over 24 weeks. Additional endpoints were: Timed Up and Go (TUG) speed, MS Impact Scale physical subscale (MSIS-29 PHYS), Berg Balance Scale (BBS), EuroQol 5-dimensions (EQ-5D) visual analogue scale (VAS) and utility index score (UIS).
Results: 383 PwMS received PR-FAM and 382 PwMS received placebo. Significantly more PR-FAM-treated PwMS achieved a clinically meaningful ≥8 point mean improvement in the MSWS-12 over 24 weeks vs placebo (44.3% vs 33.0%; OR: 1.68 [95%CI: 1.23, 2.29]; $P< 0.001$). Significantly more PR-FAM PwMS achieved a ≥15% mean improvement from BL on TUG speed (44.1% vs 34.5%; OR: 1.54 [95%CI: 1.13, 2.11]; $P=0.007$). PR-FAM PwMS had greater mean improvements from BL in the MSIS-29 PHYS (least square mean [LSM] difference: −3.18 [95%CI: −4.84, −1.52]; $P< 0.001$) and BBS (LSM difference: 0.62 [95%CI: 0.09, 1.14]; $P=0.021$) vs placebo. PR-FAM demonstrated benefits on EQ-5D VAS and UIS, albeit not significant.
Conclusions: This post hoc pooled analysis supports previous studies, strengthening evidence that PR-FAM produces clinically meaningful improvements in self-reported walking and benefits self-reported physical function, mobility, balance and quality of life, sustained over 24 weeks.

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P. Feys has served on advisory boards for Biogen and Novartis; has received speaker fees from Excemed and Teva.
M. McNeill, C. Acosta, and M. Meergans are employees of and hold stock/stock options in Biogen.

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The effects of default mode network functional connectivity modulation on cognition and quality of life of people with relapsing-remitting multiple sclerosis

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Background: Cognitive impairment has been increasingly recognised as a common manifestation of multiple sclerosis (MS). Its detrimental effects, which are best observed by assessing memory and speed of information processing, have been reported to negatively impact on patients' quality of life (QoL). Moreover, changes in brain activity, particularly in the default mode network (DMN), appear consistently linked to cognitive impairment in patients with MS. However, this wealth of knowledge has been neglected when designing cognitive rehabilitation interventions for patients with MS which have mainly relied on symptomatic approaches.
Objectives: This study investigated the impact of a cognitive stimulation programme designed to modulate the DMN functional connectivity on cognitive performance, QoL and neuroplasticity in a cohort of people with relapsing remitting multiple sclerosis (RRMS).
Methods: Forty-five patients with RRMS (Expanded Disability Status Scale ≤ 6, age = 44.6 ± 8.8, disease duration = 9.1 ± 6.5) were randomised to three groups: standard cognitive stimulation

(CS), processing-speed-loaded cognitive stimulation (PS-CS) or non-intervention control group. The CS consisted of 20 sessions of computerised multi-domain exercises aimed at inducing co-activation of DMN areas. The PS-CS was developed by limiting the amount of time for response. Participants underwent cognitive and magnetic resonance imaging (MRI) assessments at baseline and after treatment completion. Mixed repeated-measure models were used to investigate group-by-time effects both on clinical and MRI outcome measures.

Results: Significant improvements in memory and QoL were observed in the CS compared to the other two groups. No differential effects emerged when the PS-CS and the control group were compared. However, both active treatment groups induced functional up-regulation of the posterior DMN. Moreover, the CS programme was associated with greater decoupling between the DMN and the anterior cingulate than the PS-loaded version. No microstructural diffusivity changes occurred across the three groups.

Conclusions: Cognitive stimulation focussed on the DMN induced neuroplastic changes and parallel improvements in cognitive performance. There was significant improvement in of patients' perceived QoL. This hypothesis-based treatment approach appears to benefit significantly people with RRMS experiencing cognitive impairment and should be further developed for home-based settings.

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Effects and mechanisms of cued and non-cued motor imagery in people with multiple sclerosis: a randomised controlled trial

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Background: Walking impairment and fatigue are prevalent symptoms in people with multiple sclerosis (pwMS), which significantly impact on their quality of life (QoL). In our previous study, motor imagery (MI) with rhythmic auditory cueing has been shown to improve walking, fatigue and QoL in pwMS. So far, the underlying mechanisms are unclear.

Objectives: To investigate the effects and mechanisms of differently cued and non-cued MI on walking, fatigue, QoL, MI ability and sensorimotor synchronisation (SMS) in pwMS, of gait to a fast and slow music beat.

Methods: Sixty pwMS with mild to moderate disability were recruited at the MS-Clinic, Innsbruck Medical University, Austria and randomised into one of three groups: music- and verbally cued MI (MVMI), music-cued MI (MMI) and MI. Participants were familiarised with (cued) MI and practised cued (MVMI/MMI) or non-cued MI of walking for 17 minutes, 6 times per week for 4 weeks in their homes. Primary outcomes were walking speed (Timed 25-Foot Walk) and walking distance (6-Minute Walk Test). Secondary outcomes were fatigue (Modified Fatigue Impact Scale), QoL (Multiple Sclerosis Impact Scale-29), MI ability (Kinaesthetic and Visual Imagery Questionnaire, KVIQ-10, Time-Dependent Motor Imagery screening test) and SMS (step length/time variability, stepwise synchronisation and absolute accuracy).

Results: Fifty-nine participants completed the study. All interventions induced significant improvements in walking speed ($p=0.013$) and distance ($p=0.036$) while MVMI was superior ($p=0.024$; $p=0.001$). After cued MI, there was a significant improvement in fatigue and QoL, with greatest changes in psychosocial fatigue ($p=0.041$) and physical QoL ($p=0.005$) after MVMI. All participants showed high MI ability and improved their MI ability post-intervention, as evidenced by median KVIQ-10 values of 4.1 (range 2.9-5.0) out of 5.0. Post-intervention, SMS was significantly more accurate in participants in the cued MI groups, as compared to those in the MI group (all $p< 0.05$). There were no adverse events and full compliance was observed.

Conclusions: Cued and non-cued MI improved walking although MVMI was the most effective intervention. Improvements in fatigue, QoL and SMS were induced only by cued MI whilst MVMI was superior. All participants were capable of imagining movements and improved the synchronisation of their gait with music only after a cued MI practice. Results suggest that MI and SMS were underlying mechanisms of action.

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P633

Characteristics of MS patients treated with fampridine in a real-world setting based on the NeuroTransData network in Germany

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Introduction: During the past 7 years, real-world data (RWD) of fampridine (FAM) have accrued and may inform on patients characteristics, drug persistence, effectiveness and PROs in the post-approval setting. NeuroTransData (NTD) is a German network of office-based neurologists documenting in-depth practice based data for multiple sclerosis (MS) patients and constitutes the first multicenter RWD study for FAM.

Objectives: The objectives of this study were to characterize patients exposed to FAM and investigate FAM-persistence, including predictors. Longitudinal analyses were conducted to describe the clinical course, including expanded disability status scale (EDSS) and EQ-5D, and compare FAM responders with non-responders.

Methods: Eligibility of patients was based on the availability of baseline data (e.g. MS subtype, background DMT, EDSS and FAM exposure). Baseline characteristics were described for the whole cohort as well as for responders (patients with ≥ 3 months exposure to FAM) and non-responders (< 3 months exposure). A univariate Cox regression was performed to assess the influence of potential baseline predictors on FAM discontinuation.
Results: As of 1 April 2018, 1159 patients (MS subtypes: 58.8% RRMS, 31.7% SPMS, 9.6% PPMS) were exposed to FAM in 63 documenting NTD centers. In this cohort, mean (SD) time to first MS symptoms was 15.9 (10.0) years and median (IQR) FAM exposure was 17.35 (2.07, 45.83) months. At FAM initiation, 29.2% of patients were receiving interferon treatment, 13.8% oral DMT, 7.6% high efficacy DMT, and 49.4% no DMT. 820 (70.8%) patients were classified as responders. At FAM initiation, mean (SD) Multiple Sclerosis Severity Score (MSSS) was 0.67 (4.95) in responders and 1.78 (20.34) in non-responders; mean (SD) EDSS was 4.86 (1.41) in responders and 4.80 (1.48) in non-responders; and 64.0% of responders and 67.3% of non-responders had physiotherapy. Based on 1100 patients with available data, a prediction model for FAM discontinuation due to adverse events or lack of effectiveness found that response to FAM was independent of baseline disease characteristics.
Conclusions: In this study of FAM patients in a real-world setting, the observed subjective response rate, based on persistence on therapy beyond 3 months, was 71%. FAM discontinuation was not strongly associated with baseline disease characteristics, thus FAM has the potential to provide benefits across a broad range of MS populations.

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Dr. Meergans and Dr. Hyde are employees of and hold stock/stock options in Biogen.

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Modulation of cortico-subcortical functional connectivity occurs after symptomatic treatment of fatigue in patients with multiple sclerosis

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Background: Fatigue affects a large proportion of patients with MS and has been associated with functional abnormalities of cortico-subcortical circuits, involving fronto-parietal regions and basal ganglia. Aim of this study was to investigate longitudinal changes of brain resting state (RS) functional connectivity (FC) in MS patients with fatigue undergoing different treatments for this symptom.
Methods: Forty-five fatigued MS patients were randomly, blindly assigned to treatment with fampridine (n=15), amantadine (n=15) or placebo (n=15) and underwent clinical, neuropsychological (including fatigue assessment) and 3T RS fMRI at baseline (T0) and after four weeks (W4) of treatment. Fifteen matched healthy controls were acquired twice. RS FC analysis of the main brain functional networks was performed using independent component analysis and statistical parametric mapping.
Results: At T0, compared with controls, MS patients showed increased RS FC of deep grey matter regions in the basal ganglia network, as well as several clusters of higher fronto-parietal RS FC in the sensorimotor, visual, and fronto-parietal attention networks. Decreased RS FC in the left postcentral gyrus was also detected. At W4, significantly decreased global, physical and cognitive (p=0.001/0.003/0.01) modified fatigue impact scale (MFIS) scores were found in fampridine patients and, to a lesser extent, in amantadine patients (cognitive and psycho-social MFIS, p=0.04). Placebo patients also showed improved global, physical and psycho-social MFIS (p=0.02/0.01/0.02). At W4, fampridine patients showed increased RS FC of the bilateral precuneus in the default mode and left fronto-parietal networks, as well as increased RS FC of the right inferior frontal gyrus in the salience and right fronto-parietal attention networks. At W4, small clusters of increased RS FC in frontal regions and decreased RS FC in temporo-parietal regions were detected in placebo and amantadine patients. A significant decrease over time of RS FC within the thalamus and other deep grey matter regions was found in fampridine and amantadine patients.
Conclusions: Treatment with fampridine (and, to a lesser extent, with amantadine) ameliorates fatigue in MS patients. Concomitant modifications of RS FC suggest an improved regulation of cortico-subcortical functional circuits.
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Disclosure

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Others

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Year one interim analysis results of the Phase IIIb CHORDS study evaluating ocrelizumab effectiveness and safety in patients with relapsing-remitting multiple sclerosis who had suboptimal response with prior disease-modifying treatments

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Introduction: Patients with relapsing-remitting multiple sclerosis (RRMS) can show signs of disease activity despite disease-modifying treatment (DMT). Ocrelizumab (OCR) demonstrated superior efficacy to subcutaneous interferon β-1a in two Phase III trials (OPERA I; OPERA II) in relapsing MS.
Objective: To report Year one interim analysis (IA) results of the multicentre, open-label, Phase IIIb CHORDS study (NCT02637856) evaluating OCR effectiveness and safety in patients with RRMS and a suboptimal treatment response to ≥6 months of DMT.
Methods: Eligible patients discontinued their most recent adequate course of DMT (i.e. administered for ≥6 months) due to suboptimal response (≥1 clinically reported relapse, ≥1 T1 gadolinium-enhancing [Gd^+] lesion(s) or ≥2 new or enlarging T2 lesions). The scheduled OCR infusion protocol included two 300-mg intravenous (IV) infusions separated by 14 days followed by 600-mg IV infusions every 24 weeks for up to 96 weeks. This IA evaluated efficacy and safety over 48 weeks in a modified intention-to-treat population, including patients who received ≥1 OCR infusion and reached Week 48 by September 1, 2017, and excluding those who terminated treatment by September 1, 2017 for reasons other than lack of efficacy or death, with no evidence of clinical disease activity at the time of discontinuation.
Results: The CHORDS study enrolled 608 patients with RRMS who had a recent suboptimal response to a prior DMT. Baseline characteristics of the IA population (n=153) were similar to those of the total population, and patients were relatively early in their disease, with a mean (SD) time since diagnosis of 3.9 (2.80) years. Over 48 weeks, the majority of IA patients had no protocol-defined relapse (92.7%), no T1 Gd^+ lesions (96.4%), no new or enlarging T2 lesions (65.3%) and no 24-week confirmed disability progression (96.4%). Further, 58.9% of patients were free of any of these protocol-defined events (i.e. no evidence of disease activity [NEDA]). The adjusted annualised relapse rate was 0.047, and new MRI activity included five new T1 Gd^+ lesions and 177 new or enlarging T2 lesions over the 48 weeks of the analysis. Interim safety data were consistent with the overall known OCR safety profile.
Conclusions: Results of this IA of patients with RRMS who had 1 year of follow-up in the CHORDS study suggest that ocrelizumab is effective and safe in patients with a suboptimal response to an adequate course of a prior DMT.

Disclosure

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oversight committee for the Eunice Kennedy Shriver National Institute of Child Health and Human Development; and has served on consulting or advisory boards for CereSpir Inc, Consortium of Multiple Sclerosis Centers, D3, F. Hoffmann-La Roche Ltd and Genentech, Inc., Genzyme, Innate Immunotherapeutics, Janssen Pharmaceuticals, Klein Buendel Incorporated, MedDay, MedImmune, Novartis, Opexa Therapeutics, Receptos, Savara Inc, Somahlution, Spinifex Pharmaceuticals, Teva Pharmaceuticals, TG Therapeutics and Transparency Life Sciences; J. Stankiewicz has, in the past year, received consulting fees from Bayer, Biogen Idec, Celgene, EMD Serono, Genzyme and Novartis; H. Zheng is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd; B. Musch is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd; C. Csoboth is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd; J.S. Wolinsky has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities with AbbVie, Acetilon, Alkermes, Biogen, Bionest, Celgene, Clene Nanomedicine, EMD Serono, Forward Pharma A/S, GeNeuro, MedDay Pharmaceuticals, Novartis, Otsuka, PTC Therapeutics, Roche/Genentech, Sanofi Genzyme; royalties are received for out-licensed monoclonal antibodies through UTHealth from Millipore Corporation.

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Plasma exchange as rescue treatment in children with CNS inflammatory demyelinating syndromes

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Objective: To determine safety and clinical effect of plasma exchange (PE) as rescue therapy in paediatric acquired inflammatory CNS syndromes.
Methods: Single-center retrospective review of patient records over the period 2003-2017, to assess demographic/diagnostic data, attack characteristics, and short-term remission status after PE. All patients admitted to our hospital with a steroid-refractory acute event presumed to be inflammatory and who required PE were included.
Results: A total of 582 PE procedures for 87 attacks in 74 paediatric patients (63.5% neuromyelitis optica spectrum disorders, 8% acute disseminated encephalomyelitis, 4% multiple sclerosis, 12% clinically isolated syndromes, 12% others) were assessed. Mean age at PE 10.4 years (2-18), 47% girls. Serostatus in 42 patients were 17% AQP4+, 31% MOG+, 52% double negative. Attack phenotypes were optic neuritis (ON) 42%, transverse myelitis (TM) 31%, ON + TM 15%, other combined syndromes 11%. Visual outcome scale, Bladder control scale, Hauser ambulation scale, and Expanded Disability Status Scale were assessed before and after PE (at discharge, 30 days, and at 6 months) in every patient.
Overall, moderate to marked neurological improvement was observed in 67% of attacks at discharge, increasing to 77% at 6 months. No marked differences were observed in response rate among attack phenotypes or serostatus. No improvement was seen in 15% of events, mainly in children with diagnoses other than inflammatory CNS syndromes (enterovirus D68-related myelitis, chiasm glioma, LHON-related optic involvement, sarcoidosis).
Adverse events occurring during or immediately following PE were observed in 23/87 (26%) treatments, graded as moderate in 20, and severe in 3, corresponding to catheter removal-related adverse events (pneumothorax 1, pulmonary air embolism 1, and pulmonary thromboembolism with death in 1).
Conclusions: PE is a highly specialized procedure available in few hospitals in our region. Our results show that PE is an effective treatment alternative to intravenous steroids, improving neurological outcome after severe attacks of inflammatory CNS disorders in paediatric patients. Serious adverse events may occur and should be considered.

Disclosure

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A. M. Pugliese, MD, has nothing to disclose

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Healthcare resource use and disease progression among commercially insured patients with multiple sclerosis: a comparison of continuous users and non-users of disease modifying therapy over five years (2012-2016)

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Background: Disease modifying therapies for multiple sclerosis (MS) can decrease health resource utilization (HRU) and delay disease progression. Despite increasing treatment options, many MS patients with access to therapies remain untreated. It is therefore important to understand real-world disease modifying therapy (DMT) utilization patterns among MS patients and their impact on patient outcomes over time.
Objective: To identify continuous DMT users and non-DMT users among commercially insured patients with MS and compare their HRU and disability progression over 5 years.
Methods: A retrospective claims analysis was conducted with the Truven MarketScan Databases. Among continuous enrollees from 2011-2016, MS patients were identified for the index year of 2012

(≥2 ICD-9 340 claims, or 1 diagnosis + DMT) and then classified by DMT use. Continuous users included those with ≥1 DMT claim each year from 2012-2016, while non-DMT users included those with no DMT claims during this period. Propensity score matching was used to balance the cohorts across confounders from the pre-index period/index date (2011-2012), including age, gender, pre-index relapses, comorbidities, and geographic region. We then compared HRU (total, by service type) and disability progression (time to cane/walker, wheelchair) across continuous and non-DMT users.

Results: In total, 15,543 with a diagnosis of MS were identified. Approximately half (51.6%) were continuous users and 22.2% were non-DMT users over the 5 years. 3,407 propensity score matched pairs were identified and included in the analyses. Continuous vs. non DMT users had significantly less total HRU, a significant reduction in inpatient and emergency room utilization, and shorter average hospital stays ($p < 0.0001$ for all outcomes). Continuous users had a trend toward reduction in time to cane/walker (median: 28.7 vs. 24.2 months) and a significant reduction in time to wheelchair use (median: 25.2 vs. 19.2 months; $p < 0.001$), in comparison to non-DMT users.

Conclusions: Only half of commercially insured patients were identified as continuous users and a sizeable proportion were not using a DMT, despite widespread availability of and access to effective therapies. Findings suggest continuous DMT use by MS patients reduces HRU, including high cost services (e.g., hospitalizations and ER visits), and slows disease progression. These results highlight the importance of DMT treatment in patients with MS.

Disclosure

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The effects of an innovative combined Robot Assisted Gait Training and Virtual Reality on cognitive impairments and motor deficits in patients with multiple sclerosis: a pilot randomized control trial

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Background: Cognitive impairments affect up to 70% of persons with Multiple Sclerosis (MS) and the potential of gait rehabilitation with Virtual Reality (VR) to reduce clinical symptoms and disability due to cognitive deficits might be very promising. The main aim of this pilot randomized controlled trial was to compare the effects of an innovative combined Robot Assisted Gait Training plus VR (RAGT-VR) with those of standard RAGT on cognitive impairments and motor deficits in patients with Multiple Sclerosis (MS).

Methods: Subjects were enrolled and randomly allocated either in the RAGT- VR or in the RAGT group. The RAGT-VR group underwent a training on an end-effector device combine with VR while the RAGT group underwent a training on an end-effector device alone. Each patient, irrespective of group assignment, underwent individualized treatment 40-minute/day, two days/week for six consecutive weeks for a total of 12 sessions. A blinded rater evaluated patients before, after treatment, and at one month follow-up. Primary outcome was the Paced Auditory Serial Addition Test (PASAT). Secondary outcomes were the Phonemic Fluency Test (PFT), Rivermead Behavioral Memory Test (RBMT), Digit Symbol (DSymb), Multiple Sclerosis Quality of Life-54 (MSQOL-54) and Two Minute Walking Test (2MWT), 10 Meter Walking Test (10MWT) and Berg Balance Scale (BBS).

Results: Seventeen MS patients (7 males and 10 females) were randomized to the RAGT-VR group (n =8) or the RAGT group (n =9). At baseline no significant differences were noted. Between groups comparisons showed significant change in 2MWT after treatment (p=0.012) in favor of RAGT-VR group. In the RAGT-VR group, within-group comparison showed significant improvements after treatment and at follow-up on PASAT (*p=0.012*; *p=0.012*), PFT (p=0.012; p=0.012) and RBMT NT-IR (p=0.012; p=0.012). Significant improvements after treatment were found on MSQOL-54 PHC composite (p=0.017), MSQOL-54 MHC composite (p=0.018), 2MWT (p=0.012), 10MWT (p=0.012) and BBS (p=0.011). In the RAGT group significant improvements were found for MSQOL-54 MHC (*p=0.018*), MSQOL-54 PHC (p=0.017), 10MWT (p=0.018) and BBS (p=0.016) after treatment.

Conclusion: RAGT combine with VR could be consider a novelty training and more effective on improving gait abilities compare to RAGT alone and could ameliorated cognitive impairments in subjects suffering from MS. Further studies on larger patients samples are warranted to confirm these preliminary findings.

Disclosure

No conflicts of interest have been reported by the authors of the content of this study.

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Subgroup analysis to evaluate the efficacy of ocrelizumab versus interferon β-1a in African-descended patients with relapsing multiple sclerosis in the OPERA I and OPERA II studies

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Introduction: African-descended patients with multiple sclerosis (MS) have more severe disease than and may not respond as well

to disease-modifying therapies as European-descended patients. Ocrelizumab (OCR) demonstrated superior efficacy vs interferon β-1a (IFN β-1a) in patients with relapsing MS (RMS) in two Phase III studies (OPERA I [NCT01412333], OPERA II [NCT01247324]).

Objective: To evaluate the efficacy of OCR vs IFN β-1a in African-descended patients enrolled in OPERA I and II.

Methods: Patients in the OPERA studies received double-blind treatment with OCR 600 mg or IFN β-1a 44 µg for 96 weeks. This *post hoc* analysis in African-descended patients evaluated protocol-defined annualised relapse rate (ARR), time to onset of 12- and 24-week confirmed disability progression (CDP) on the Expanded Disability Status Scale (EDSS), rate of T1 gadolinium-enhancing (Gd^+) and new/enlarging T2 lesions, proportion of patients with no evidence of disease activity (NEDA; no protocol-defined relapses, no 12-week CDP, no T1 Gd^+ or new/enlarging T2 lesions) and no evidence of progression or active disease (NEPAD; NEDA and no 12-week confirmed progression of ≥20% on timed 25-foot walk or 9-hole peg tests).

Results: African-descended patients in the OPERA studies who received OCR (40/827, 4.8%) or IFN β-1a (32/829, 3.9%) were mostly female (72.5% and 68.8%) with a mean (SD) age of 35.8 (9.9) and 34.2 (9.1) years, baseline disease duration of 2.98 (4.48) and 2.66 (3.03) years and baseline EDSS of 2.89 (1.42) and 2.66 (1.27), respectively. Over 96 weeks, findings with OCR vs IFN β-1a were as follows: ARR (0.131 vs 0.262; rate ratio [RR], 0.497; 95% CI 0.180-1.371; p=0.2), 12-week CDP (15.0% vs 15.6%; hazard ratio [HR], 0.81; 95% CI 0.25-2.67; p=0.7) and 24-week CDP (12.5% vs 15.6%; HR, 0.67; 95% CI 0.19-2.32; p=0.7). OCR significantly reduced the rate vs IFN β-1a of T1 Gd^+ lesions (0.026 vs 0.717; RR, 0.037; 95% CI 0.006-0.223; p=0.001) and new/enlarging T2 lesions (0.372 vs 2.650; RR, 0.140; 95% CI 0.062-0.315; p< 0.001). A greater proportion of OCR- vs IFN β-1a-treated patients achieved NEDA (45.5% vs 10.0%; RR, 4.365; 95% CI 1.443-13.204; p=0.002) and NEPAD (36.4% vs 6.9%; relative risk, 5.56; 95% CI 1.34-23.00; p=0.005).

Conclusions: Among a small sample of African-descended RMS patients in the OPERA studies, ocrelizumab demonstrated a treatment benefit on MRI and composite efficacy outcomes, consistent with that seen in the overall pooled OPERA I/II population.

Disclosure

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Real-world treatment utilization and effectiveness of onabotulinumtoxinA in multiple sclerosis patients treated for spasticity from the ASPIRE study

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Background: OnabotulinumtoxinA treatment for spasticity is individualized and dependent on numerous factors. This analysis examines onabotulinumtoxinA utilization and effectiveness to treat spasticity in multiple sclerosis (MS) patients.

Methods: International, multicenter, prospective, observational registry (NCT01930786) examining adults with spasticity treated with onabotulinumtoxinA at the clinician's discretion. Assessments include onabotulinumtoxinA utilization (each visit) and clinician (next visit)/patient (5±1 weeks post-treatment) satisfaction.

Results: Patients (N=731) were on average 54 years old, female (52%), and continuing botulinum toxins for spasticity (63%). Most patients had spasticity due to stroke (n=411; 56%) or MS (n=119; 16%). In MS patients (n=119), the most common upper limb presentation was flexed elbow (18%), with onabotulinumtoxinA doses ranging from 25-550U. Muscles injected include: biceps brachii (100%), brachioradialis (54%), brachialis (46%), and other (4%); anatomical localization (60%) was most frequently utilized. The most common lower limb presentation was equinovarus foot (61%), with onabotulinumtoxinA doses ranging from 15-875U. Muscles injected include: gastrocnemius (79%), soleus (73%), tibialis posterior (46%), flexor digitorum longus (15%), other (11%), and flexor hallucis longus (2%); EMG localization (57%) was most frequently utilized. Overall (N=731), ≥72% patients and ≥91% clinicians reported extreme satisfaction/satisfaction that onabotulinumtoxinA helped patient's ability to participate in therapy/exercise, and 92% of patients and ≥98% of clinicians would definitely/probably continue treatment. Overall (N=731), 261 patients reported 831 adverse events (AEs); 23 AEs in 20 patients were considered treatment-related. 94 patients reported 195 serious AEs; 3 serious AEs in 2 patients were considered treatment-related. No new safety signals were identified.

Conclusions: ASPIRE provides valuable, real-world data on dosing, injection guidance, and muscle targeting over 2 years, that may help guide clinical strategies. ASPIRE captured the individualized nature of onabotulinumtoxinA utilization for spasticity in MS patients, while consistently demonstrating high satisfaction among patients and clinicians, with the majority indicating that onabotulinumtoxinA helped patients participate in therapy/exercise. These results add to the body of evidence on the safety and effectiveness of onabotulinumtoxinA for spasticity.

Disclosure

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J. Largent - Full-time employee of IQVIA (formerly QuintilesIMS), the contract research organization responsible for the management of this study and was formerly a full-time employee of Allergan plc.
G. Francisco - Consulted for, and received research grants from, Allergan, Merz, and Ipsen.

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Dimethyl fumarate treatment in relapsing multiple sclerosis: a prospective observational postmarketing study of effectiveness

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Background: Dimethyl fumarate (DMF) efficacy in relapsing multiple sclerosis (RMS) has been demonstrated in 2 randomized clinical trials (RCT), these outcomes could be influenced in clinical practice by factors controlled in RCT, such as comorbidities and disease duration. Post-marketing studies are needed to assess its effectiveness in a real clinical practice.
Objective: The aim of this observational, prospective, multicenter and post-marketing study was to evaluate DMF effectiveness in a real-world clinical setting.
Methods: RMS patients on DMF treatment and at least one year of follow-up were included. Three subgroups were considered: naïve, switching to DMF for suboptimal response (SR) and for adverse effects (EA). The main efficacy endpoints were annualized relapses rate (ARR) and number of gadolinium-enhancing lesions (T1gd). Secondary objectives included: proportion of patients without relapses, disability progression and new T2 lesions. Negative binomial regression was used for evaluating effect on relapses and T1gd lesions.
Results: A total 456 patients (70.6% women, aged 39.6±9.7, baseline EDSS 2.06±1.07, duration disease 8.9±7.5) completed 1 and 233 two years of follow-up. Twenty four percent belong to naïve, 46.7% to SR and 29,2% to EA subgroups. Comparing to prior year, at 12 months after DMF treatment, ARR was significant lower in total population (76.3%, 0.69 to 0.16 -95% CI:0.12-0.21-p=.000), SR (75%) and naïve (92%,1.06 to 0.09-95%CI:0.04-0.18-p=.000). T1gad lesions number was significantly reduced a 79% in total population and 92% in naïve. These rates were maintained at 24 months. Eighty-five percent and 89% of patients were free-relapses by 12 and 24 months on DMF, respectively. The 86% and 77.6% were free of disability progression, 80% and 86% of new T2 lesions, after 12 and 24 months on treatment.
Conclusions: Our results suggest that DMF may be an effective treatment option over the first two year in both RMS, naïve and those switching from other MS treatment.

Disclosure
The investigators do not have any conflict of interests to disclose

P642
Exit strategies for "needle fatigue" in multiple sclerosis: a propensity score-matched comparison study

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Background: Patients with multiple sclerosis (MS) on long-term injectable therapies may suffer from the so-called "needle fatigue" (i.e. a waning commitment to continue with the prescribed injectable treatment), due to a variety of different factors, including difficulties with injections, anxiety/depression, or inaccurate beliefs about the MS disease process.
Objective: To directly compare switching to dimethyl fumarate (DMF), teriflunomide (TRF) or pegylated interferon (PEG) on treatment persistence and time to first relapse over a 12-month follow-up.
Methods: In this multicentre post-marketing study we considered 488 patients who were free of relapses and gadolinium-enhancing lesions in the year prior to switching to DMF (n=266), TRF (n=121), or PEG (n=101) due to needle fatigue. Since patients were not randomized to treatment group, we performed a 1:1:1 ratio propensity score (PS)-based matching procedure (calliper of 0.1, no replacement). According to the common-referent approach, we derived two separate PS using logistic regressions to estimate the conditional probability to receive DMF vs. PEG and TRF vs. PEG. Pairs of subjects with overlapping PS in DMF and TRF groups were then matched. Time to discontinuation and time to first relapse were explored in matched samples by Cox regression models, adjusted for sex and age, and stratified by matched cases.
Results: There was significant imbalance in pre-matching baseline characteristics across treatment groups, due to older age, longer time since first symptom, and higher EDSS score in TRF group (p-values< 0.001). The PS-based matching procedure retained 180 patients (60 per group). At follow-up, 7 (12%), 13

(22%) and 24 (40%) discontinued TRF, DMF and PEG, respectively. Switching to PEG was associated with a greater risk of discontinuation when compared to TRF (HR=5.1, p=0.003), but not when compared to DMF (HR=1.9, p=0.10). There was no significant difference between DMF and TRF (HR=2.4, p=0.12). The highest discontinuation rate observed in PEG recipient was mainly due to poor tolerability. The low number of patients who relapsed over the 12-month follow-up (10 out of 180 analyzed, approximately 5%) prevented any analysis on the short-term risk of relapse.

Discussion: This real-world study suggests that oral drugs, especially TRF, are a better switching option than low-frequency interferon for promoting the short-term treatment persistence in stable patients who do not tolerate injectable drugs.

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A modified Mediterranean dietary intervention for multiple sclerosis: results of a pilot study and lessons learned for future dietary research in MS

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Introduction: Interest in the role of diet among MS patients is quite high. At the same time, there is increasing scientific evidence for the importance of dietary factors in MS incidence and disease course. Major barriers to conducting large clinical trials include lack of data on 1) which type of diet should be studied and 2) clinical trial feasibility. Based on available literature, we developed a rationally-designed dietary intervention (restrictive, modified Mediterranean diet) and conducted a randomized pilot study in women with MS for 6 months.

Objective: Main aims relate to clinical trial feasibility and adherence. Additional aims relate to general health and wellness effects on MS symptoms and quality of life.

Methods: Participants were randomly assigned to the modified Mediterranean dietary intervention or control arm (educational seminars). The intervention group received training with the study nutritionist and attended monthly meetings to assess and promote adherence. Formal assessments were completed at baseline and 6

months. Monthly self-assessments were also completed by the intervention arm.
Results: We screened 131 patients between December 2016 and October 2017. Of these, 36 (27.5%) were eligible and willing to commit to the study. At this time,18/18 assigned to the diet group and 14/18 "controls" are complete; an additional 3 are expected to complete in the coming weeks, with only 1 anticipated dropout. Analyses will be updated accordingly. Self-reported adherence was excellent (mean at 6 months= 90.3%). Additional adherence data utilizing food frequency questionnaires and other measures will be reported. 16/18 participants reported some benefit to their overall health and 14/18 reported specific benefits regarding MS symptoms. Mean change on the Neurological Fatigue Index-MS was -2.5±5.4 compared to +1.5±2.9 for controls (p=0.015) and mean change on Multiple Sclerosis Impact Scale-29 after exclusion of 1 outlier was -5.3±9.5 vs +2±9.3 (p=0.04).
Conclusions: It is feasible to enroll MS patients into a rigorous dietary intervention study requiring significant commitment and randomization and reasonable to expect high adherence to this type of dietary program utilizing educational methods to promote adherence. Preliminarily, this diet may improve fatigue and quality of life. Larger scale clinical trials to assess the role of diet for symptom management and even as a disease-modifier in MS are feasible and warranted.

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Multiple sclerosis, fatigue and disease modifying therapy impact: differences in sleep architecture in patients with multiple sclerosis - Copaxone versus interferons

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Background: People with Multiple Sclerosis commonly report fatigue, which can vary in degree. Fatigue in PwMS has been related to physical disability, depression, medication and sleep disorders. Polysomnography (PSG) can identify unrecognized sleep disordered breathing (SDB) and quantify the degree of SDB in PwMS. Disease modifying therapies (DMT) are prescribed in an attempt to reduce disease activity/progression without adding to disease burden. Many factors (route, frequency, efficacy) determine choice of DMT, but the relationship of specific DMT to the presence/degree of fatigue potentially due to SDB is not well described. DMT choice should also take this factor into account.
Objective: To compare PSG documented sleep parameters in both Interferon and Copaxone treated PwMS who reported fatigue to identify if different sleep architecture is observed in groups utilizing different DMT.
Methods: Retrospective cross-sectional analysis of PwMS who reported fatigue, were not diagnosed with SDB and agreed to overnight PSG study. Patients reported DMT at time of PSG study.
Results: 130 PwMS (46.53±9.748 years, 72% female). Abnormalities in sleep architecture (SA) were common in both Interferon (n=86) and Copaxone (n=44) treated PwMS. PwMS SA DMT Copaxone was significantly different from PWMS SA Interferon regarding two sleep parameters: sleep latency (minutes) (p=0.035) and REM latency (minutes) (p=0.021184). 52% of PwMS DMT Copaxone had normal sleep latency (< 30 minutes), while 44% of PwMS DMT Interferons had normal sleep latency. 13% (n=11) of PwMS DMT interferon did not achieve REM sleep; of those who did (n=72), 10% had normal REM latency (REM-L) (80-110 minutes), 21% were below normal, 22% had REM-L 110-180 minutes, and 47% had REM-L >180 minutes. 7% (n=3) of PwMS DMT Copaxone never achieved REM sleep; of those who did (n=38), 21% had a normal REM-L (80-110 minutes), 21% REM-L < 80 minutes, 32% had REM-L 110-180 minutes, and 26% had REM-L >180.
Conclusions: Fatigue in PwMS is not only multifactorial, but DMT type might contribute to altered SA and fatigue reported. A higher percentage of PwMS DMT Copaxone had normal sleep latency than PwMS DMT interferons. PwMS treated with interferons were likely to have a greater prolonged REM latency compared to PwMS DMT Copaxone, especially in the REM latency >180 range. Further investigation into the relationship of how DMT choice might impact sleep architecture might impact treatment choice is needed.

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Usability of an educational intervention to overcome therapeutic inertia in multiple sclerosis care

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Introduction: Educational interventions are needed to overcome knowledge-to-action gaps in clinical care. We previously tested the feasibility and potential efficacy of an educational intervention that facilitates treatment decisions in multiple sclerosis (MS). A demonstration of the usability of such an intervention is crucial prior to demonstration of efficacy in a large trial.
Objective: To evaluate the usability of a novel, pilot-tested intervention aimed at neurologists to improve therapeutic decisions in MS care.
Methods: We surveyed 50 neurologists from Chile, Argentina, and Canada randomized to an educational intervention arm of a pilot feasibility study using the System Usability Score (SUS) to assess the usability of a traffic light system (TLS)-based educational intervention. The TLS facilitates therapeutic decisions, allowing participants to easily recognize high-risk scenarios requiring treatment escalation. The SUS is a 10-item validated questionnaire with five response options. The primary outcome was the average and 95% confidence interval (CI) of the SUS score. Values above 68 are considered highly usable.
Results: Of 50 neurologists invited to be part of the study, all completed the SUS scale and the study. For the primary outcome, the average usability score was 74.7 (95%CI 70.1-79.2). There was one outlier with a score of 35. The usability score excluding the outlier was 76.8 (95%CI 72.7-80.8). Multivariable analysis revealed no association between participants' characteristics and the SUS score.
Conclusions: Our educational intervention has shown high usability among neurologists. The next step is to evaluate the effectiveness of this educational intervention in facilitating treatment decisions in the management of multiple sclerosis in a large trial.

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A patient survey on the initiation and switch of disease-modifying drugs for multiple sclerosis in Sapporo, Japan: the current status and challenges regarding patient's preference and shared-decision making

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Background: As of May, 2018, 6 disease modifying drugs (DMD) for multiple sclerosis (MS) have been marketed in Japan. Patient's preference and shared-decision making are important in choosing DMD. We surveyed these issues in Japan.
Methods: Among 221 MS patients seen at Sapporo Neurology Hospital, Sapporo, Japan, 168 visited the hospital in February and March, 2018, and 130 (98.5%) out of 132 patients treated with DMD gave consent to the survey. Each patient was interviewed on whether she/he proactively participated in choosing DMD, the reasons for initiating and switching DMD, and the sources of information (multiple answers allowed).
Results: The profile of the 130 patients are as follows, female/male=90/40, age (years) median 45 (range 24~67), disease duration (years) 13 (2~49), EDSS 1.5 (0~7.5), 99 with RRMS and 31 with SPMS.
In initiating DMD, 120 treatment-naïve patients (92.3%) replied that they positively chose DMD, while 10 (7.7%) felt they were passive in the decision-making process. The two commonest reasons for the choice of DMD were doctor's advise (53.8%) and mode of administration (oral or injectable) (44.6%).
Seventy-eight patients (60%) switched DMD and 47% of them experienced multiple switches. The majority (97.3~100% in switches) of them responded that they positively chose DMD, and the frequent reasons for the switches were adverse events (50~62.8%), followed by launch of a new drug (44.9~87.5%) and lack of efficacy (12.5~23.1%). From the patient´s perspectives, mode of administration (oral drug or less frequent injection were preferred) (51.4~75%) and doctor's advise (27.0~53.8%) were important. With more switches in recent years, higher proportions of patients (10.0%→15.4%→37.8%) cited concerns about severe complications, PML in particular.
Throughout the treatment course, 116 (89.2%) continued some DMD. Common sources of information other than treating physicians were Internet (42.3%) and MS patients (9.2%).
Conclusion: Our survey in Sapporo showed that most MS patients were well-informed and positively participated in the treatment decision. However, we need to take ample time to inform patients, especially treatment-naïve ones, of MS and DMD. Switching DMD was often experienced and mode of administration was crucial in our patients. The details of DMD including adverse events and how to cope wth them must be explained clearly for shared-decision making. Moreover, Internet information should be patient-friendly.

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Preferences of German physicians for features of injectable, oral, and infused disease-modifying treatments for relapsing-remitting multiple sclerosis

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Introduction: This study quantified German physician preferences for attributes of disease-modifying treatments for multiple sclerosis (MS) and examines subgroups with distinct preferences.
Methods: Physicians treating MS completed an online discrete-choice-experiment survey with one series of treatment-choice questions for each of two hypothetical patient profiles: more advanced and less advanced. The order in which the hypothetical patient profiles were shown was randomised. Each hypothetical treatment had seven attributes with varying levels: years until disability progression; number of relapses in the next 10 years; mode of administration; dosing frequency; and risks of mild, moderate, and severe adverse events (AEs). Latent class analysis was used to estimate preferences for subgroups. Logit regression analysis examined physician characteristics associated with likely subgroup membership.
Results: Three subgroups with distinct preferences were identified among 308 respondents (n = 155 neurologists; n = 153 internists).
Subgroup 1 members (45% of sample) placed greatest importance (conditional on study attribute levels) on delaying disability progression, followed by minimising risks of severe AEs. Members of this subgroup were more likely to have considered the more advanced hypothetical patient profile first. They were more likely to be in their 40s than their 50s and less likely to be concerned about immunosuppressive effects of treatment.
Subgroup 2 members (33% of sample) placed the greatest importance on minimising risks of severe AEs, followed by delaying progression. Members of this subgroup were more likely to have considered the less advanced hypothetical patient profile first and more likely to believe that disease progression would affect other MS symptoms in additional to ambulation.
Subgroup 3 members (22% of sample) placed greatest importance on minimising risks of mild, moderate, and severe AEs. Members of this subgroup were more likely to treat more than 10 patients with MS per week, more likely to be concerned about immunosuppression, more likely to be in their 50s than their 40s, and more likely to believe that the hypothetical treatments would only affect progression of ambulation symptoms and no other symptoms.
Conclusion: These findings suggest that physicians' age and experience may determine their treatment preferences and recommendations. These data may shed light on treatment patterns and MS treatment outcomes.

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Family planning and pregnancy in multiple sclerosis

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Background and aims: many women with multiple sclerosis (MS) want to have children. However patients are frequently worried if the disease or treatment prescribed will affect their chances of getting pregnant. Also they want to know the chance that the newborn will inherit the disease or if the treatment has adverse effects on the child. This study evaluates the point of view of female patients with multiple sclerosis (MS) regarding pregnancy within the disease and the impact that the diagnosis had on family planning.
Methods: our prospective study was conducted on the basis of a questionnaire of 20 questions in the period April 2017 - March 2018 on a sample of 250 female patients, of fertile age, diagnosed with MS and following immunomodulatory therapy at the Neurology Clinic of Colentina Hospital, Bucharest.
Results: In the 250 patients: 150 were receiving interferon therapy, 70 glatiramer acetate and 30 natalizumab therapy. 80% said they were informed about the contraindications of therapy during pregnancy; 165 patients wanted children before diagnosis - of which most (66.66%) did not change their options after diagnosis; 85 women did not want children before diagnosis, their option remaining, also, unchanged (88.23%). With regard to risks, women would most easily accept a pregnancy that would only be at risk for the mother (28%), only five women would accept to be pregnant if the pregnancy poses a risk to the fetus. 12 patients were pregnant after starting treatment, 75% taking into account the physician´s advice on family planning. 92% would accept

abortion if the fetus had malformations. Most (72%) said that the couple´s life did not suffer as a result of the inconveniences related to family planning.

Conclusions: neither multiple sclerosis nor immunomodulatory therapy reduces fertility, but patients are reluctant to become pregnant in the context of the disease. Considerations on pregnancy and family planning should be part of the therapeutic decision; the teratogenic risk of different immunomodulatory therapies should be carefully evaluated at the time of initiation of therapy for women of childbearing potential. In our study the patient´s choice of pregnancy has generally remained unchanged, but they take into account the physician´s advice for choosing the right time to get pregnant.

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I.A. Ionescu: nothing to disclouse

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Fecal microbial transplantation in multiple sclerosis: trial design

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Introduction: Multiple sclerosis (MS) is a demyelinating central nervous system disorder with poorly understood etiology. Recent studies suggest that gut microbiota can powerfully modulate immune-mediated demyelination. Fecal microbial transplantation is used already to restore healthy gut microbiome composition and treat *Clostridium difficile* colitis. We proposed that fecal microbial transplantation (FMT) from healthy donors to MS patients may have a measurable effect on disease inflammation biomarkers.

Objective: To describe a trial designed to evaluate FMT effects on MS patients and to describe preliminary results.

Methods: A single site, randomized, open-label, controlled, crossover study. Forty patients will be randomized 1:1 into two groups. One group (early intervention) will receive FMT by rectal enema, while the other group will receive treatment as per standard of care only (control group) for the first 6 months of the study. Thereafter, the early intervention group will no longer receive FMT and the initial control group will receive FMT for the remaining 6 months. The primary outcome will be peripheral blood cytokines´ levels measured by Luminex assay. A group of 10 healthy volunteers will be a reference control for cytokines. The secondary outcomes are blood DNA bacteria and gut permeability. Head MRI scans are also done as a safety marker.

Results: Sixteen patients were enrolled in this study so far, 12 (75%) females. The mean age of disease onset is 30 years old (16 - 40). Mean current EDSS is 4.0 (1.5 - 7.0). Patients manifested their MS symptom in average 18 years ago (7-38). All, except five, are currently using disease-modifying therapy. Thus far, a total of 24 interventions were performed in 6 patients. No serious adverse event was reported up to now.

Conclusions: This proof of concept, first in humans, independent pilot study will shed light on the relationships between gut bacteria and MS. We aim to explore FMT feasibility in MS and its possible impact on disease inflammation. Moreover, we hope that this study results can guide future large-scale researches**.**

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