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Diagnosis and differential diagnosis

EP1291
Diagnostic value of enhancing lesions on post-contrast T1-weighted magnetic resonance images in patients with a clinically isolated syndrome

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The previous magnetic resonance imaging (MRI) criterion for dissemination in time (DIT), based on a single scan, requires the simultaneous detection of asymptomatic enhancing and non-enhancing lesions on post-contrast T1-weighted scan. This criterion was highly specific for predicting early conversion to clinically definite multiple sclerosis (CDMS) but its sensitivity was rather low. In the 2017 revision of the McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required for DIT demonstration.

We aim to investigate whether inclusion of lesions in the symptomatic region influences the performance of DIT criterion, based on a single scan, for a diagnosis of multiple sclerosis (MS) according to the McDonald 2017 criteria. We also analyse its value for predicting conversion to CDMS.

We performed an observational study based on a prospective clinically isolated syndrome (CIS) cohort. Inclusion criteria: 1)CIS suggestive of central nervous system demyelination (since 2008); 2)clinical assessment and baseline brain MRI within 8 weeks of CIS onset; 3)clinical follow-up of at least 24 months.

We included 143 CIS patients, 98 women (68.53%), with a mean age at onset of 34 year. After a mean follow-up of 56 months, 91 (63.63%) patients were diagnosed as having MS according to the McDonald 2017 criteria. The overall conversion rate to CDMS was 43.35%. Forty patients (43.95%) initiated a disease-modifying treatment before the second clinical event. In 28 patients (19.58%) baseline MRI simultaneously showed asymptomatic enhancing and non-enhancing lesions, whereas in 47 patients (32.63%) simultaneously enhancing (symptomatic or not) and non-enhancing lesions were detected. The DIT criterion recently proposed, based on a single MRI scan, was more sensitive (48.4% v 30.8%) maintaining a high specificity (94.2% v 100%). Both DIT criteria identified a subset of patients with CIS who were at high early risk of developing CDMS (hazard ratio: 2.68 and 4.15, $p< 0.001$; respectively).

The new DIT criterion based on a single scan, incorporated in the last revision of the 2017 McDonald criteria, is more sensitive that the original one with a slight decrease in specificity.

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The role of IgG index versus oligoclonal bands in patients with suspected multiple sclerosis

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Background and objectives: A cerebrospinal fluid (CSF) analysis is not mandatory for the diagnosis of multiple sclerosis (MS) in patients with a clinical syndrome suggestive of MS. However, in the 2017 McDonald diagnostic criteria presence of ≥2 oligoclonal IgG bands (OCB) in the CSF, but absence in the corresponding serum, can be used to fulfill the distribution in time (DIT) criteria, possibly leading to an earlier diagnosis. However, the finding of an elevated IgG index (CSF IgG:serum IgG/CSF albumin: serum albumin) ≥ 0.7 should be interpreted with caution. The aim of the study was to investigate the diagnostic value of IgG index versus OCB in suspected MS in a population based real life setting.
Methods: 2141 MS patients according to the McDonald criteria with known OCB status and/or IgG index from the three Norwegian counties Buskerud, Oslo and Telemark ("BOT-database") from 1972-2018 were included. CSF-OCB analyses were for the earlier years performed by agarose gel electrophoresis (AGE) and since 2005 by isoelectric focusing with immunoblotting (IEF).
Results: 1785 (87.2%) of the patients were OCB positive and 263 (12.8%) were OCB negative. Of the 384 patients with known IgG index 294 (76.6 %) had a value ≥0.7, and 90 (23.4%) < 0.7. 285 (74.2%) of the patients had both an IgG index ≥0.7 and were OCB positive. Only 9 of 294 patients (3.1%) with IgG index ≥ 0.7 were OCB negative whereas 28 of 90 (31.1%) with IgG index < 0.7 were OCB negative.
Conclusions: The frequency of OCB positive patients in our population was as expected. The vast majority of patients with IgG index ≥ 0.7 were also OCB positive. Thus both presence of ≥2 OCB or an IgG index ≥0. 7 may be used as a supplement to fulfill the diagnostic criteria for DIT in MS.

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EP1293
Clinically isolated syndrome: natural course and diagnostic criteria

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Introduction: Clinically isolated syndrome (CIS) is a first demyelinating event targeting the central nervous system. It can latter fulfil the criteria for Multiple Sclerosis (MS) but in some patients it is an isolated episode, without new clinical events or paraclinical evidence of disease.
Objectives/Aims: To analyse our population of CIS patients and the role of OCB in the 2017 revision of the McDonald criteria
Methods: We selected those patients who had ever had a diagnosis of CIS, observed in our MS clinic (N= 69), according to the 2010 McDonald criteria. Clinical and laboratorial features were analysed to compare those who converted to MS and the non-converters.
Results: From the total cohort, 71% converted to MS, at a median follow-up of 2 years (0-11 years). Those who converted to MS were tendencially younger (28 vs 33 years; p=0,066) and had an elevated level of cerebrospinal fluid (CSF) proteins (0,51 vs 0,30 g/L; p=0,072). Our analysis found no association between the presenting symptom, altered visual potentials with conversion to MS. OCB were present in 64,1% of patients who were diagnosed with MS, but also in 68,4% of those who remained CIS (p=0.745). Stratifying the results by treatment, there was also no statistical significant association between the presence of oligoclonal bands and conversion to MS.
Conclusion: The present study showed that OCB is prevalent in patients with CIS, even in those who, until now, do not fulfil the 2010 diagnostic criteria for MS. This raises questions about the early assumption of MS diagnosis, resulting in chronic treatment and a possibly lifelong stigma in patients who could never develop new lesions or have a second attack.

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EP1294
Autonomic nervous system dysfunction in people with neuromyelitis optica spectrum disorders

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Background and aims: The aim of this study was to determine the extent of autonomic symptom burden measured with the Composite Autonomic System Score-31 (COMPASS-31) and presence of objective dysautonomia measured with adrenergic index (AI) and cardiovagal index (CI) in people with neuromyelitis optica spectrum disorders (pwNMOSD). Furthermore, we wanted to compare both parameters in pwNMOSD and people with multiple sclerosis (pwMS).
Design/Methods: 20 pwNMOSD (16 females, mean age 48.2±10.8, disease duration 9.8±8.0) and 20 pwMS, matched for age, sex and disease duration were enrolled. All patients completed the COMPASS-31. The following ANS tests were performed: heart rate (Valsalva ratio (VR)) and blood pressure responses to the Valsalva maneuver, heart rate response to deep breathing (respiratory sinus arrhythmia (RSA)) and the tilt table test. The quantification of autonomic dysfunction was made using the two indices of the Composite Autonomic Scoring Scale (CASS): adrenergic index (AI) and cardiovagal index (CI).
Results: In all pwNMOSD, COMPASS-31 was >0. AI >0, indicating sympathetic dysfunction, was present in 8 (40%) and CI>0, indicating parasympathetic dysfunction, was present in 10 (50%) pwNMOSD. Orthostatic hypotension on tilt-table test was present in 6 (30%) of pwNMOSD. The frequency of presence of autonomic symptom burden was higher in pwNMOSD for the vasomotor and pupilomotor domains of the COMAPSS-31 compared to pwMS (p=0.048 and p=0.006, respectively). There was no difference in AI and CI between groups (all p>0.05). pwNMOSD had significantly greater drop in diastolic blood pressure (dBP) during tilt-table test compared to pwMS, p=0.044. A binary logistic regression model showed that drop in dBP during tilt-table test and normal function of autonomic nervous system, defined as

AI=0 and CI = 0, are independent predictors of pwNMOSD (p=0.042 and p=0.029, respectively).
Conclusion: Significant proportion of pwNMOSD experience dysautonomia, which seems to be different from dysautonomia observed in pwMS.

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EP1295
Russian cohort of patients with NMO and NMO spectrum disorders

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Antibodies to aquaporin-4 (AQP4-Ab) is a sensitive and highly specific serum marker of neuromyelitis optica (NMO) and NMO-spectrum disorders (NMOSD). *Area postrema* syndrome is the third most frequent after optical neuritis and myelitis in NMOSD. Clinical manifestations of this syndrome include indomitable nausea, vomiting and hiccups, which in most cases persist for several weeks. Frequently the area postrema syndrome is the first clinical manifestation of NMOSD, which significantly complicates proper diagnosis.
Objectives: The aim of our research was to analyze the characteristics of patients with NMOSD according to demographics, clinical symptoms and MRI findings and estimate frequency of AQP4-Ab in Russian group patients with NMOSD.
Methods and patients: Serum samples from 67 neurological patients with NMOSD were analyzed. We used cell-based assay for the detection of AQP4-Ab (Euroimmun).
Results: 67 patients (83% female) aged 16-67 years (mean age 40.2 years) were included in the study. AQP4-Ab were detectable in 89.6% patients with NMOSD. The mean age of onset of symptoms was 35.2 years. The mean time to diagnosis was 20 months (range: 1 month-5 years). In most patients, the onset symptoms were longitudinally extensive transverse myelitis (LETM) and optic neuritis(ON). In total, during disease course 11 patients developed area postrema syndrome and in seven cases, the disease manifested with area postrema syndrome. Time to diagnosis in cases with area postrema syndrome manifestation was higher than LETM and ON manifestation. These patients have been supposed as patients with gastrointestinal pathology or infectious disease at first.
According to MRI, 83% of the patients had LETM lesions and 14% had short transverse myelitis lesions extending fewer than three vertebral segments. Spinal cord lesions spanned 1-13 vertebral segments (mean 5.5). The cervical cord was involved in 30% of cases, thoracic cord - in 30%, both cervical and thoracic cord - in 40%. 19% of patients had brain lesions.
Our results confirm high clinical heterogeneity of NMOSD and specificity of AQP4-Ab as a marker of NMOSD

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Name: nothing to disclose

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Establishing the diagnosis of multiple sclerosis in Croatian patients with clinically isolated syndrome: 2010 versus 2017 McDonald criteria

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Aim: To compare the sensitivity, specificity and accuracy of the 2010 and 2017 revisions of the McDonald criteria in a Croatian cohort of patients with a clinically isolated syndrome (CIS).
Methods: Prospectively collected data from 113 patients were retrospectively analyzed. Sensitivity, specificity and accuracy for both criteria were calculated regarding conversion to clinically definite multiple sclerosis (CDMS) or multiple sclerosis (MS) (defined as fulfilment of clinical or MRI evidence for dissemination in space and the development of a second relapse and/or ≥1 new T2 lesions on the follow-up MRIs) during a two-year follow-up. Survival analysis was performed to estimate the cumulative risk of patients developing CDMS. Binary logistic regression model was used to determine which variables are statistically significant predictors for the conversion to MS.
Results: The 2017 revision had higher sensitivity (85 vs. 30% and 85 vs. 41%) and lower specificity (33 vs. 63% and 63 vs. 85%) compared to the 2010 revisions, for conversion to CDMS and MS, respectively. Patients who did not meet the 2017 McDonald criteria had a higher chance of conversion-free survival for CDMS than those who met the 2017 McDonald criteria (p=0.037). Results of the multivariate regression analysis revealed that patients who at baseline fulfilled 2017 revisions of the McDonald criteria have the increased likelihood of conversion to MS (Exp(B) 9.68, 95%CI 3.62 - 25.90, p< 0.00001).
Conclusion: This study provides new information about the application of the 2017 revisions of the McDonald criteria in a Croatian cohort of patients with typical CIS.

Disclosure

Nothing to disclose

EP1298

Application of the Matthews's criteria to differentiate MS from NMOSD at disease onset in a Latin American cohort

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Background: An overlapping of symptoms among multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) may be found at disease onset. Recently, magnetic resonance imaging (MRI) criteria (Matthews's criteria, MC) were described to differentiate MS from NMOSD in clinical practice. However, these criteria were not evaluated in non-Caucasian population. The aim was to evaluate these criteria in Latin American population.
Methods: medical records and brain MRIs were assessed by a blind evaluator and scored on the MC (lesions adjacent to the body of the lateral ventricle, lesions in inferior temporal lobe, S-shaped/curved U-fibre lesions and Dawson's fingers) in a Latin American cohort (Argentina, Brazil and Venezuela) of patients with MS and NMOSD (previously diagnosed by current validated diagnosis criteria and used as gold standard). MC sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were determined.
Results: We included 282 patients (MS = 188 and NMOSD = 94, ratio 2:1). Patients from Argentina (MS = 92, NMOSD = 38), Brazil (MS = 55, NMOSD = 27) and Venezuela (MS = 29, NMOSD = 41) were evaluated at disease onset. The MC applied to the entire cohort at disease onset showed a 97.8% sensitivity, 82.9% specificity, 92.0% PPV, and 95.1% NPV in differentiate MS from NMOSD. The sub-analysis applied only to non-Caucasian populations (mestizos, natives and zambos, MS = 89 and NMOSD = 47) showed a 100% sensitivity, 80.8% specificity, 90.8% PPV, and 100% NPV.
Conclusion: These findings suggest that the MC distinguished MS from NMOSD at disease onset in a Latin American cohort.

Disclosure

None of the authors has any potential financial conflict of interest related to this poster

EP1299

Brucellosis presenting as a longitudinally extensive transverse myelitis

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Introduction: We report an unusual case of a patient who presented with a longitudinally extensive transverse myelitis (LETM) secondary to brucellosis.
Case: This previously healthy 44 year old man presented with left sided numbness. His history goes back to 2 weeks prior to presentation when he developed a progressively increasing numbness over his left side associated with gait ataxia and urinary urgency. His exam was significant for weakness of the left upper and lower extremities, bilateral hyperreflexia and sustained ankle clonus on the left. Magnetic resonance imaging (MRI) of brain and cervical spine revealed a cervical non-enhancing intramedullary lesion extending from the level of C3 to C6 with associated meningeal enhancement extending from the brainstem to the lower cervical levels. Serological studies revealed high Brucella titers (>1:640), negative anti-aquaporin 4 antibodies and vasculitis panel. Cerebrospinal fluid (CSF) showed a white blood count of 260 per µl with 62 % neutrophils, a low glucose 20 mg/dL, elevated protein (4.92 g/dl), and high Brucella titers (>1:640). Additionally, CSF showed no oligoclonal bands, and negative toxocara canis antibodies, viral and tuberculosis polymerase chain reactions, and bacterial cultures. Patient was started on ceftriaxone, rifampicin, and doxycycline.
Conclusion: Neurobrucellosis should be considered in the differential diagnosis of longitudinally extensive transverse myelitis. This is only the second reported case of neurobrucellosis presenting with LETM.

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EP1300

Experts' opinion on 2nd-line treatments failure criteria for patients with multiple sclerosis

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Introduction: Failure criteria for patients with multiple sclerosis (MS) under 1st-line treatment are well documented. However, the literature is poor regarding 2nd-line treatments failure criteria.
Objectives: This work aimed at identifying convergences and differences in therapeutic attitudes among French MS experts, regarding 2nd-line treatments failure criteria.

Methods: A 2-phase approach was set out. Experts in 5 regional boards worked on identifying 2nd-line treatments failure criteria. These results were then collected and discussed by a national board of 11 experts.
Results: Patient evaluation is based on the Expanded Disability Status Scale (EDSS) test, at least once a year, and MRI. Brain and spinal rebaseline MRI must be performed at 6 months, then brain MRI once a year, without considering structures atrophy.
Bad prognosis criteria are age (>40 years old), high baseline EDSS, ethnicity and comorbidities.
Disease progression must be confirmed at 6 months because of frequent fluctuations under 2nd-line treatments and pseudo-relapses. Any confirmed disease progression is considered a therapeutic failure. Therapeutic failure is also based on clinical relapses and MRI activity.
Any change of 2nd-line treatment must be discussed in multidisciplinary meeting, not before 1 year of treatment, except in case of tolerance issues. Failure criteria are no longer valid after 3 years of treatment.
To avoid disability evolution, more stringency is necessary with 2nd-line treatments, despite the risk of therapeutic exhaustion.
Experts also highlighted differences in progression evaluations. Annual Symbol Digit Modalities Test (SMDT), 9 Hole Peg Test (9-HPT), Time 25 Foot Walk (T25-FW), decreasing walking distance despite unchanged EDSS, or low contrast visual acuity, could be considered as markers of treatment failure.
Other differences concern the reliability of a single MRI activity, depending on its location, or of a single relapse, whether it is a sensitive or a motor one, to change or not 2nd-line treatments.
Conclusions: Experts identified convergences and differences in therapeutic attitudes regarding 2nd-line treatments failure criteria.
They agree that disease progression must be considered along with EDSS, after 1 year of treatment.
As for differences, they are justified in the absence of published data.
These proposals should be evaluated in real life prospective cohorts.

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EP1301
Recurrent myelitis with CLIPPERS imaging: a case report

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Introduction: In 2010 was described by Pittock et al. an inflammatory syndrome with subacute clinical signs of pontine lesion, in relapses, responsive to corticosteroid therapy but not to all immunosuppressants, called Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids - CLIPPERS. After the first report, several cases appeared showing more extensive attacks involving other central nervous system areas such as midbrain, medulla, spinal cord and subcortical white matter.
Objective: Report a clinical case of a young man with recurrent myelitis responsive to corticosteroid and CLIPPERS imaging.
Case description: A 20-year-old black male with a history of recurrent lower limb weakness and urinary incontinence. He had the first myelitis at age 13, when he began to walk with assistance after a week. At the time he was admitted at the hospital and received corticosteroid therapy with complete recovery. He had a new event at age 16 with paraparesis and got restricted to wheelchair, with urinary incontinence, that partially responded to pulse therapy. After another 2 episodes, was started Mycophenolate Mofetil as maintenance therapy, but nevertheless he had another 6 incidents within 2 years when they decided to switch for Interferon 1A. He continued with frequent relapses but recently with upper limbs weakness, which was not noted before. He had another myelitis in November / 2017 with extensive laboratory and radiological investigation without diagnostic conclusion. His magnetic resonance imaging (MRI) of brain and spinal cord showed multiple lesions, of 1-2 mm, with increased signal in Fluid attenuation inversion recovery (FLAIR) at the pons and spinal cord, with contrast enhancement. After case review, was suggested diagnosis of CLIPPERS base on imaging features, despite the atypical clinical presentation. Prednisone

was started at 1mg / kg / day dosage with partial response and he currently walks with the aid of crutches.
Conclusion: CLIPPERS is a rare syndrome recently reported that should be considered when there is suggestive neurologic features and typical imaging, excluding other causes. This case describes an atypical clinical presentation without brainstem symptoms or signs, with typical imaging of the syndrome, rarely documented on literature.

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EP1302
Challenges in diagnosing OCB-negative MS - the importance of imaging

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Introduction: Up to 5 % of the patients with MS lack oligoclonal bands (OCB) in the CSF. Recent reports highlight the importance of an accurate MS diagnosis particularly in OCB-negative patients. Around 10% of progressive MS patients may have been misdiagnosed. We have previously reported on the inventory of OCB-negative patients in the National Swedish MS Registry, locally in Uppsala. Out of altogether 750 MS patients, 42 were OCB-negative. Ten of these were reexamined and two were rediagnosed with leukodystrophies,based on genetics (mutations in the ABCD1-, DARS gene respectively).
Aim: A retrospective imaging study was done in order to scrutinize the preceding diagnostic process.
Method: Previous MRIs of the brain and spine according to a MS protocol were analysed. and new MRIs were performed, including axial projections of the spine.
Results: Both patients were women in their fifties, having had an MS diagnosis for many decades. Both had motor symptoms of the lower extremities, and one had polyneuropathy.
The first patient with adrenomyeloneuropathy had one single ovoid supratentorial lesion, cerebellar atrophy and T2 lesions along the dorsal cervical and thoracal medulla, the latter displaying a discrete widening of the central channel and atrophy.
The second patient with leukodystrophy had several supra- and infratentorial white matter lesions, engaging the pons, cerebellum and brainstem but no new lesions between two MR scans eleven years apart. Symmetrical confluent white matter changes in the brain stem and cervical spinal were sharply delineated. An intramedullar cavity along the thoracal medulla supported atrophy
Conclusion: Female carriers of leukodystrophy genes may have a late, slow and mild phenotype and may lack typical radiological features associated in males with early onset. White matter changes may to some extent mimic MS, and a thorough radiological investigation is needed, with special focus on axial projections of the spinal cord.

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EP1303
Neurosarsoidosis: report of 30 cases. What about diagnosis dilemma?

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Neurosarcoidosis (NS) is a rare and polymorphic entity, often inaugural and isolated. To date, diagnostic assessment is still a matter of debate.
We sought to describe a cohort of patients diagnosed with NS and to establish the relevance of diagnostic investigations.
A retrospective study of all patients diagnosed with NS was conducted in Rouen University Hospital between 1993 and 2018. We included patients diagnosed with definite, probable and possible NS, as described by Zajiceck et al., and collected clinical, biological and imaging data. We distinguished patients with inaugural NS from those already diagnosed with systemic sarcoidosis.
A total of 30 patients were included, 18 (61%) of whom with inaugural NS. Sex ratio male/female was 0.87. The mean age of onset was 43.26 years. NS was considered as definite in two patients (7%), probable in 20 (66%) and possible in eight (27%). The median time to diagnostic was 4.2 months. In cases of already known sarcoidosis, neurological symptoms mainly occurred within 6 months after the onset of sarcoidosis (0.83). Pulmonary manifestations were associated in nine patients (30%). Headache (56%), cranial neuropathies (56%), such as facial nerve palsy, and seizure (30%) were the most common signs. Only three patients (10%) presented longitudinal extensive traverse myelitis and four patients (13%) peripheral nervous impairment. Biological tests showed: lymphopenia (86%), increased ACE levels (47%), stigmata of autoimmunity (37%). CSF analysis revealed : lymphocytic pleocytosis (47%), high protein content (82%). Diffuse T2 white matter hyperintensities (85%) and focal meningeal enhancement (55%) were the most common brain MRI finding. Sensitivity of CSF analysis and MRI was about 84%, whereas, in other tests, about 41%. No difference was found in terms of demographic features, biological tests and imaging between the two groups. Patients with inaugural NS had significantly more parenchymal symptoms than others (44% vs 8%, p= 0.049).

No statistically significant difference was seen between the two groups except for parenchymal symptoms more frequent in inaugural NS patients than others. Sensitivity of CSF analysis and MRI was 84% showing the interest of these two investigations in suspected cases of NS.

Disclosure

Nothing to disclose

EP1304

Safety of rituximab in NMOSD patients: a long time prospective observational study

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Introduction: Considering the significant promising results of several studies on rituximab in various neurological disorders like NMOSD. There are concerns about long-term complications of rituximab therapy. Rituximab definite long term safety and its infusion related side effects have not been well clarified yet. The goal of our study was to evaluate safety of rituximab in some NMOSD patients after two years of prospective observational follow up.
Methods: Rituximab was injected intravenously every 6 months. The initial course of rituximab was 345 mg/m2 (on average 500 mg) that was administered intravenously (IV) every week for 4 weeks (on average 2 gr administered overally). Further infusions of 345 mg/m2 were given (on average 500 mg) every week for 2 weeks (on average 1 gr administered overally); this was repeated every 6 months. Based on new neurological symptoms and new side effects of rituximab therapy, we had phone follow up monthly and completed a specific checklist. If we suspected to any problems or needed to examine the patients or collected supplementary.
Results: In our investigation, we included 48 NMOSD patients initially and 44 patients were successfully followed up for 2 years, (35 female and 9 male). Infections were reported in 36.6% of patients. From our experience, urinary tract and respiratory infections are the most common complication after a long-term treatment with rituximab among NMOSD patients.
Conclusion: Patients especially males tolerated repeated injection of rituximab without any significant reactions except one case of reported anaphylactic shock. Focus on NMOSD patients, and also simultaneously evaluation of long-term and injection-related complications and overally safety of rituximab therapy in these patients are some positive aspects of this study. It would be better to do such a research in a larger number of NMOSD patients with a longer period of time for follow up.

Disclosure

On behalf of all authors, the corresponding author declares there is no conflict of interest. This study was carried out without any financial support from private or public institutions.

MS Variants

EP1305

The clinical spectrum of MOG antibody-associated demyelination: a retrospective case study

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Introduction: Antibodies to myelin oligodendrocyte glycoprotein (MOG) have been demonstrated in a subset of patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) without the presence of aquaporin-4-IgG antibodies, as well as in patients with acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), transverse myelitis (TM), brainstem syndrome and cerebral dysfunction without fulfilling criteria for NMOSD.
Objectives: To describe the clinical course, treatment and outcome in patients with MOG antibody-associated demyelination.
Methods: This is a retrospective case study. Demographic, clinical, cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) data were collected from the clinical records.
Results: Eleven patients with MOG-antibody associated demyelination were identified. The male/female ratio was 1.7. Mean age was 45.18 (range 22-71 years), while the mean disease duration was 6.72 (range 8 months-28 years). Three patients had an initial presentation of Longitudinally Extensive Transverse Myelitis (LETM) and one had TM. Three patients had bilateral ON and one had unilateral ON. There was one patient with a simultaneous LETM and unilateral ON. One of our patients had an ADEM-like initial presentation and one a cerebral-cortical dysfunction. MRI findings were compatible with the patient's clinical presentation, with or without additional asymptomatic brain lesions. Two of our patients had positive CSF oligoclonal bands. All cases were initially treated with intravenous steroids, while two patients with LETM required plasma exchange. Four out of five patients with TM had a very good outcome with Expanded Disability Status Scale (EDSS) score < 2. All ON cases had an excellent response to steroids. Six patients had only one episode, while five patients had a polyphasic course. Four out of five cases with a polyphasic course, had either clinical or/and radiological cerebral involvement at presentation and a worse outcome with moderate to severe disability. Additional immunosuppressive treatment has been added to our relapsing cases**.** Current EDSS scores ranges from 0-8 (mean value 2.54). Only four patients fulfilled diagnostic criteria for NMOSD.
Conclusions: MOG antibodies are associated with an increasing spectrum of clinical phenotypes that often do not fulfil criteria of NMOSD. Further large prospective studies are needed, to better characterise MOG-associated demyelination.

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EP1306
Clinical characterization of patients suffering from both central and peripheral demyelinating autoimmune disorder

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Multiple sclerosis (MS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are both demyelinating autoimmune disorders of the nervous system with unknown underlying pathomechanism. Whereas MS is restricted to the central nervous system, CIDP comprises demyelination of the peripheral nervous system. There are a few reports in the literature about patients suffering from both, CNS and PNS manifestation in similar extent.
In this case series, we describe ten patients showing a heterogeneous clinical spectrum with primary central nervous system or peripheral nervous system involvement and a monophasic or chronic disease course. Mean age was 55.9±10.8 years, without sex preference. Disease duration was 14.4± 7.6 years. Seventy per cent of the patients developed central demyelination before peripheral disease with fulfilled diagnostic criteria for MS according to McDonald criteria. However, oligoclonal bands were positive in only five patients (50%), elevated protein was found in 80% of the patients. In contrast, demyelinating criteria for CIDP according to the European Federation of neurological society (EFNS) was fulfilled in only 30%. Interestingly, only the minority of patients suffered from a high lesion load (40%) and had a progressive disease course (10%) with a mean EDSS Score of 4.0 (2.5-6.5), whereas course for neuropathy was progressive despite ongoing treatment in 40 %. In contrast to previous publications, some of the patients described here became stabilized under a monotreatment of regular IVIG treatment for long-term whereas others need a combination of different immunmodulatory treatment regimens. So far tested, paranodal antibodies had not been detected in this cohort (in progress).Taken together, in this case series patients suffered from a moderate and non-progressive course of multiple sclerosis when additionally affected by peripheral demyelination. However, sufficient treatment of concomitant demyelinating neuropathy may become a challenge over the course of disease.

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EP1307
Clinical and imaging features of 14 patients with tumefactive multiple sclerosis

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Introduction: Tumefactive multiple sclerosis (MS) is an atypical form of MS with lesions bigger than 2 centimeters (cm), associated mass effect, perilesional oedema or atypical enhancement pattern that may mimic a brain tumour, abscess or other inflammatory disorders.
Objectives: Our goal is to describe the clinical and imaging patterns of 14 patients with tumefactive MS in order to characterize better this uncommon entity.
Methods: This is a retrospective review of clinical and radiographic material from 14 patients with tumefactive MS that were diagnosed and followed up in our hospital. We have done a descriptive analysis of the demographic features, clinical presentations and outcomes, disability progression measured by Expanded Disability Status Scale (EDSS), brain magnetic resonance imaging (MRI), histopathology of the brain biopsies, cerebrospinal fluid (CSF) and evoked potential results.
Results: There were 9 women and 5 men. The median age at onset was 28 years (2-45). Median disease duration was 8 years (1-17). The most common clinical presentation was motor symptoms (4/14) followed by cognitive and cerebellar dysfunction (2/14). The clinical course at onset was a first neurological event in 9/14, relapsing-remitting in 4/14. One patient only developed tumefactive lesions during his follow-up. Only 3/14 had a monophasic course. Median EDSS was similar at onset and last visit (2.5). 10/14 had demyelinating abnormalities in sensitive and motor evoked potentials. 6/14 had positive oligoclonal bands, 5/14 intratechal synthesis of IgG. In only 3 patients a biopsy was performed and 2/3 biopsies were initially misdiagnosed as a non demyelinating disorder. 1 patient was misdiagnosed as astrocytoma which was surgically removed and treated with radiotherapy. Most lesions had well-defined margins (10/14), with a size 2.1-5cm (8/14), moderate oedema (6/14), T2 hypointense ring (8/14) and ring enhacement (8/14). Lesion volume in subsequent MRIs was reduced in 9/14.
Conclusion: Most had multifocal disease at onset, positive oligoclonal bands and/or abnormal evoked potentials. This along with the reduction of volume lesion during follow-up made it possible to obviate biopsy in many cases.
A better knowledge of the imaging and clinical features of central nervous system inflammatory diseases may facilitate diagnosis, reduce unnecessary biopsies and ensure proper management of theses conditions.

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EP1308

Tocilizumab after autologous hematopoietic stem cell transplantation in refractory neuromyelitis optica: a case report

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Introduction: Autologous hematopoietic stem cell transplantation (ASCT) is a treatment used in patients with Neuromyelitis Optica (NMO) refractory to conventional pharmacologicaltherapies but often guarantees only a temporary control of the disease. Tocilizumab, an interleukin 6 receptor-blocking antibody, can be effective in therapy-resistant cases of NMO, but its role, after ASCT, has not yet been well investigated.
Aims: We present a case of NMO patient showingdisease activity after ASCT, which was managed by tocilizumab administration.
Methods: A 29-year-old woman developed a disseminated demyelinating disease with encephalic and optic nerve lesions, and a longitudinally extensive myelitis on MRI (Expanded Disability Status Scale [EDSS] score: 2.0).Mitoxantrone was administrated for four cycles and a six-year period of clinical and radiological stability was obtained (EDSS:1.0). Subsequently, the patient developed a bilateral optic neuritis; serum anti-aquaporin 4 antibody testing was positive anda diagnosis of NMO according to established criteriawas formulated. In the following two years, she developed new relapses which resulted in a dramatic worsening of her clinical condition and an increased lesion burden on spinal MRI with the presence of gadolinium-enhancing T1 lesions(EDSS: 5.5).Oral steroids, plasmapheresis, azathioprine and rituximab failed to control the disease. ASCT was performed obtaining a progressive decrease in the EDSS score (EDSS:2.5).
Results: 9 months after transplantation, patient showed a relapseanddisability progression, with only a partial recovery after i.v. methylprednisolone administration and a cycle of plasmapheresis(EDSS: 3.5). Due to the poor response to the previous medical treatments, therapy with tocilizumab was initiated at a dose of 8 mg/kg every 4 weeks. After a follow-up of more than 12 months, no relapses, MRI activity, or adverse events occurred.
Conclusions: Tocilizumab could represent a promising and safe treatment in patients with aggressive NMO who have failed ASCT.

Disclosure

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EP1309

MS mimics; MRI-negative relapsing-remitting autoimmune encephalomyelitis, hidden in the psychogenic disorders population

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Objective: To examine cases with a clinical course, signs, and symptoms mimicking multiple sclerosis (MS), but without abnormalities on conventional magnetic resonance imaging (MRI).
Background: The widely used 2010 McDonald criteria allow diagnosis of MS in cases without abnormalities on conventional brain and spinal cord MRI. Nevertheless, such patients have generally been excluded from MS cohort studies, under the assumption that negative MRI findings could never coexist with demyelination.
Methods: Among 550 people with a tentative diagnosis of MS or neuromyelitis optica spectrum disorder (NMOSD), we selected patients, who met the 2010 McDonald diagnosis criteria for MS, but did not show abnormal findings on conventional 3 tesla-brain and spinal cord MRI. After evaluating their clinical data, we analyzed fractional anisotropy (FA) values in the brain white matter on diffusion tensor MRI, normalized brain volumes on 3D-T1 weighted MRI, and frequencies of B cell subsets with activation states in the corresponding cases as compared with healthy controls.
Results: Eleven patients met the selection criteria. They were functionally disabled, with a median expanded disability status scale of 6.0. Oligoclonal bands were negative in all cases. Intravenous methylprednisolone and plasmapheresis were found to be efficacious, whereas there was no evidence for efficacy of interferon beta. The normal-appearing white matter structural integrity was significantly reduced as shown by lower FA without any atrophy of brain parenchyma as well as anti-NMDA receptor encephalitis. The plasmablasts in the peripheral blood were significantly activated and increased in these patients, similar to NMOSD.
Conclusions: The neurological disabilities in these patients could be ascribed to brain white matter damage, as revealed by advanced MRI analysis, whereas the efficacy of plasmapheresis and B cell abnormalities in the patients suggested an autoimmune-mediated pathogenesis. In the differential diagnosis of MS, we propose that this condition be called as, "Normal-appearing Imaging-associated, Neuroimmunologically Justified, Autoimmune encephalomyelitis" (NINJA).

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EP1310

Impact of cigarette and hookah smoking on NMOSD patients´ disability status

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Introduction: Few data are available to investigate the effect of smoking history on disease severity in NMOSD.
Objective: To determine the association between patients´ smoking histories and their disability status (EDSS).
Methods: This cross-sectional study was performed among 62 NMOSD patients registered in Isfahan MS Center(IMSC), Isfahan, Iran. Patients were interviewed using a structured 19-item checklist (items were designed to obtain patients´ demographic information, their EDSS, active/passive cigarette and hookah (traditional water-pipe) smoking histories). Patients´ EDSS scores were used to assess their level of disability.
Results: We enrolled 62 patients in this study of which 71% were female and 80% were married. Mean age, mean age at disease diagnosis and EDSS of patients at the time of data collection were 37.5±10.16, 32.9±10.8 and 1.8±1.6, respectively. Numbness and weakness of the limbs (43%) and optic neuritis (30%) were the two most prevalent first clinical presentations. An association between present or former passive hookah smoking and a higher EDSS among the patients was calculated (p-values< 0.05). However, no associations between having a higher EDSS and having a history of present/former active cigarette smoking, present/former passive cigarette smoking was reported (p-value>0.05). We also found no associations between present/former hookah smoking (p-value>0.05) and a higher EDSS. Analyzing the smoking duration among active and passive smokers, we also found a significantly higher EDSS for passive hookah smokers who were exposed to hookah smoking for more than 20 years (in comparison with those who were exposed for less than 10 years and 10 to 20 years).
Conclusion: Our results show that hookah smoking may aggravate NMOSD patients´ disability status(EDSS). However, cigarette smoking seems to not affect patients´ EDSS scores.

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EP1311

Neuromyelitis optica spectrum disorder in third level hospitals of Ecuador

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is a severe inflammatory disorder of the central nervous system that predominantly affects the optic nerve and spinal cord. So far in Ecuador, there are no reports regarding this disease.
Objective: To report demographic, clinical, and radiological data of NMOSD patients in third level hospitals of Ecuador.
Methods: Using the 2015 revised NMOSD criteria, we retrospectively reviewed the medical records of patients who were attended at Hospital Carlos Andrade Marín, Hospital General de las Fuerzas Armadas and Hospital Eugenio Espejo in Quito, Hospital Teodoro Maldonado Carbo in Guayaquil and Hospital José Carrasco Arteaga in Cuenca, all of which are references centres for NMO in Ecuador, from January 2015 to Abril 2018.
Results: We recruited 59 patients, 47 of whom were female (80%). The ratio female to male was 3.9/1. The median age was 43 years SD +/- 15.21 (range 15-73). Mean age at onset of the 1st symptom was 37.2 years (range 11-69). At presentation of the first symptom, 10 patients (16.9%) had transverse myelitis (TM), 22 (37%) had optic neuritis (ON), 24 (40.6%) had simultaneous TM and ON and 9 (15%) had hiccups and/or vomiting. The clinically established manifestations were, unilateral ON 32%, bilateral ON 49.15%, motor symptoms (93.2%), sensory symptoms (79.6%) and autonomic symptoms 42.37%. Longitudinally extensive transverse myelitis (LEMT), which was established by magnetic resonance imaging was present in 88% of patients. Cervical, cervical/thoracic and thoracic spinal cord damage was present in 37.2%, 35.59% and 15.25% respectively. Brain MRI abnormalities were present in 5 patients (8.4%). Out of the 51 patients tested, 40 (78%) were AQP4-IgG (+). The Median Expanded Disability Status Score (EDSS) was 4.9.
Conclusions: This is the first cohort of NMOSD described in third level hospitals in Ecuador, 80% of patients were female. At the onset of the disease, simultaneous TM and ON were present in

78% of patients. In MRI scans, LEMT was present in 88% of patients and brain abnormalities were infrequent. Positive antibodies for AQP4 were present in 78% of patients. The behaviour of this disease in Ecuador is different if compared with studies of cohorts from other countries.

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EP1312
A longitudinal study of cognitive function in a Japanese cohort of NMO and MS

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Objective: Neuromyelitis optica spectram disorders (NMOSD) and multiple sclerosis (MS) are autoimmune diseases of the central nervous system. The aim of this study was to elucidate dynamics of cognition in a Japanese cohort of NMOSD and MS during long-term courses.
Methods: We performed a longitudinal study for 16 patients with MS and 12 patients with NMOSD. All patients were investigated for clinical features and were performed using the Brief Repeatable Battery of Neuropsychological Test (BRB-N) at baseline and at least 3 year-follow-up.
Results: The mean follow-up periods for assessments were 6.8 years and 5.6 years in NMOSD patients (male/female = 1/11) and MS patients (male/female = 6/10), respectively. Three patients (19%) with MS had progressive courses, but other patients with NMOSD and MS did not. The mean ages at basement of assessments were 49.5 (SD 10.8) years and 39.3 (SD 8.5) years, and frequencies of taking treatments were 75% (steroid treatments) and 69% (disease-modifying treatments including interferon β) in NMOSD and MS patients, respectively. During the follow-up study, the mean annualized relapse rates were 0.2 (SD 0.2) and 0.1 (SD 0.1), the mean annualized changes of EDSS change were 0.1 (SD 0.3) and 0.0 (SD 0.3) in NMOSD and MS patients, respectively. During the follow-up study, the BRB-N index of MS patients had significantly deteriorated compared to NMOSD patients ($P < 0.001$). Among the items of the BRB-N, symbol digit modality test ($P = 0.012$), delayed selective reminding test ($P = 0.013$), spatial recall test (SPART)($P = 0.049$) and delayed SPART ($P = 0.038$) had significantly deteriorated in MS patients, compared to NMOSD patients.
Conclusion: BRB-N is a useful assessment in evaluating cognitive function of NMOSD and MS during long-term courses. These data suggest that dynamics of cognitive impairment and neurodegenerative processes were distinct differences between NMOSD and MS during at least 3 year-follow-up.

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EP1313
Early relapse after rituximab initiation in a patient with neuromyelitis optica spectrum disease and side effects to subsequent tozilizumab therapy: need for further treatment options?

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Background: Neuromyelitis optica spectrum disease (NMOSD) is an autoimmune disease with severe potentially life threatening relapses and thus needs long term immunsuppressive therapy to prevent relapses and disability accumulation. However multiple immunosuppressive therapies may increase the risk for side effects and limit further therapy escalation.
Methods: To report a single patient with the diagnosis of NMOSD and concomitant systemic lupus erythematodes (SLE) who showed insufficient response to multiple immunosuppressive therapies. All medical data including clinical disease course, therapies and laboratory results e.g. B-cell counts were continuously recorded and collected.
Results: This female patient was diagnosed with SLE in 1994 at the age of 20. In 1994 bilatereral optic neuritis (ON) occurred resulting in blindness of the right eye which was followed by recurrent myelitis since 1995. Initially ON and myelitis were regarded as a manifestation of SLE. Immunosuppressive treatments with azathioprine, cyclophosphamide methotrexate and ciclosporine), could not stabilize the disease course and led to side effects. At first presentation in our outpatient clinic she tested positive for anti-aquaporin-4 antibodies (AQP-4-Ab) and was diagnosed with NMOSD (EDSS = 3.5). Therapy with rituximab (RTX) was started in 7/2015 with 2 x 1g i.v. two weeks apart and led to B-cell depletion. Five weeks after the first RTX infusion she experienced another relapse with myelitis. B-cells returned six

months later, however no complete B-cell depletion could be achieved with ongoing RTX therapy and further relapses occurred. RTX therapy was stopped (normal B-cell count) and treatment with tocilizumab (TZ, 8 mg/kg/body weight) i.v. started in 3/2017. After the second TZ dosage recurrent granulocytopenia (grade 2) associated with bladder as well as bronchial infections occurred and subsequent dosages had to be postponed. She experienced two more relapses (EDSS 4.0) and TZ was stopped after the 6th infusion. Currently, further therapeutic options include mycophenolate mofetil, combination therapies, as well as off label therapy with eculizumab. However this must be weighted against the risk of further side effects.

Conclusions: Insufficient response to RTX and severe side effect to subsequent TZ therapy complicated the clinical course in this patient and illustrates possible risks after frequent and various immunosuppressive therapies in NMOSD.

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EP1314

Successful intravenous immunoglobulin treatment in a patient with relapsing MOG antibody-associated disease

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Background: Anti-MOG (myelin oligodendrocyte glycoprotein) antibodies (Abs) have been recently related to aquaporin-4 (AQP4) Ab negative neuromyelitis optica spectrum disorder (NMOSD) cases. Treatment of MOG Ab-associated disease is poorly standardized: several drugs have been employed, with variable results, in small case series. Very few adult patients with MOG Ab-associated disease have been treated with long-term intravenous immunoglobulins (IVIg), with different schedules. Here we report a case of relapsing MOG Ab-associated disease treated with an IVIg empirical therapeutic strategy.

Case report: A 50-year-old Caucasian male was admitted to hospital in 2009, with symptoms and signs of severe acute transverse myelitis (urinary retention, paraparesis and legs dysesthesias). Expanded disability status scale (EDSS) score was 6.0. Moreover, he reported three previous episodes of dizziness and diplopia, suggestive of demyelinating attacks. Brain and spinal cord MRI showed multiple demyelinating lesions. Cerebrospinal fluid analysis revealed no oligoclonal bands (OCBs). Many rheumatologic, infectious and autoimmune diseases were excluded by biochemical tests, including anti-AQP4 Abs. After steroid pulse therapy, he had good recovery (EDSS 2.0) and a diagnosis of multiple sclerosis (MS) was made. A subsequent MRI showed disappearance of all the lesions. He was treated with interferon-beta 1a, then with fingolimod, and finally with rituximab. All these treatments were ineffective: he experienced several spinal and brainstem relapses, with residual disability. In July 2016 an empirical therapy with IVIg was started at the dosage of 2 gr/kg in five days (first cycle), then 0,8 gr/kg in two days every three weeks. Calling into question the diagnosis of MS, we performed another lumbar puncture (OCBs still negative), serum anti-AQP4 test (negative) and anti-MOG test (positive). After the diagnosis of MOG Ab-associated disease, we decided to continue with IVIg therapy, considering the initial good results. During a 22-month follow-up, the patient experienced only one mild relapse (annualized relapse rate decreased from 3.0 to 0.57), while EDSS remained stable (4.0). Two consecutive brain and spinal MRI revealed no new lesions.

Conclusions: Our patient, with an aggressive and atypical MOG Ab-associated disease, showed a very good response to long-term IVIg treatment. IVIg therapy should be considered in all the cases of aggressive MOG Ab-associated disease.

Disclosure

Elena Tsantes served on scientific advisory boards for Roche and has received funding for travel from Biogen, Merck Serono and Sanofi Genzyme.

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Franco Granella served on scientific advisory boards for Biogen, Merck Serono, Novartis, and Sanofi Genzyme. He received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, and Sanofi Genzyme. His institution received research grants from Biogen and Sanofi Genzyme.

EP1315

Familial multiple sclerosis

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Introduction: Multiple sclerosis is a neurodegenerative disease of the central nervous system resulting from the combination of various complex etiological mechanisms (viral, genetic, vitamin D deficiency ...). The forms of familial MS represent 10-15%

Study aim: To describe the clinical aspects and the evolutionary profile of the familial forms of MS

Patients and method: Retrospective descriptive study of the forms of familial MS in the neurology department, Ibn Rochd university hospital of Casablanca. We report the case of 4 families of which at least 2 members are suffering from the disease.

Results: Families with 2 affected members had a 2nd degree relationship and 1st and 2nd degree in families with more than 2 affected subjects. The average age at symptoms' onset was 27.83 years with a sex ratio (female /male) of 1.5

The remitting form represented 85.71%. Oligoclonal bands were found only in 25% of patients.

Discussion: Genetic susceptibility in multiple sclerosis has already been clearly defined
And this was initially suggested by the increased incidence of the disease in some families. The oligoclonal bands were only found in 25% of cases, in contrast to sporadic MS.
Conclusion: It shows from this first analysis that the remitting forms dominate the clinical presentation and that the oligoclonal bands are often negative in the CSF.

Disclosure
Nothing to disclose

EP1316
Baló's concentric sclerosis: study of clinico-radiological characteristics and therapeutic outcomes

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Background and goals: Baló's Concentric Sclerosis(BCS) is a multiple sclerosis (MS) subtype characterized by concentric alternated lamenae of normal and destroyed myelin, histopathologically more consistent with type III pattern of MS. Our goal was to study MRI characteristics and therapeutic outcomes in BCS.
Methods: Our study included three patients with acute symptom onset due to a BCS lesion on brain MRI.
Results: Patient-A a 30-year-old female, experienced dysarthria, left facial droop and left hand dexterity problems for four days, due to a mass lesion (3.10cm x2.85cm x3.05cm)involving the right centrum semiovale with contrast enhancement (Gd+). Patient-B a 24-year-old man presented with right-sided hemiparesis and hemianaesthesia; a large Gd+ lesion (2.8cm x2.47cm x2.45cm) of the left corona radiata was revealed. Patient-C developed Wernicke´s aphasia and right-sided hemianaesthesia as a result of a Gd+ concentric lesion(2.6cm x1.8cm x1.2cm) involving the left corona radiata and the adjacent parietal subcortical white matter. These lesions were solitary, tumefactive, with hyperintense-isointense-hypointense concentric rings on T2-weighted images. On DWI images concentric layers of high and low intensity were noticed without low signal on ADC map(T2 shine-through)with the exception of a part of the outer layer which showed minimal restriction. All the patients initially received intravenous methylprednisolone course with poor response, while one underwent seven plasmapheresis sessions with subsequent MRI activity deterioration. However, after immunosuppresive treatment they all had a remarkable clinical response, no Gd+ and significant reduction of lesion size : patient-A 1.88cm x1.35cm x1.75cm, patient-B 1.74cm x1.37 x1cm, patient-C 1.93cm x1.61cm x1cm. Two patients after six monthly IV pulses of cyclophosphamide(800mg/m^2/pulse), while the third after four doses of IV mitoxantrone(10mg/m^2 every 3months).
Conclusions: Immunosuppresive treatment with cyclophoshamide or mitoxantrone seems to be the basis of therapeutics in BCS as it can affect both activated microglia and macrophages that highly express nitric oxide synthetase associated with apoptosis.

Disclosure
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G. Koutsis has received research grants from Genesis Pharma and Teva, consultation fees, advisory board renumeration and honoraria from Genzyme, Genesis Pharma, Teva and Novartis.
M.E. Evangelopoulos has provided consultation services for and received honoraria from Novartis, Biogen and Teva.
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EP1317
Clinical and demographic characteristics of relapsing-remitting multiple sclerosis in Kazakhstan

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Relevance of the study and purpose: multiple sclerosis (MS) in most cases has a wave-like (remitting) course with alternating episodes of exacerbations (exacerbation) and remissions. The disease affects mainly young and middle-aged people. The purpose of research is to study the clinical and demographical characteristics of multiple sclerosis in Kazakhstan.
Materials and methods: the study includes 260 patients with the RMS in the northern regions of Kazakhstan. During of the study, parameters such as sex, ethnicity, average age of patients and the average age of debut of the disease, clinical manifestations in the MS debut, degree of disability using the double evaluation system (including the scale of the functional systems Kurtzke (FS) and the extended disability status scale (EDSS)). Statistical processing performs using the SPSS PASW Statistics 18 program.
Results: the total number of patients is 260 people. The study identified 4 cases with clinic optionality, 256 people with RMS. The RMS registers in 184 women (71.95%) and 72 men (28.1%), 4 women with the Neuromyelitis Optica Spectrum Disorders (NOSD). Asian population of 44 people with the RMS (17.2%), the European population of 212 people with the RMS (82.8%). 4 patients with the NOSD are persons from Asian population. The average age of patients with RMS made up 42,41±11,35, the average age of patients with a range of optionality (the NOSD) was 30±3,67. Age of debut when RMS made up 31,02±9,55, with a NOSD of 25±4.24 years. The debut of the clinic RMS starts with visual impairment in 44

patients (17.2%), cerebellar - in 59 (23%), pyramid - 97 (37.9%), sensory - 45 (17.6%), stem - 10 (3.9%), and sphincter - 1 (0.4%). The debut of the clinic NOSD in all 4 patients manifested visual disorders. The degree of disability according to EDSS within 0-1 points have-25 patients (9.8%), 1.5-4.5 points-121 patients (47.3%), 5.0-6.5 points- 92 (35,9%), 7,0-9,5 score-18 patients (7.0%).
Conclusion: among women with RMS, women prevail, in the ratio of men and women-1:2.5, as well as persons of the European population 1:4,8, the disease in the debut affects people older than 20-30 years, the manifestation of the disease is more often characterized by the defeat of the pyramidal function, with a high degree of disability, corresponding to the 2nd and 3rd group of disability. Individuals with NOSD were found exclusively in individuals of the Asian population, female, with loss of visual function.

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S. Kozhakanova: nothing to disclose
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A. Zhusupova: nothing to disclose

Pediatric MS

EP1318
Retinal nerve fiber layer and ganglion cell inner plexiform layer in youth with serum myelin oligodendrocyte glycoprotein antibody positivity

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Introduction: Structural changes in the retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GCIPL) have not been described in youth with neuroinflammatory syndromes who were positive for MOG antibody in the serum (MOG+).
Objective/Aim: To describe structural changes in the anterior visual pathway in MOG+ youth.
Methods: This cross-sectional study includes consecutive youth with MOG+ neuroinflammatory syndromes (positive ≥3 months from incident demyelination; n=28, 22 female, 11.05(5.80) years old, 22 with 1+ episodes of ON, 6 without ON) followed at The Hospital for Sick Children, Canada. MOG testing was performed at a single laboratory (Oxford University Laboratories) using a cell-based assay. Comparisons were made to healthy controls (HC) (n=44, 27 female, 15.68(2.32) years old). Participants were evaluated using spectral-domain optical coherence tomography (Zeiss, Cirrus HD-OCT). For all patients the earliest OCT was analysed. However, to avoid confounding due to changes associated with acute ON, only OCT data obtained ≥3 months from an ON episode was used. Generalized linear models were fitted using generalized estimating equations to account for the correlation between pairs of eyes per participant, age and sex. Bonferroni corrections for multiple comparisons were used. Adjusted $p < 0.05$ was considered significant. Ethics approval was obtained.
Results: MOG+ patients were younger than controls ($p < 0.001$). OCT was performed 0.99(4.42) years (median(IQR)) from incident demyelination. RNFL was thinner in MOG+ than in HC eyes (median(IQR): 72(37)µm vs 100(13)µm, $p < 0.001$)). GCIPL was thinner in the MOG+ than in HC eyes (median(IQR): 64(20)µm vs 86(5)µm, $p < 0.001$).
In MOG+ patients, lower average RNFL and GCIPL thickness was observed in eyes with more episodes of ON. RNFL thickness was 25.03µm less in eyes affected by 1 ON episode (n=29) vs none (n=16), 13.60µm less in eyes affected by 2 ON episodes (n=8) vs 1, and 14.39µm less in eyes affected by 3+ ON episodes (n=3) vs 2. GCIPL thickness was 11.28µm less eyes affected by 1 ON episode vs none, 5.29µm less in eyes affected by 2 ON episodes vs 1, and 5.77µm less in eyes affected by 3+ ON episodes vs 2.
Conclusions: The presence of MOG antibodies in serum is associated with thinning of the RNFL and GCIPL layers in pediatric patients, particularly in the context of repeated episodes of ON. Future studies will assess the association of these structural changes with visual function.

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EP1319
Diagnostic value of oligoclonal bands in children: a Danish nationwide multicenter population-based cohort study

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Background: Oligoclonal bands (OCB) are increasingly being examined in children, but their diagnostic value remains uncertain owing to numerous and age-dependent differential diagnoses.
Aim: To evaluate the diagnostic value of OCB and cerebrospinal fluid (CSF) leucocytes in children (< 18 years).
Methods: In a nationwide population-based setting, we retrieved data on first OCB examination in 2,002 children, including CSF leucocytes and differential count, protein, albumin ratio, erythrocytes, glucose ratio and lactate from Danish laboratory databases during 1994-2018. We categorized the children into diagnostic groups based on hospital discharge diagnoses from 2 month before and 1 year after the date of OCB examination.
Results: Median age at OCB examination was 14.2 years (range=0.02-18.0). Among 2,002 children, 200 children (10%) were OCB positive, and 21% had CSF pleocytosis (>4 CSF leucocytes). Among children with central nervous system (CNS) disease, 165 (18%) were OCB positive. The proportion was higher in the subgroup of children with inflammatory CNS diseases (48%), while only 5% had positive OCBs among non-inflammatory CNS diseases. The distribution of OCB positivity for CNS diseases was: epilepsy (3%), hypersomnia syndromes (6%), malignancy (15%), movement disorders (4%), progressive (3%) and static (8%) encephalopathy, stroke (3%), demyelinating (51%), immune- and infection-mediated disease (both 13%), and other CNS diseases (2%). However, only 14% of children with demyelinating disease younger than 12 years of age had positive OCBs. For CNS diseases we found: a) positive OCBs without pleocytosis were rare (4%), but mostly seen in CNS demyelinating diseases (10%) and malignancies (11%); b) positive OCBs with pleocytosis were more common (11%) and mostly seen in demyelinating diseases (43%), immune- or infection-mediated disease (both 11%); c) negative OCBs and pleocytosis were seen in CNS infections (54%), immune-mediated CNS disease (32%) and stroke (29%), but rarer in demyelinating disease (19%). 4% of children with non-CNS disease had positive OCBs.
Conclusion: OCB positivity was related to CNS demyelinating disease, but less often so in children before age 12, presumably due to lower incidence of multiple sclerosis and higher incidence of acute disseminated encephalomyelitis; therefore caution is advised in interpreting OCB in children< 12 years. Negative OCBs and pleocytosis favoured infection, immune or cerebrovascular disease.

Disclosure

Dr. Boesen has served on scientific advisory board for Teva; has received speaker honoraria for lecturing from Novartis and support for congress participation from Teva, Novartis and Roche.
Dr. Jensen, **Dr. Rosenberg**, **Dr. Thomassen, Dr. Børresen**, **Dr. Jørgensen** and **Dr. Lydolph** report no disclosures.
Dr. Born has received speaker honoraria from Novartis and has served on an advisory board for Biogen.
Dr. Sellebjerg has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, EMD Serono, Genzyme, Lundbeck, Merck Serono, Novartis and Teva.

EP1320
Fatigue, depression and quality of life in children with multiple sclerosis: a French cohort study

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Objective: To evaluate fatigue, depression and quality of life of children with multiple sclerosis (MS).
Methods: Children with MS, followed in the national referral centre for neuro-inflammatory diseases, were included from January 2014 to December 2016. Fatigue severity scale (FSS) for fatigue, Multiscore depression inventory for children (MDI-C) for depression and Pediatric quality of life inventory (PedSQL) for quality of life were used in order to evaluate these children between 6 months and one year after diagnosis and/or relapse. They were compared to children with other acute demyelinating disorders (ADS).
Results: A total of 37 children were included in this study, 23 (63%) were girls and 14 (37%) were boys. They were 11,6 ± 3,5 years old at disease onset and they were 13,7 ± 2,8 years old during their assessment. Multiple sclerosis (MS) was diagnosed for 26 (70%) children and other ADS for 11 (30%) children (4 (11%) relapsing MOG, 3 (8%) ADEM, , 4 (11%) CIS). EDSS score at test was 0,1 ± 0,4 in MS group and 0,5 ± 0,7 in ODS group. 44% of the MS children and 63% of the ADS children reported severe fatigue. The signs of depression were superior in the MS group (28%) comparing to ADS group (18%) for all features of depression, except introversion which was more important in the ADS group. In MS group, both parents and children reported a poorly emotional and academicals functioning. Physical and social functioning was rated as being good in both parents and children.
Conclusion: In this prospective study, children with ADS reported fatigue more frequently then MS children. In contrast, signs of depression were reported more frequently in MS group than ADS group. Difficulties in school and emotional functioning were the main concerns for parents and children in the MS group.

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Kumaran Deiva : nothing to disclose

EP1321

Decreased thickness of peripapillar retinal nerve fiber layer may be present after years of the episode in some patients with pediatric acute disseminated encephalomyelitis

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Objective: The aim of this study was to evaluate the anterior optic pathway in children with the diagnosis of acute disseminated encephalomyelitis (ADEM) with or without clinical Optic neuritis measuring the peripapillar retinal nerve fibre layer (RNFL) thickness by optical coherence tomography (OCT)
Methods: A cross-sectional study of 8 patients (2/8 with positive titles of anti-MOG IgG) diagnosed with monophasic ADEM between 2010-2017 in a tertiary pediatric hospital. Data about onset symptoms, subjective complaints and school performance after the episode were collected. The presence of dyschromatopsia was evaluated with the Ishihara test, the manual ability through the Nine Peg Hole test (NPHT) and the presence of executive alterations with parts A and B of the standardized Trail Making test(TMT). Brain MRI of the episode was evaluated using the 16-parameter score system suggested by Verhey et al. The average and segment thickness of the RNFL was measured by OCT (Heidelberg Spectralis) in both eyes.
Results: Median age at onset was 44 (range: 4-96) months and the evaluation was made at 8 (range: 4-10) years. Symptoms at onset were fever and encephalopathy (8/8), brainstem focality (6/8) cerebellar focality (5/8) and epileptic seizures (2/8). Learning difficulties during the follow-up, although one of them had psychomotor retardation prior to the ADEM episode. The Ishihara test was normal, the NPHT in 7/8. Basal MRI showed involvement of gray matter and white matter (8/8 patients), thalamic (6/8) and optic nerves (1/8, anti-MOG +) involment. Only 2 patients have a pRNFL thickning and they were anti-MOG +; presenting a global alteration in the case with MRI involvement of the optic nerves and a crossed alteration of the nasal and temporal segments in the other case.
Conclusions: OCT may be a valuable tool for the evaluation and monitoring of optic pathway dysfunction in children with demyelinating diseases. Patients with positive anti-MOG may be more susceptible of sequelae which can be detected by OCT.

Disclosure

Nothing to disclose.

EP1322

Differences in cerebrospinal fluid CXCL8, CXCL10, CXCL13 and MCP1 chemokines levels in paediatric clinically isolated syndrome and definitive multiple sclerosis

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Background: Clinically isolated syndrome (CIS) is the first demyelinating episode that may or may not result in definitive diagnosis of multiple sclerosis (MS). All cellular components of immunity (T and B cells, monocytes and also neutrophils) have been recently shown to play role in MS pathogenesis. The chemokine system ensures migration and immune cells interactions to the site of inflammation and thus is beyond the scope of investigation. Important one is the chemokine for B cells attraction (CXCL13) that has been elevated in many studies. There are various data about chemoattractants for T cells (CXCL10), monocytes (MCP1) and neutrophils (CXCL8). These data from paediatric MS population are limited.
Objectives: We measured chemokines concentration in cerebrospinal fluid (CSF) of paediatric MS patients and compared them to paediatric patients with CIS and controls.
Methods: Luminex multiple bead technology and software were used to determine the levels of CXCL8, 10, 13 and MCP1 in CSF of **1)** 17 MS patients (age: median 16 years, range 12-18 y; female: male =12:5), **2)** 25 CIS patients (age: median 13 years, range 4-17 y; female: male = 15:10) and **3)** 37 controls (age: median 11 years, range 2-18 y; female: male = 23:14). Controls represented patients with different non-inflammatory neurological conditions. Non-parametric test were used, a P value < 0.05 was considered to be significant.
Results: CSF CXCL8 concentration was significantly increased in MS and CIS patients compared to controls. There was no difference between CSF CXCL8 levels in MS and CIS patients. CSF CXCL10 concentration was increased in MS but not in CIS patients compared to controls. CSF CXCL13 concentration was significantly increased in both MS and CIS patients in comparison with controls and that was most prominent in MS patients. CSF MCP1 concentration was increased in CIS but not in MS patients compared to controls.
Conclusion: Differences in CSF chemokines levels within MS and CIS patients and controls indicated engagement of possibly different immune populations during CIS and MS course. The CNS attraction of B and T cells was more prominent in MS then in CIS patients. The attraction of monocytes was observed only in CIS patients, while the attraction of neutrophils was similar in both MS and CIS patients. Our data supported the importance of further investigation of chemokines levels and their association with the pathogenesis and prognosis of demyelinating disorders.

Disclosure
The authors declare that there are no conflicts of interest.

EP1323
The challenges of predicting the future after the first inflammatory CNS event in pediatric patients

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Introduction: The diagnosis of chronic inflammatory central nervous system (CNS) diseases in pediatric patients is challenging given the variety of differential diagnosis and high frequency of monophasic events. Also, initial clinical presentations of chronic inflammatory CNS diseases such as multiple sclerosis (MS) may have lower predictive value in pediatric patients regarding the final diagnosis.
Objectives: We aim to describe the clinical and serologic characteristics of Brazilian pediatric patients after the first CNS inflammatory demyelinating event.
Methods: We analyzed the data of patients included in an ongoing Brazilian pediatric multicentric cohort (EMOCEMP Study) recruited from 4 centers.
Results: Thirty-three patients were included with a median age of 10 years (0-17 years) with a male to female ratio of 1.2. Of these, 69.7% (23) were Caucasian, 24.2% (8) were Mullatoes, one African and one Asian. Regarding clinical presentation, 33,3% (11/33) presented with optic neuritis (ON), 27.3% (9/33) presented with myelitis, 21% (7/33) with acute disseminated encephalomyelitis and 12% (4/33) had multifocal neurologic symptoms without encephalopathy. Thirty patients were tested for antibodies against aquaporin-4 (AQP4-Ab) and myelin oligodendrocyte glycoprotein (MOG-Ab). Of those 5 were MOG-Ab positive and one was AQP4-Ab positive. Most patients (90%) were treated in the acute phase with intravenous methylprednisolone. We did not observe significant differences in initial clinical presentations between patients younger and older than 10 years. However, isolated ON and/or myelitis was observed as initial presentation of 68% of the patients older than 10 years.
Conclusions: These preliminary results confirmed the difficulties of predicting the evolution of chronic inflammatory CNS disease after the first clinical episode in pediatric patients. As we expect a higher incidence of conversion to MS in patients older than 10 years, ON / myelitis presentations might add additional difficulties in the differential diagnosis with neuromyelitis optica spectrum disorders and MOG-Ab associated ON, encephalitis and myelitis (MONEM). The follow-up of these patients might allow us to identify the predictors to the conversion to MS and other diseases in this age group.

Disclosure
EMOCEMP study has received support from TEVA, FAPERGS, CNPq/Brazil. Bruna Klein da Costa receives scolarship from CNPq/Brazil and received travel grant from Merck. Rafael Canoni Sommer has nothing to disclose. Ricardo Zalewsky has nothing to disclose. Jefferson Becker has received reimbursement for developing educational presentations, educational and research grants, consultations fees and travel stipends from Bayer, Biogen, Ipsen, Merck, Novartis, Roche, Sanofi, Teva. Renata Barbosa Paolilo has received travel grant from Biogen and Roche. José Albino da Paz has nothing to disclose. Dagoberto Callegaro: Research support from CAPES/Brasil (CSF-PAJT—88887.091277/2014-00). Fernanda Silveira de Quadros has notjing to disclose. Marlise de Castro Ribeiro has nothing to disclose. Hanaie Cavalli has nothing to disclose. Henry Koiti Sato received grants and consulting fees from Bayer, Biogen, Merck-Serono, TEVA, Sanofi, Genzyme, Roche, Novartis. Douglas K. Sato has received a Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (KAKENHI 15K19472); research support from CNPq/Brasil (425331/2016-4), TEVA (research grant for EMOCEMP Investigator Initiated Study - NCT no. 61080516.4.1001.5336), and Euroimmun AG (Neuroimmunological Complications associated with Arboviruses); and speaker honoraria from Biogen, Novartis, Genzyme, TEVA, Merck-Serono, Roche, Bayer and is an advisory board member of Shire, Roche, TEVA, Merck-Serono and Quest/Athena Diagnostics.

EP1324
Pediatric acquired demyelination syndromes profile in a Brazilian center

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Introduction: acquired demyelination syndromes (ADS) represent a group of inflammatory disorders of the central nervous system (CNS) such as Multiple Sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), acute disseminating encephalomyelitis (ADEM), clinically isolated syndromes (CIS) and the recently described Myelin Oligodendrocyte Glycoprotein antibody (MOG) associated disease. ADS is rare in childhood and its prevalence is unknown in Brazil.
Objective: to describe the demographic and clinical aspects of pediatric ADS patients in a Brazilian center.
Methods: medical records review from patients followed at pediatric neuroimmunology clinic of Hospital das Clinicas, University of São Paulo-Brazil from january 2010 until december 2017. All patients whose symptoms started before 18 years of age and fulfilled International Pediatric Multiple Sclerosis Study Group (IPMSSG) current diagnostic criteria for MS, NMOSD, ADEM, CIS were included in addition to patients with MOG-IgG seropositivity.
Results: 150 patients were identified, 145 were analyzed (5 missing data): 80 were females (55,1%); median age of onset was 14 (1-17) years. 61 (42%) patients were tested for autoantibodies

(MOG-IgG and aquaporin4-IgG). MS patients: 75 (52%), all recurrent course. NMOSD patients: 26 (18%), 18 were aquaporin4-IgG positives (69%), all recurrent; 5 were MOG-IgG positives (19%), 4 recurrent; 3 were double seronegatives. ADEM patients: 11 (7,5%), all monophasic. Optic neuritis (ON) patients: 15 (10%), 8 monophasic. Transverse myelitis (TM) patients: 9 (6%), 7 monophasic. CIS patients, other than ON and TM: 8 (5,5%), all monophasic. One patient with MOG-IgG had leukodystrophy-like phenotype.

Conclusions: most patients had recurrent ADS (75%) and MS was the most common. Autoantibodies tested in some patients revealed 19% of seropositivity and MOG-IgG patients showed heterogeneous clinic manifestation.

Disclosure

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EP1326

The usefulness of evoked potentials in the initial diagnosis of multiple sclerosis in children

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Introduction: Multiple Sclerosis (MS) is a chronic inflammatory and demyelinating CNS disease and is one of the most common causes of disability in young people. In the diagnosis of MS, endo- and exogenous evoked potentials are widely used. The aim of the study was the neurophysiological characteristics of patients with relapsing-remitting MS qualified for interferon treatment.

Material and methods: The study included 22 children aged 11.5-17 years (mean 14.5) hospitalized with newly diagnosed multiple sclerosis, hospitalized in 2016-2018 in the University Children´s Hospital in Krakow. According to the type of the first clinical symptoms, children were divided into three groups. Group I consisted of 11 children with visual impairment, group II of 7 children with sensory and motor abnormalities, while in group III there were 4 children with impaired vision and sensation. In all children, in the initial diagnostic process, exogenous evoked potentials (VEP,BAEP,SEP) and endogenous evoked P300 potential were made.

Results: In the VEP study, elongated P100 latencies in all patients, P100 amplitude was normal in 20 children and in 2 was decrease. In the BAEP examination, normal latencies and interlatencies of waves I-III, III-V, I-V in all children was obtained. At the median nerve, slightly elongated latency N9 was obtained in group I-9.62+/-0.81ms, in group II-9.76+/0.75ms, in group III-9.41+/-0.81ms, P14 in group I-14.46+/-1.25ms, N18 in group III 18.43+/-1.3ms, N20 was normal in all groups. In the study of endogenous potentials, a slight elongation of the P300 latency in group I-332.55+/-26.70ms and, in group II-327.43+/-17.70ms, in the group III- 329.75+/-21.86ms, and a reduced amplitude in group II-2.37+/-4.82uV, compared to the control group.

Conclusions:

1. VEP is a sensitive neurophysiological method in the objective assessment of retrobulbar optic neuritis, and in clinically silent optic pathways involvement
2. The integrity of the auditory pathway in children with MS at the early onset of the disease remains unaffected
3. The prolongation of the latency of waves in the SEP study corresponds to the clinical symptoms
4. The prolongation of P300 latency may indicate a cognitive impairment in children with newly diagnosed MS

Disclosure

Witek : I have nothing to disclose
Kroczka: I have nothing to disclose
Stolarska: I have nothing to disclose

EP1327

Clinical trials in pediatric multiple sclerosis : a British-French patient and parent perspective

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Aim: Since 2013, clinical trials in pediatric multiple sclerosis (pMS) have emerged and patient recruitment in this rare disease was challenging. Understanding the limiting factors, for both parents and children, to participate in these clinical trials would help to desgin better trials in the future.
Methods: Children with pMS and their parents, who had been approached to participate in a clinical trial, were asked to complete an anonymous survey. They were either followed in Bicêtre Hospital, France or the Birmingham Children's Hospital, United Kingdom.
Results: The survey was proposed to 90 persons and 58 responded, 35 parents and 23 children. 33 responders (11 children, 22 parents) had not participated in a clinical trial. In this 'non-paritipicipant" group, the main concerns for parents were school absence (50%) and the risk of being on placebo (55%), and only 19% of children expressed difficulties in participating in clinical studies. In that group, more than 72% of children and 45% of parents were willing to participate in a future clinical trial.
25 responders (12 children, 13 parents) had participated in a clinical trial. The main concerns for parents and children were the number of visits (54% and 50%) and school absence (46% and 50%). Interestingly, for children, the number of blood samplings (75%), blinding for treatment (67%) and getting injections (58%) were not limitations In this group 50% of children and 85% of parents were ready to participate again in a clinical trial.
Conclusion: The main concerns for parents and children are the frequency of visits and missing school during a clinical trial. Interestingly, children are more willing to participate in clinical trials than their parents and the opposite is true after having participated. Children and parents suggested to do blood tests at home, less visits and not during the school days. Future clinical trials may need to be adapted according to their wishes.

Disclosure

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EP1328

Efficacy of therapy in pediatric MS during 2 years (single-site study)

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Introduction: It is known that pediatric MS proceeds with a greater frequency of exacerbations and higher inflammatory activity compared with a later onset. Standard drugs have their age limitations and there is insufficient information on their effectiveness in children
Objective: to evaluate the effectiveness of standard injection therapy in pediatric MS.
Methods: The city center of the MS in St. Petersburg has been working since 2011. A total of 351 patients (9.6%) with onset before 18 years were registered in the database (about 4000 patients). Retrospectively, the data of 66 patients with pediatric MS, who fell ill in 2011 to 2017, were retrospectively evaluated (3.5% of registered MS debuts in adult patients during the same period) . The effectiveness of standard injection therapy (relapses and MRI activity) in the first 2 years of the disease was assessed. Statistical analysis was performed with the program GraphPad Prism v7.0.
Results: The ADEM-like onset was registered in 5 patients (7.5%). In 33 patients (50%) there were sensory disorders, in 30% of cases there were motor and coordination disorders, optic neuritis was performed only in 14% of patients. During 1 year of glatiramer acetate therapy 88% of patients (n = 8) had no relapses, but at 2 years - only 33% did not experience an exacerbation. With the 1 year use of interferon beta 1 a 44, 81% patients (n = 13) were stable, at 2 years of therapy - 67% had an exacerbation. In the low-dose interferon in 61% of patients (n = 8) had no relapses, at the end of 2 year - half of the patients were transferred to other therapy due to inefficiency. Most patients with ineffectiveness of GA or interferones received therapy in clinical trials (n = 12). 2 patients received mitoxantrone, 2 patients - natalizumab and 1 patient - rituximab with stabilization of MS activity. 5 patients are waiting escalation by natalizumab or alemtuzumab.
Conclusion: Fast enough standard injection therapy stops restraining inflammation in pediatric MS. 40% of children require a change in therapy by the end of the second year due to inefficiency (relapses and/or high radiological activity).

Disclosure

M Shumilina: has recieved and dedicated to research support fees for board membership, consultancy or speaking, or grants, in the last 3 years from Novartis, Biocad, Sanofi/Genzyme, Roche, Johnson & Johnson/ Janssen, R-Pharm and Generium.

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EP1329

What changes with the 2017 McDonald criteria in CIS pediatric patients

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Introduction: Multiple Sclerosis (MS) is the main chronic inflammatory central nervous system (CNS) disease. Approximately 10% of MS cases begin at pediatric ages. In these patients, an early diagnosis of MS remains challenging, especially after the first demyelinating event. The International Pediatric Multiple Sclerosis Study Group (IPMSSG) suggested that the fulfillment of the dissemination in space (DIS) and dissemination in time (DIT) of the 2010 McDonald criteria for MS could be applied in children older than 12 years. However, in 2017 the diagnostic criteria of MS in adults was reviewed. Until now, the new criteria were not validated for the pediatric age group.

Objective: to compare the fulfillment of the 2012 IPMSSG criteria and the 2017 McDonald criteria in patients with the first acute demyelinating syndrome (ADS) from the ongoing Brazilian multicentric pediatric cohort.

Methods: Data from patients with ages ranging from zero to 18 years with clinical and radiological evidence of the first ADS were included in a web-based online plataform (Qualtrics®). The fulfillment of MRI criteria for DIS and DIT were evaluated accordingly to the IPMSSG criteria of 2012 and McDonald criteria of 2017.

Results: Twenty-five children with first acute demyelinating syndrome (ADS) (mean age 9.1 years, range 3-202 months, male to female ratio 1.7:1, white to non-white ratio 2.8:1) were evaluated. Most common first ADS were myelitis (34.6%), optic neuritis (30.8%) and ADEM (23.1%). Children younger than 10 years were more likely to present with ADEM (p=0.04). Eleven patients fulfilled the criteria for Clinical Isolated Syndrome (CIS; first ADS suggestive of MS). Of these, 18.1% had radiological evidence of DIS (IPMSSG 2012 radiologic criteria) but no patient had evidence of DIT nor fulfilled the MS IPMSSG criteria. Whereas, 27.2% of the CIS patients (all older than 12 years-old) fulfilled the 2017 McDonald diagnostic criteria for MS.

Conclusion: The 2017 McDonald diagnostic criteria for MS might allow the diagnosis of MS in pediatric patients older than 12 years even after the first clinical event. The long-term follow-up of these patients might help to identify possible caveats and mimics of MS in the pediatric group.

Disclosure

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Disclosure

Lydia Marcus: nothing to disclose
Jayne Ness: nothing to disclose

EP1331
Two pediatric cases of Anti-NMDA receptor encephalitis with MS-typical lesions

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Objective: To examine two pediatric cases of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis with brain lesions consistent with multiple sclerosis (MS)
Background: NMDAR encephalitis is a neurologic disorder involving psychiatric symptoms, movement disorders, sleep disorders, seizures and autonomic dysfunction in conjunction with NMDAR antibodies. There are reports in the literature of cases of NMDAR encephalitis who later develop relapsing remitting multiple sclerosis (RRMS), bringing into question a potential underlying link between the two disease processes.
Methods: Details regarding the patients' clinical courses were obtained by chart review.
Results: The first patient had subacute onset of psychiatric symptoms and memory difficulties, then progressed to seizure activity. She was found to have positive NMDAR antibodies in both serum and cerebrospinal fluid (CSF) and was treated for NMDAR encephalitis with minimal residual deficits. Initial magnetic resonance imaging (MRI) of brain showed both enhancing and nonenhancing periventricular lesions typical of those seen in MS. These lesions either improved or resolved on subsequent imaging. The second patient initially presented with optic neuritis with optic nerve enhancement on MRI. He then clinically progressed to develop catatonia, hallucinations, and seizure activity with positive serum and CSF NMDAR antibodies. After he was treated for NMDAR encephalitis and gradually recovered, he developed asymptomatic periventricular enhancing and T2 hyperintense brain lesions typically seen in patients with MS.
Conclusions: These two cases of NMDAR encephalitis with MS-like brain lesions illustrate a possibly meaningful association between these disorders, and argue for further investigation into potential common pathophysiological pathways.

EP1332
Clinical observation and treatment approaches of child Devic opticomyelitits in Kazakh

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Classical Devic Neuromyelis optica (NMO) is a rare severe demyelinating disease presenting with the clinical triada of optic neuritis, longitudinally extensive myelitis and positive serum anti-AQP4 antibodies and has a female predisposition (F:M 6.5:1) in Asians, Indians and Africans. However the disease is poorly studied in Kazakhstan.
The aim of the study was to describe 3 cases of **Devic NMO hospitalized to our clinic within the last 5 years.**
Materials and methods: 3 cases of child NMO, 2 girls and 1 boy of Kazakh (Asian) origin. The diagnosis was proven by brain and spinal cord MRI, **o**ptical coherent tomography and presence of serum anti-AQP4 antibodies in dynamics.
Results: One boy developed NMO at 9 years, one girl at 6 years and another girl at 14 years old. The hallmark of the disease in all patients was severe bilateral optic neuritis. All patients showed spastic paresis as a disease debut: a 14-years old girl had tetraparesis, the 6 years old girl - right side hemiparesis and the 8-years old boy - spastic paraparesis and ataxia. Further they had exacerbations every 4-6 months. The MRI of brain showed T-2 active periventricular lesions in all patients, and classical long. Longitudinally extensive myelitis was seen in 2 patients - a boy (at cervical level) and a 14-years old girl (at cervical and thoracic level). Optical coherent tomography showed significant retinal nerve fiber layer (RNFL) thickness decrease (up to 50% of normal) in all children. Anti-AQP4 antibodies performed in all children dynamically varied 1:80-1:160 (minimal positive titer < 1:10). The basic treatment with high dose methylprednisone (10-30 mg/kg 5-7 days) had mild effect on spasticity, but vision progressively worsened. Vision improvement was achieved by of Intravenous immunoglobulin IgG (IVIG) - 10% Octagam dosed 2 gram/kg for 3-5 days, each course was **r**epeated every 2 months, totally 3-7 courses were done. A 14 years old girl developed severe encephalitic symptoms with necrotic lesion in left hemisphere, deep perifocal and optic disk edema which was stabilized on high dose IVIG (4 g/kg for 5 days) and 0,4 mg/kg of dexamethasone i.v, for 5 days followed by methylprednisone 20 mg/kg i.v. for 5 days, yet, plasma exchange had no effect.
Conclusion: Child Devic NMO seen in Kazakh Asian patients had severe clinical course with rapid development of partly irreversible vision loss and spastic syndrome with good clinical recovery when high dose IVG was repeatedly applied.

Disclosure

Name: nothing to disclose

EP1333

Cognitive and psychiatric problems as the first manifestation of multiple sclerosis in children

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Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS) in which a chronic demyelinating and inflammatory processes lead to damage of myelin sheaths of neurons and loss of axons. The appearance of various neurological symptoms are related to the location of focal CNS damage. First symptoms of the disease may develop suddenly or slowly. They could manifest as single or multifocal sensory symptoms (about 23%), motor symptoms (about 46%), disturbances of vision due to the optic neuritis (about 21%), hearing problems, brain stem symptoms (about 10%) or autonomic symptoms i.e. urinary problems, constipation (approx. 1%). Quite frequent are also transient paroxysmal symptoms i.e. Lhermitt's symptom, Uhthoff˙s symptom.

Neurological manifestation may be accompanied by cognitive, psychiatric problems or chronic fatigue which were reported in few reports (Zarei et al. 2003, Habek et al. 2005; Staff et al. 2009, Coebergh et al.2010, Assaouad et al. 2014; Berna et al 2016; Zambon et al. 2017; Amato et al. 2017).

The authors present pediatric patients with isolated cognitive impairment or psychiatric symptoms as the first manifestation of the MS in children preceding typical neurological symptoms. Its subsequent recognition is very important for diagnosis of MS and quick implementation of proper treatment .

Disclosure

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Michał Ciastoń: nothing to disclose
Łukasz Dropczyński: nothing to disclose

Natural course

EP1334

Analysis of longitudinal free-living features from wearable biosensors in multiple sclerosis patients

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Introduction: Wearable biosensors allow for continuous physiological monitoring of patients, which may improve treatment and management of chronic illnesses such as MS.
Objective: To estimate longitudinal change in the daily averages of 12 free-living biosensor measurements collected in 23 multiple sclerosis (MS) patients and to compare the measurements in different severity groups.
Methods: 25 MS patients were enrolled in a biosensor study at Brigham and Women's Hospital. Patients wore digital biosensors during three in-clinic visits and eight weeks continuously at home between the second and third visit. 23 patients (96% females, baseline mean age 46.4±7.7) completed the at home period. Patients wore three biosensors (wrist, ankle and sternum) and 12 average daily free-living measurements were derived. Patients were stratified into three groups based on baseline Expanded Disability Status Scale (EDSS) score (0.0-2.5 = 10 subjects (~44%), 3.0-4.5 = 6 subjects (~26%), and ≥5.0 = 7 subjects (~30%)). Linear mixed effects regression models assessed longitudinal change in daily free-living measurements with fixed effects for time, baseline severity groups, and time by group interaction as well as a random intercept and slope.
Results: Four free-living features including stance time (p=0.0036), swing time (p=0.0083), max turn velocity ankle (p=0.0278), and turn velocity ankle SD (p=0.0078) showed significant difference in the three severity groups. There was no significant change in the measures over time or difference in the longitudinal change between groups. During this same period, there were no clinically significant changes in disease status observed within any individuals as measured by EDSS.
Conclusions: This study demonstrated that a novel digital biosensor signature correlated with baseline physician severity ratings using EDSS. The biosensor data was acquired without patient effort in the free-living environment, suggesting that home biosensor tracking may substitute for, or supplement in-office physician assessment for monitoring MS.

Disclosure

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employee and equity holders at Verily Life Sciences. Alaa Kharbouch is an employee and equity holders at Verily Life Sciences. Amy A. Lee is an employee and equity holders at Verily Life Sciences. Manway Liu is an employee and equity holders at Verily Life Sciences. Swaminathan Mahadevan is an employee and equity holders at Verily Life Sciences. Linda C. Norton is an employee and equity holders at Verily Life Sciences. Tushar A. Parlikar is an employee and equity holders at Verily Life Sciences. Anupam Pathak is an employee and equity holders at Verily Life Sciences. Ali Shoeb is an employee and equity holders at Verily Life Sciences. Erin Soderberg is an employee and equity holders at Verily Life Sciences. Philip Stephens is an employee and equity holders at Verily Life Sciences. Aaron H. Stoertz is an employee and equity holders at Verily Life Sciences. Florence Thng is an employee and equity holders at Verily Life Sciences. Kashyap Tumkur is an employee and equity holders at Verily Life Sciences. Hongsheng Wang is an employee and equity holders at Verily Life Sciences. Jane Rhodes was an employee at Biogen during the study period. Dr. Rudick is an employee of Biogen and holds stock and/or stock options in the company. Richard M. Ransohoff was an employee at Biogen during the study period. Glenn A. Phillips was an employee at Biogen during the study period.

Effie Bruzik is an employee at Biogen. William J. Marks is an employee and equity holders at Verily Life Sciences. Dr. Weiner has research support from NIH, NMSS, Verily Life Sciences, EMD Serono, Biogen, Teva Pharmaceuticals, Sanofi, and Novartis. Research support and consulting fees from Genentech, Inc., Tilos Therapeutics, Tiziana Life Sciences, and IM Therapeutics. Personal and consulting fees from vTv Therapeutics and MedDay Pharmaceuticals. Thomas M. Snyder is an employee and equity holders at Verily Life Sciences. Dr. Chitnis has served on the advisory boards for clinical trials sponsored by Novartis and Sanofi-Genzyme, and has received consulting/advisory fees from Bayer, Biogen, Celgene, Genentech-Roche, Novartis and Sanofi-Genzyme. She has received research grant support from Biogen, Octave, Serono and Verily.

EP1335

Unmet needs of patients transitioning to secondary progressive multiple sclerosis: qualitative findings for a resource development

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Background: About 50% of relapsing multiple sclerosis (MS) patients convert to secondary progressive (SPMS) 15 years after clinical onset. Despite the complexity and potential impact of this transition, no targeted interventions to promote patients´ wellbeing are available. Managing the Transition to SPMS (ManTra) aims to develop and assess the efficacy of a user-led resource for newly diagnosed SPMS patients. Here, we describe a key project phase: assessment of the experiences and needs of SPMS transition.

Methods: Training on qualitative methods was performed from February 2017 to March 2018 in Milan, and consisted of 5 one-day meetings. Participants were 10 investigators from 6 centres. Personal semi-structured interview (PSI) and focus group meeting (FGM) grids were developed and refined during the training. The methods of framework analysis was applied to the PSI and FGM transcripts. The transcripts were analysed in six successive steps, each of which embodies an increasing level of generalisation. To enhance the validity of this process, two researchers analysed the transcripts independently (FGMs, steps 1-4; PSIs, steps 1-5) and jointly (step 6).

Results: With regard to the Italian sample, 15 PSIs were performed (N=7, Milan; N=4, Chieti; N=4, Bari). The sample was composed of 8 women, mean age 48.7 (SD 7.5), median EDSS 6.0 (range 4.0-7.0). The 3 FGMs were conducted (May 24, 25, 2017: neurologists, other HPs; September 25, 2017: significant others). Framework analysis revealed 104 sub-categories, grouped into 17 categories and four themes. All the stakeholders agreed on the following unmet needs: Management of SPMS at the MS Centre; Psychological support; MS HP training; Communication and information; Job and welfare.

Conclusion: We observed a general lack of communication of the transition by neurologists or other HPs and low awareness by SPMS patients who massively used defensive mechanisms. All stakeholders unanimously asked for a better management of the MS centre, provision of psychological support, specific HP training, access to more information about SPMS, dedicated worker protection policies and job out-placement in this disease phase.

Disclosure

None

EP1336

Predictors for conversion of radiologically isolated syndrome to multiple sclerosis

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Introduction: Asymptomatic white matter lesions are frequently encountered due tothe widespread use of magnetic resonance imaging (MRI). Patients with lesions that suggest multiple sclerosis (MS) without a clinical event are definedas radiologically isolated syndrome (RIS). The identification of risk factors for conversion to multiple sclerosis (MS) is important for early diagnosis.
Objective: Our study aims to determine predictive factors ofconversion from RIS to MS.
Methods: We collected data ofpatients with RIS including demographic features, radiological data such as number and location of lesions, contrast enhancement,andoligoclonal band status.We calculated the timeto conversion to MS and determined the effect of the predictors usinglog-rank test.
Results: Eighty-one patients (58 female, 23 male) who met the RIS criteria were included in our study.The mean follow-up duration was 2.2 (±2.3) years.Of 81 patients, 15 (18.5%) had a clinical attack and diagnosed with MS. Presence of cervical spinal lesions (log-rank test; p=0.027), brain stem lesions (log-rank test; p=0.048), and oligoclonal bandstatus (log-rank test; p=0.005) predicted a higher conversion rate. On the other hand, gender, T2 lesion count, family history, smoking, and pregnancy status did not increase the risk of conversion to MS(log-rank test; p>0.05).
Conclusions: Our study confirms previous studies on RIS. The presenceof the oligoclonal bands, brainstem and cervical spinal lesions increasethe risk of MS considerably. However, larger prospective studies are neededto define the effect of other possible predictors with marginalimpact on conversion to MS.

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EP1337

Upper extremity function and its relation with ambulatory impairment in multiple sclerosis

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Background: Ambulatory impairment is common in multiple sclerosis (MS) and may lead to early disability. When ambulation deteriorates, preservation of upper extremity function (UEF) becomes increasingly relevant to maintain the ability to perform activities of daily living (ADL). Currently, the exact relation between UEF deterioration and ambulatory impairment is unknown.
Objective: To examine the prevalence of UEF deficits in MS for different levels of ambulatory impairment, and to assess the relationship between UEF and ambulation impairment.
Methods: Patients were derived from a cohort of MS patients that participated in the Assess MS study, a project to improve clinical disability assessment through automated quantification of motor function. The Expanded Disability Status Scale (EDSS) and timed 25-foot walk (T25WT) were used to stratify patients into clinically different ambulation subgroups: fully ambulatory (EDSS 0-3.5; T25WT < 6 s), mild (EDSS 4.0-5.5; T25WT 6-7.99 s) and severe ambulatory impairment (EDSS 6.0-7.0; T25WT ≥8 s). UEF was assessed with the nine-hole peg test (9HPT), the Arm Function in MS Questionnaire (AMSQ) and three clinical tests from Assess MS, including an ADL task 'drinking from a cup' (CUP), and compared between subgroups. Associations between UEF measures and ambulation were examined with logistic regression models.
Results: A total of 255 patients were included. Preliminary results revealed differences between the EDSS ambulation subgroups (all p-values < 0.001) with worse UEF measures in the mildly (n=68) and severely impaired groups (n=58). Larger group differences were found between the mild and severely affected patients (9HPT 6.3 seconds, AMSQ 30 points), than between the fully ambulatory (n=121) and mildly impaired patients (9HPT 4.4 seconds; AMSQ 17 points). Regression analysis revealed that worse ambulation was associated with worse UEF scores (p< 0.001 for all associations), with the largest magnitude effect for CUP [lowest vs highest: OR 0.008(95% CI 0.001-0.061)]. Further analyses of T25WT subgroups are pending.
Conclusion: MS patients with severe ambulatory impairment showed UEF deficits in all domains with larger differences between the clinically worse ambulatory impaired groups. These findings suggest that to some extent UEF and ambulation develop independently, which implicates possible different treatment windows. Furthermore, ambulatory impairment was most prominently associated with UEF related ADL-tasks.

Disclosure

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J. Dorn is an employee of Novartis Pharma AG.

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L. Balk has nothing to disclose
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EP1338
Initial MRI lesion load: a predictor of long-term disability independent of suggestive event

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Background: The identification of predictors of long-term prognosis is a major concern in early phase of the disease and is a purpose of treatment optimisation at individual level.
Objectives: To identify long-term disability predictors in initial brain MRI and relation with history of suggestive event
Methods: A cohort of clinically isolated syndromes with a first documented event that occurred more than 14 years ago was analysed. Suggestive event was systematically screened. The Initial brain MRI was analysed by 2 readers to determine the number of T2 and gadolinium enhanced lesions. The outcome measure was time to reach EDSS 3 and 6. The explicative variables were, suggestive event (yes / no) , T2 lesions ($n \geq 14$ / < 14), gadolinium lesions ($n \geq 2$ / < 2). Cut-off for number of T2 and gadolinium lesions were determined by ROC curve. A univariate survival analyse was performed to assess each variable regarding the time to reach EDSS 3 and 6. A cox model was used for multivariate analysis.
Results: 227 patients with available brain MRI data and a median follow up of 13.5 years (6.53-15.5) have been analysed. Median age at onset was 31.1 years (11.8 -66.4) with 70% of women. A suggestive event supported by MRI lesion was presented in 26.8% of cases. A second relapse occurred in 60% of patients and 70% fulfilled McDonald 2010 MS criteria at the end of follow-up. The mean number of brain T2 and gadolinium lesions at baseline were 9.2 ±8.9 and 1.41 ±2.7 respectively. The proportion of patients who reached an EDSS 3 and 6 were not significantly different depending on gadolinium lesions and history of suggestive event. Conversely a number of T2 lesions ≥ 14 increases the risk to reach EDSS 3 ($p = 0.009$), data confirmed by multivariable analysis ($p = 0.014$).
Conclusion: A high T2 lesion load independently increases the risk of long-term disability

Disclosure
Dr A Gueguen has received speaking honoraria from Sanofi Genzyme, Roche, serves on scientific boards for Novartis, Merck, Roche, Mylan and received travel expenses for participation in scientific meeting from Roche, Teva, Sanofi-Genzyme

EP1339
Exploring the outcome of multiple sclerosis (MS) among Saudi adult patients: a single-centered cross-sectional study at King Abdulaziz Medical City (KAMC)

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Background: The outcome and prognosis of MS is unpredictable in nature. Famous scales are used to assess the outcome and impact of MS. The utility of several scales for predicting the outcome is limited. The aim of this study is to assess the outcome of MS in Saudi adult patients using validated scales.
Method: A single-centered, cross-sectional study at KAMC. All Saudi adult patients diagnosed with MS between 2000-2016 (269 patients) were included. Patients were contacted via phone-calls to assess their outcome using a newly developed and validated multi-component questionnaire. It included demographic data, disease course, and validated Arabic version of [Barthel Index (BI), Multiple Sclerosis Impact Scale (MSIS-29), Modified Rankin Scale (mRS) and EDSS].
Results: Out of 269 patients, 210 (78.2%) responded. The average patients' age was 37.44±10.3 years. The majority (69.5%) were females. 51(24.3%) patients reported worsening condition. Annually, the average relapse rate was 2.29±1.923. In regard to patients' outcome,120 (57.1%) showed no significant disability in mRS, 146 (69.5%) were ambulatory without aid in EDSS, and 96 (88.9%) patients were independent in BI score. The average of "Multiple Sclerosis Impact Scale" MSIS-29-PHYS score was 38.2±25.81 and MSIS-29-PSYCH score 33.6±27.6. MRS showed significant association with delayed diagnosis (P=0.025) and current use of DMT (P=0.002). EDSS also showed significant association with current use of DMT (P=0.042). BI showed significant association with medication compliance (P=0.044) and absence of attacks (P=0.054).
Conclusion: Majority of patients had favorable outcome which was linked significantly with the use of DMT, compliance, early diagnosis and absence of attacks. Further studies are recommended in larger sample size to examine the association of outcome with other factors.

Disclosure
authors have nothing to disclose

Epidemiology

EP1340

Mental health status among children of mothers diagnosed with multiple sclerosis: a Danish cohort and register-based study

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Introduction: Multiple sclerosis (MS) is associated with an increased risk of developing physical, cognitive and mental health problems. Current studies have demonstrated an adverse association between parental MS mental health problems and their offspring's mental health development.

Objective/aim: The purpose of this study was to investigate whether the maternal multiple sclerosis is associated with mental health status of their child.

Methods: Data from the Danish National Birth Cohort (DNBC) were merged with information from the Danish Multiple Sclerosis Registry. Two proxies - total difficulties score and prediction of any psychiatric diagnosis, based on the Strength and Difficulties Questionnaire, were used to measure mental health status of the children.

Results: For the total difficulties score the control and exposed group consisted of respectively 42,016 children of mothers without MS and 40 children of mothers with MS. For the prediction of any psychiatric diagnosis, 16,829 children of mothers without MS were in the control group and 17 children in the exposed group. We found no statistical significant association between maternal MS and mental health status on neither of the proxies.

Discussion: Unlike previous studies, it seems that in our cohort maternal MS is not associated with mental health status of the children up to age 11. However, we did not have information about maternal mental health status, which in other studies shows a mediating effect on mental health status of their children, and it may be that participation of more resourceful women in the DNBC favours our results.

Conclusion: Maternal multiple sclerosis showed no association with mental health status of their children at age eleven.

Disclosure

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Bjarne Laursen
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Melinda Magyari
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EP1341

Burden of multiple sclerosis in Eastern Mediterranean Region: findings from the 2016 Global Burden of Disease study

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Introduction: Multiple sclerosis (MS) is among the leading causes of disability in Young Adults worldwide. Current estimates of MS burden in Eastern Mediterranean Region (EMR) are necessary for planning effective interventions.

Objectives: To estimate Prevalence, incidence, mortality, years lived with disability (YLDs), years of life lost (YLLs) and disability-adjusted life-years (DALYs) in EMR by country age, and sex from 1990 to 2016.

Aims: To inform healthcare professionals and decision making authorities of increasing MS burden.

Methods: We estimated regional and country-specific prevalence, incidence, mortality, DALYs, YLLs, and YLDs for MS. YLLs were computed by multiplying the number of deaths from MS in each age group by the reference life expectancy at the average of age of death among those who died in the age group. Prevalence of MS was multiplied by the disability weight for the corresponding health state to calculate YLDs. DALYs were computed as the sum of YLDs and YLLs.

Results: There was a rapid increase in the burden of MS in the region, it increased from 23,564 in 1990 to 71,775 in 2016 for males and 46,238 to 130,143 for females. Total DALYs in EMR countries was 12,810 in 1990 for males and increased to 36,391 in 2016 and from 18,962 to 53,851 for females. Lowest DALYs in both sexes were observed in Somalia (248) while the highest were in Iran (26,394). YLDs in males increased from 6,511 in 1990 to 19,515 in 2016, and in females from 12,247 to 33,937. The highest age-standardized prevalence, incidence, YLDs and DALYs were in Iran (72.11, 2.49, 18.03, and 32.5, respectively). The highest burden was among females and adults aged 30 to 45.

Conclusions: MS poses a significant public health problem in EMR region and prevalence rates have increased since 1990. Our findings provide valuable information to guide the development and implementation of measures to address the rising burden of MS in the region.

Disclosure

All authors declare no conflict of interest regarding this study.
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EP1342

Treatment patterns of multiple sclerosis patients treated with disease-modifying therapies in Puerto Rico

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Introduction: Disease-modifying therapy (DMT) utilisation patterns in MS patients in the United States are readily available. However, currently limited data exist on treatment patterns among MS patients in Puerto Rico, a region with reported MS incidence rates higher than those observed in other countries in Latin America and the Caribbean.
Aims: To describe treatment patterns in MS patients in Puerto Rico using a large, longitudinal database.
Methods: Retrospective, observational study using data collected between January 1, 2010 and December 31, 2016 from the Special Care Pharmacy Services (SCPS) database. SCPS serves approximately 65% of DMT prescriptions for MS in Puerto Rico; the database includes information on patient demographics, DMT use classified by administration route (oral, injectable, infusible), and treatment duration. Baseline was defined as the most recent DMT prescription.
Results: 2070 MS patients received ≥1 DMT during the study period (67,412 prescriptions). From 2010 to 2016, uptake of oral DMTs (which were introduced to market in Puerto Rico in 2012) increased (0% to 28.4%), whereas that of injectable and infusible DMTs decreased (55.7% to 44.9%, and 44.3% to 26.7%, respectively). Over the study period, 1483 (71.6%) patients remained on 1 DMT type (injectables: 39.4%; infusions: 20.4%; oral agents: 11.8%). 587 (28.4%) patients switched DMTs at least once (449 [21.7%] patients used 2 DMTs, and 138 [6.7%] used ≥3 DMTs). Of those patients switching DMTs, the most recent prescriptions were for oral agents (55.5%), followed by infusions (27.3%) and injectables (17.2%). The most common treatment switches were from injectable to oral DMTs (36.3%), injectables to infusions (21.5%), and infusions to oral DMTs (19.3%). On average, patients were on injectables for 525 and 433 days before switching to oral and infusible DMTs, respectively, and on infusions for 737 days before switching to oral DMTs.
Conclusion: This study on treatment patterns in MS patients in Puerto Rico provides new insights in trends. Our findings indicate that injectables remain the most commonly used medications, despite the launch of oral and high-efficacy therapies. However, there is a trend toward increased oral DMT use. During the study period, patients were most frequently switched from injectable to oral DMTs. This study may serve as a useful resource for further MS research in Hispanic populations.

Disclosure

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EP1343

Temporal trends on the incidence of multiple sclerosis in Santiago de Compostela (Spain)

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Introduction: The incidence of multiple sclerosis (MS) is increasing around the world. However, it is controverted if it is a real change or just a consequence of the improvement in diagnostic procedures and the update of the criteria.
Objectives: To determinate the actual incidence of MS and analyze its temporal trend in our reference population.
Methods: A capture-recapture study was conducted in Santiago de Compostela (north-west of Spain) between 2010 and 2015, in order to determinate the current incidence of MS. Mc Donald 2010 criteria were used to identify cases. Moreover, clinical charts were reviewed to determinate if Poser criteria were also fulfilled. The results were compared with those obtained for another study done with the same methodology in the same area between 1998-2002.
Results: The mean incidence was 8.02 cases/100.000 habitants/year. It was almost double in women (10.08 vs 5.63 cases/100.000 habitants/year). Mean age at the first symptom was 34 years (SD:10.4), 67.39% were female and 89.13% were relapsing remitting MS. Previous incidence was lower (5.3 cases/100.000 habitants/year), nevertheless the difference was not significant (p=0.134).
Conclusions: An increment in the incidence of MS was detected in our area. It is the highest rate of Spain as it was in the previous study.

Disclosure

Costa Arpín E.: has served as speaker or consultant for Biogen Idec , Merck Serono, Bayer Health Care, Genzyme, TEVA and UCB Pharma. Puente Hernández M and Lagorio A: nothing to disclosure. Arias Gómez M has served aadvisor, consultant and speaker for Bayer HealthCare Pharmaceuticals, Biogen Idec Inc., Genzyme Corporation, Novartis Pharmaceuticals Corporation, Sanofi Aventis and Teva Pharmaceuticals. Prieto González JM. has served as advisor, consultant and speaker for Bayer HealthCare Pharmaceuticals, Biogen Idec Inc., Genzyme Corporation, Novartis Pharmaceuticals Corporation, Sanofi Aventis and Teva Pharmaceuticals. He also has received grants for clinical research from Biogen Idec Inc and Novartis Pharmaceuticals Corporation.

EP1344

Validity and reliability of multiple sclerosis minimum data set form for national registry system in Iran

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Background: As Multiple Sclerosis (MS) prevalence is increasing in Iran and designing a national registry system is needed.

Objective: We aimed to design a valid and reliable MS registry form, to utilize in MS minimum dataset.

Method: The population-based minimum dataset form consists of six subgroups including patient identification, family history of MS, disease course and diagnosis, disability status and Medication with related questions.

The pilot study was done to evaluate validity and reliability. The content validity was assessed based on 27 experts' opinions. Item-content validity index (i-CVI) and scale-content validity index (s-CVI) were used to assess question and the whole form validities, respectively. Test-retest reliability was also assessed by using intra-class correlation coefficient (ICC).

Statistical analysis was done by using SPSS.

Results: Totally 74 patients were recruited for the pilot study.

For validity 27 experts reviewed the form. The critical value for CVI was considered 0.78 based on literature review. All items had i-CVI>0.78 in relevance, clarity and simplicity (In 18 items out of 20,20 out of 20, and 19 out of 20, respectively) except for "Each medication start date and end date" in relevance (i-CVI=0.75 and 0.73, respectively), and "MS type" in simplicity (I-CVI=0.76). S-CVI scores for relevance, clarity and simplicity were all > 0.9.

Reliability: 27 patients (Out of 74 interviewed patients) were re-interviewed to assess test-retest reliability. The critical value for ICC was considered 0.7 based on literature review. ICCs were all >0.7 (In 14 items out of 16) except for progression to secondary-progressive MS and reason for medication discontinuance (ICC=0.68 and 0.64, respectively).

Conclusion: The use of standardized validated questionnaires will assist the researchers and policy makers to perform national registry system based on standard form. The minimum dataset form of MS registry had suitable validity and reliability to be used.

Disclosure

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EP1345

Clinical characteristics and personality traits influence how people with MS look for medical information

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Introduction: People with multiple sclerosis (PwMS) are increasingly demanding access to reliable information regarding disease symptoms and management. High-quality information is a key factor in patient empowerment and shared decision-making.

Objectives: To assess the information requirements of PwMS and their related factors.

Methods: A multicenter, non-interventional, cross-sectional study in adult subjects with MS (McDonald 2010 criteria) was conducted. The self-rated InfoSeek-MS questionnaire and the NEO Five-Factor Inventory-3 (NEO-FFI-3) were used to collect data on search behavior and information needs, and personality traits, respectively. Exploratory factor analysis was used to explore relations, ANOVA and logistic regression to test for differences. CRT segmentation trees were used to explore different personality profiles.

Results: A total of 302 PwMS (mean age: 42.3 ± 10 years, 64% female, mean time of diagnosis: 9.6 ± 7.0 years, 90% with relapsing-remitting MS) were studied across 19 hospitals in Spain. Mean Expanded Disability Status Scale (EDSS) score: 2.6 ± 1.9. Internet (either via mobile or computer) was the most frequently reported source of information. PwMS more frequently searched information about: lifestyle-related information (67.2%), research and emerging treatments (63.6%), management of symptoms (49.7%), sharing experiences with other PwMS (46.4%) and prognosis (46.4%). Neurologists and nurses were the most trusted source of information. Patients with a greater number of relapses and higher EDSS scores showed higher frequency of information searches (rho=0.233 and rho=0.222, respectively; $p< 0.001$). Neuroticism and openness to experience were the personality traits related to a more frequent information quest.

Conclusions: Information needs may differ according to disease status and personality characteristics. Personalized strategies combining online and offline sources are necessary to optimize the information offered to PwMS.

Disclosure

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EP1346

Mastery is significantly associated with greater physical and mental health-related quality of life in two independently recruited international samples of people with multiple sclerosis

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Background: Mastery is the sense of being in control of one's life. Improvement in mastery may help to improve quality of life, the pathway potentially being through stress modulation or greater utilisation of healthy lifestyle behaviours known to improve

outcomes in MS. Despite this, there is a relative paucity of research in this area, both in terms of the determinants of mastery in people with MS and its association with quality of life.
Objective: To explore the association between mastery and health-related quality of life (HRQOL) in people with multiple sclerosis.
Method: Two cross-sectional samples of adults with MS (n=1,401 & n=573), recruited through convenience sampling, completed an online survey which measured mastery using the Pearlin Mastery Scale (PMS; range 14-28), physical and mental HRQOL (both range 0-100) via the physical and mental composite scores of the MSQOL-54, along with other covariates, including demographics, clinical characteristics and lifestyle factors. Associations between mastery and HRQOL were assessed using linear regression, adjusted for age, sex, disability, fatigue and depression.
Results: Greater mastery score was associated with significantly higher physical and mental HRQOL in both samples, such that a one-point increase in the PMS was associated with a 1.75 ($p< 0.001$) and 1.80 ($p< 0.001$) rise in physical HRQOL in the two samples, and a 1.54 ($p< 0.001$) and 1.66 ($p< 0.001$) increase in mental HRQOL in the two samples, all associations highly robust to adjustment. A strong dose-dependent relationship was demonstrated between a quartile categorical mastery variable and both physical and mental HRQOL ($p_{trend}< 0.001$ for all models). Mastery was significantly related with all subscores of both physical and mental HRQOL, with similar magnitudes of associations demonstrated between subscores.
Conclusions: These results provide initial evidence that greater mastery is associated with a better quality of life, both physical and mental, with replication in a separately recruited cohort. Efforts to improve patients' sense of self control and agency may have benefits for their quality of life, even despite clinical features of their MS.

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EP1347

Use of mobile health technology in establishment of multiple sclerosis (MS) registry in Iran: a study of stakeholders' attitude

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Introduction: A system for registration of multiple sclerosis (MS) data in Iran is in its beginning. To establish a functional and effective registry and in order to plan suitable strategies to motivate participation of stakeholders, it is essential to recognize attitudes of all relevant stakeholders.
Objective: To explore attitudes and opinions of patients and physicians toward using mobile phone applications for MS data registration in Iran.
Methods: Study was performed in two phases. In the qualitative phase, which included focus group discussions and interviews, we collected and analysed stakeholders' attitudes and opinions. Results of the first phase was used to design the questionnaire required for the second phase. In the second phase, a questionnaire was sent to 31 physicians and 102 MS patients to quantify the challenges in use of mobile phone technologies.
Results: 84% of physicians and 71% of patients were females. Age ranged from 25 to 54 years in physicians and from 18 to 65 years in patients. The level of education for the patients ranged from illiterate (1%) to Master's degree or higher (16%) with majority having high school diploma (31%) or Bachelor degree (28%). We found that most of patients and physicians own or have access to smartphone, use them frequently, and majority stated enough confidence and comfortability in use of them. Physicians and patients' views on most of items (such as "ambiguity in legal and regulatory affairs" and "not enough stability in decision making" as barriers or "saving time or decreasing cost" as benefits) were mainly in the same direction. However, we found significant differences in few items such as "decrease inequalities in access to MS healthcare", and "increase patients' collaboration" as benefits. Overall, more patients (87%) than physicians (58%) were positive about possibility of using mobile applications for MS registration in Iran.
Conclusions: We reported the first qualitative and quantitative study of stakeholders' perspectives on the mobile phone technology use in MS data registration in Iran. Our results were compatible, in many aspects such as frequency of smartphone ownership and frequency of MS specific applications usage, with other studies in high-income countries. Discrepancies found among respondents suggest MS patients, physicians and other stakeholders should be consulted thoroughly during the design phase of an application to ensure those factors have appropriately been considered.

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EP1348
Epidemiology of multiple sclerosis in Ardabil, northwest of Iran

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Introduction: The epidemiology of Multiple Sclerosis (MS) in Ardabil, north-western region of Iran is unknown.
Aims: We aimed to design a study to evaluate the epidemiology of MS in Ardabil.
Methods: A retrospective population-based cross-sectional study was conducted from 2007 to 2017 in Ardabil based on the data of Iran's ministry of health. Collected information includes gender, age, age at disease onset, educational level and type of MS. We used Chi-squared test to analyze the relationship among variables and Logistic regression to estimate the odds ratio (OR) for individual variables, by SPSS software.
Results: The total number of patients was 800 with 564(70.5%) females, 236 (29.5%) males and the sex ratio of 2.38:1.The prevalence and incidence rate of MS was 62.16 and 7.61 per 100,000 in 2017.The prevalence was 89.43 and 35.95 per 100,000 in females and males respectively. The mean age at disease onset was 32.26±8.94 and there was no significant difference in the mean onset age between females and males. Totally 47(5.9%) patients experienced their first clinical attack before the age of 18. The relapsing-remitting(RR) form was the most prevalent type of MS (48.5%).The significant difference between females and males in MS types was observed (p value≤0.05). The secondary progressive(SP) form was higher in males (OR=1.76, CI=1.00-3.12).There was no significant association between MS type and education level.
Conclusions:The prevalence of MS is high in Ardabil. The most common type is RR form while male gender increases the risk of SP form .Our results also suggest a higher mean age of disease onset in Ardabil comparing other parts of Iran. Considering the different climate and environmental features of northwest of Iran, this can be a key to identify the related risk factors on the age of disease onset.

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EP1349
Clinico-demographic characterization of a large cohort of neurological patients referred to the neuro-immunology outpatient clinic of Columbia University Medical Center

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Background: Multiple Sclerosis (MS) is the most common autoimmune disorder of the central nervous system (CNS) and a leading cause of neurologic disability in young adults. In view of the negative impact of treatment delay on disease progression and the increasing complexity of therapeutic options, it is strongly advocated that patients with suspected MS are referred to highly specialized centers.
Aims: to describe the clinico-demographic characteristic of patients referred to the MS center at Columbia University Medical Center, and explore current therapeutic strategies in a highly specialized setting.
Methods: Diagnostic codes and clinico-demographic information for patients seen at our MS center from 2012 to 2018 were collected through automatic data capture from electronic medical records and descriptive statistics were obtained.
Results: 2110 patients were referred to an MS specialist for a suspected CNS inflammatory disorder. Of these 53% eventually received a MS diagnosis and 13.4% were diagnosed with other CNS immunological disorders: 3.6% transverse myelitis, 2.6% optic neuritis, 2.2% neuromyelitis optica, 1.2% acute disseminated encephalomyelitis or viral/post-viral disorders and 3.8% unspecified demyelinating diseases. 1.3% of subjects consulting an MS neurologist had an abnormal brain scan without any clinical symptom. Among MS patients currently followed at our MS center, 2.4% had only one clinical episode consistent with a clinically isolated syndrome (CIS), 80.3% have a relapsing remitting (RR) course, while the remaining have either primary (6.3%) or secondary (11%) progressive disease. As expected, the majority of patients are female (F:M ratio 2.97) with mean age at diagnosis of 36.7 years and mean disease duration of 8.4 years; 11.3% of patients also report other autoimmune disorders. Among treated patients, 31.3% were prescribed a first line injectable therapy (12.1% interferon and 19.2% glatiramer acetate) and 41.4% an oral medication (25.5% dimethyl fumarate and 3.9% teriflunomide and 12% fingolimod). The remaining patients are treated with monoclonal antibodies (11.6% natalizumab, 9.3% monoclonal antibodies anti-CD20, anti-CD52, anti-CD25) or treated off- label with immunosuppressants (6.4%).
Conclusions: Referral of suspected MS cases to a highly specialized center is recommended to rule out alternative diagnoses and establish the most appropriate treatment, including highly effective drugs for which close monitoring is required.

Disclosure

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EP1350

Does socio-economic status influence early diagnosis and access to MS services?

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Background: Early symptoms of MS are usually evaluated by non-MS specialists. Early treatment has been associated with improved outcomes whilst social deprivation has been shown to affect access to MS treatments. Is it unknown how low sociecomic class patients face delays in their diagnosis especially as it has been found that the average primary care consultation time was shorter in deprived areas.
Objective: To test if there is an association between social deprivation and delayed presentation of MS patients to specialist services.
Methods: MRI is an essential test in the diagnosis of MS. Time from symptom onset to 1st MRI was recorded for 108 patients from the Nottingham MS Register. As a secondary and more objective outcome measure, two independent raters evaluated T2 lesion volumes using anonymised MRIs at the first diagnostic MRI or at early MRIs if the first was not available. Patient postcodes were matched to the 2015 English Index of Multiple Deprivation (IMD) rankings. Cox and multiple linear regression analyses examined the significance of IMD on time to MRI and lesion volume, respectively. Additional covariates were age, sex, MS type and year of scan.
Results: Median time to 1st MRI was 15.63 months (range = 0-336). Deprivation was not a significant predictor for MRI delay (p=0.308). In 59 patients whose 1st MRI scan was accessible for analysis, deprivation did not predict higher lesion volume (p=0.256). For the patients who we did not have access to the first scan, early scans were evaluated. Accounting for time since the 1st scan, the previous non-significant finding was replicated in all 108 patients with early scans (p=0.688).
Conclusions: This study found no association between social deprivation and delayed presentation of MS patients to a typical UK MS centre. Therefore, in our study we find no evidence that interventions to improve symptom awareness should be targeted at specific population groups.

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EP1351

High prevalence area of multiple sclerosis in the far west of Algeria

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Introduction: Multiple sclerosis is a degenerative inflammatory demyelizing disease of the central nervous system. Algeria is considered a medium prevalence area of MS.
Objectives: Calculate the prevalence of MS in the city of Tlemcen and compare it with previous studies.
To study the demographic and clinical characteristics of MS in the city of Tlemcen
Patients and methods: Tlemcen is located in the far west of Algeria, 64 km from the Moroccan border and 520 km from the capital Algiers. Our study is descriptive transversal, it was extended over a period of 10 years (May 2008-May 2018) .the positive diagnosis was made according to the criteria of Mc Donald (2005,2010,2017). All our patients benefited from brain and spinal MRI as well as lumbar puncture. the statistical study was done by SPPS software version 17.0.
Results: The prevalence of MS as of May 1, 2018 was 41.5 / 100,000. The sex ratio was 3.05. The mean age of onset was 28.15 ± 6.1 years. A positive family history was found in 12.6%. 72.7% have relapsing-remitting MS 20.9% were secondary progressive MS, 69.3% were primary progressive MS.
Conclusion: The prevalence of MS in the city of Tlemcen has almost doubled in six years. Further studies are currently needed in other parts of Algeria as well as other Maghreb countries.

Disclosure

nothing to disclose”

EP1352

The impact of stigma in people with primary progressive multiple sclerosis

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Introduction: The stigma associated with neurological disorders contributes to poor health-related quality of life outcomes. Understanding stigma in multiple sclerosis (MS) may be important to carry out specific education intervention strategies. However, limited information is available in people with primary progressive multiple sclerosis (PPMS).
Objective: To assess the perception of stigma and its impact in PPMS.
Methods: A multicenter, cross-sectional study was conducted in a sample of adult patients with PPMS (McDonald 2010 criteria). The 8-item Stigma Scale for Chronic Illness (SSCI-8), the 29-item Multiple Sclerosis Impact Scale (MSIS-29), and the Beck Depression Inventory-Fast Screen (BDI-FS) were used to gather information on stigma, health-related quality of life and depressive symptoms, respectively.
Results: Fifty-five subjects were studied (mean age 55.8 ± 9.5 years, 56.4% male). The mean time since MS diagnosis was 4.1 ± 4.5 years and the median Expanded Disability Status Scale (EDSS) score was 5.5 (interquartile range 4.0, 6.5). Stigma prevalence was 78.2% (n=43). Twenty-four subjects (43.6%) were classified as depressed and six (11%) had a moderate-to-severe depression. SSCI-8 score correlated with physical (rho=0.464, p< 0.001) and psychological (rho=0.358, p=0.007) MSIS-29 subscores. Stigma predicted concurrent depression (OR=1.135; 95%CI: 1.002-1.286; p=0.046).
Conclusion: Stigma is highly prevalent in people with PPMS with a detrimental effect on their quality of life and mood.

Disclosure

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EP1353
Epidemiology of multiple sclerosis in the Highlands of Scotland: prevalence, incidence and mortality

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Introduction: Multiple sclerosis (MS) is the commonest cause of neurological disability in young people and is more common in Northern hemisphere. Epidemiological data may be helpful to take decisions about implementation of new services for MS.
Objectives: To get updated data about MS prevalence, incidence and mortality in the Highlands.
Methods: Study population was the population living in the Scottish Highlands. The catchment area covered by NHS Highlands includes North (Wick, Thurso, Brora, Invergordon), Center (Inverness, Avimore, Nairn, Fort William), and West coast (Ullapool, Sky Isle).
Prevalence data was obtained from the MS database at Raigmore hospital (2017). Incidence data was obtained from Scottish MS register and hospital records. The 2010 McDonald criteria were used for those incident patients diagnosed between 1st January and 31st December 2016.
Crude prevalence and incidence rates, and 95% confidence intervals (CI), were calculated assuming a Wilson distribution and standardized against the Scottish population. Cause-specific mortality rates and Case-fatality rate were also analysed.
Results: 745 MS patients were registered in the database. The 75.4% (562 cases) were females, and male-to-female ratio was 1:3. Mean age of population was 54.1±14.1 years. Mean age at diagnosis was 45.4±13.3 years. Mean number of years of evolution since diagnosis was 8.5±4.6 years. Estimated crude prevalence rate was 300 cases per 100,000 inhabitants (95% CI: 280-320).
36 incident new MS cases were registered. The 88.8% were females. Mean age was 40.4±12.1 years. Annual incidence rate in NHS Highlands was 14.4 per 100,000 inhabitants (95% CI: 10.1-19.9).
Mortality rate was 8 MS cases per 1000 MS patients. Cause-specific mortality rate was 3.6 MS deaths per 100,000 population. Case-fatality rate for MS was 25%.
Conclusions: Prevalence and incidence of MS in the Highlands is high. There is an increasing population living longer with MS, and this fact has important implications for resource allocation for MS.

Disclosure

Dr Carod-Artal have participated in advisory boards with Merck, Biogen, Teva, and Novartis, and have received travel grants from Biogen, Sanofi, Merck, Roche, TG Therapeutics and Novartis.

EP1354
Time to get proper diagnosis in multiple sclerosis and start disease-modifying therapy: the Highlands MS incidence study

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Introduction: Delay in multiple sclerosis (MS) diagnosis and delayed time to start disease-modifying therapy (DMT) are risk factors associated with burden of disease that could be prevented.
Objectives: Time between symptom onset and MS diagnosis was evaluated in incident MS cases and pattern of use of DMT was analysed.
Methods: Data were obtained from the MS incidence study in the Highlands, a prospective hospital-register based study that was carried out over a 12-month period, from 1st January 2016 to 31st December 2016. The 2010 McDonald criteria for diagnosis of MS were used for those incident patients diagnosed during that period.
Results: 36 incident new MS cases were registered in the NHS Highlands in 2016. They included 32 females (88.8%) and 4 males (11.1%). Mean age was 40.47±12.14 years [range: 15-67 years].
Initial symptoms/syndrome were: poor balance and gait ataxia, 1 case (2.7%); fatigue and poor balance, 1 case (2.7%); hemisensory syndrome, 2 cases (5.5%); lower limb weakness, 9 cases (25%); optic neuritis, 7 cases (19.4%); and sensory symptoms, 16 cases (44.4%).

Mean period of time between first assessment at Neurology clinic and diagnosis was 10.5±13.7 months [median: 4 months]. The mean period of time from symptoms onset to diagnosis of MS was 38.8±43.2 months [median: 22 months].
A significant correlation (Spearman´s coefficient 0.34; p=0.04) between age and time to diagnosis was observed. No significant differences were observed in time "initial symptoms-to-diagnosis" by gender.
19 patients (52.8%) started a DMT: first line therapy (17 cases; 47%) and second line therapy (2 cases; 5.8%). Most commonly used DMTs were injectables (8 cases; 22%) and oral ones (9 cases; 25%). Three patients stopped medication due to tolerability issues during the follow up.
The 47.2% of new MS patients (17/36) were not taking any DMT. Reasons for not taking DMTs were: not keen to use traditional pharmacological therapy, 4 cases (23.5%); progressive MS in absence of identified relapses, 4 cases (17.6%); planning or thinking in pregnancy, 3 cases (17.6%); mild MS symptoms, 3 cases (17.6%); cancer, 1 cases (5.8%); interested only in treating sensory symptoms, 1 case (5.8%); waiting list/locum assessments, 1 case (5.8%).
Conclusions: Although the gap period between symptom onset and diagnosis is moderate, a significant proportion of recently diagnosed MS patients are not keen to start with a DMT.

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EP1355
Prevalence of multiple sclerosis in Cuenca, Ecuador

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Introduction: Ecuador has a low prevalence of multiple sclerosis (MS). An epidemiological study conducted ten years ago showed that the prevalence of MS in Cuenca was 0.75/100,000 inhabitants. Since 2006, no new epidemiological studies have been carried out and we do not know if the prevalence has increased in the same way as it has in other regions of the world.
Objective: To determine the prevalence of multiple sclerosis in Cuenca and describe its epidemiological characteristics.
Methods: We performed a retrospective descriptive study from January 1, 2016 to December 31, 2016. Patients included in the study were those who met the McDonald2010 criteria for MS and lived in Cuenca for at least one year. Patients come from third-level hospitals; Vicente Corral Moscoso, José Carrasco (third level public hospital), Del Río hospital, Santa Ana and Monte Sinaí (third level private hospitals), which are institutions of national reference for diagnosis and treatment of MS. Patients who did not live in Cuenca for over a year were excluded from the study.
Results: We identified 23 patients with MS, with a prevalence of 3.88 per 100.000 inhabitants (IC 95%, 2.29-5.47). The average age was 37.22 years old (SD +/- 12.42). Sixty one percent was female. The female to male ratio was 1.5:1. Seventy eight percent were relapsing-remitting MS, 8.7% clinical isolate syndrome and 13.05% progressive MS. The expanded disability status scale (EDSS) mean was 2.54 (SD +/- 1.73).
Conclusion: The prevalence of MS in Cuenca has increased in comparison to a previous report from 10 years ago. A limitation of this study is that it is not a community study and it is necessary to create a surveillance system which will allow for a better patient registry.

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EP1356
Pattern of demyelinating disorders in a tertiary medical center in India

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Introduction: Demyelinating disorder of CNS constitute an important group of diseases with variable outcome & prognosis. India falls in low prevalence zone for multiple sclerosis. Recent availability of investigations and clearly laid guidelines have led to better & earlier recognition of these disorders.
Objective and aims: To study the pattern of demyelinating disorder.
Methods: The data of all patients admitted to the Neurology ward of the tertiary care Institute situated in the capital of the most populated state of India were retrospectively analysed from 2014 to 2017 to delineate disorders with demyelinating diseases. Each case was included only if it fulfilled clear internationally accepted diagnostic criteria.
Results: The hospital based study revealed 31 patients with demyelinating disorders (Males 15,Females 16, age range 14-62 years) Acute Demyelinating encephalomyelitis (ADEM) was the commonest demyelinating disorder (15 patients) followed by

Neuro Myelitis Optica Spectrum Disorders (NMOSD) in 8 & Multiple Sclerosis (MS) in 6 (Relapsing and Remitting MS 5, Tumefactactive MS in 1) and optic neuritis in 2 patients. The patients with ADEM were younger with male dominance (M:F = 2:1)while those with MS or NMOS had female dominance (M:F 1:2 & 3:5 respectively). Patients with MS were younger compared to those with NMOSD. (age 30± 19.0 years & 37.8± 19.0 years respectively). While those with NMSOD were older compared to all. ADEM presented with diffuse encephalopathy in 8 patients & brain stem involvement in two patients. Patients with multiple sclerosis had short segment myelitis in two and brainstem involvement in one. NMOSD was dominantly characterized by long segment myelitis(5 patients)and optic neuropathy in three patients.
Conclusion: In country with low prevalence of MS, a relatively higher number of patients with MS are being recognized, though ADEM remains the commonest demyelinating disorder.

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EP1357

Early versus late start of vitamin D supplementation in multiple sclerosis predicts short term disease course: a two-year observational study

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Background and aims: Consistent amounts of studies support the role of Vitamin D (vitD) in multiple sclerosis (MS) pathogenesis. Few however, investigated if vitamin D supplementation is able to modify MS disease course.
Our aim was to investigate the relationship between time of beginning of vitD supplementation and prognosis.
Objective: To investigate by mean of a cohort study, the relationship between time of initiation of vitamine D supplementation and MS short term prognosis.
Methods: We included consecutive MS patients who started vitD treatment, determining vitD blood levels before treatment initiation. We considered two groups according to the time of treatment initiation: within the first three years from disease onset or later. We considered the following variables: age at MS onset, age at baseline, relapse rate, new MRI gadolinium enhancing lesions and T2/FLAIR lesions, EDSS at the end of follow-up (September 1st 2017), type of disease modifying therapy initiated, baseline values of hydroxy-vitamins D. We used t test, Chi square analyses Kaplan-Meyer estimates to compare means or frequencies distribution between groups according to quartiles of vitD at baseline. We used Cox proportional analyses to calculate the effects of time to initiation of vitamin D on disease activity and progression.
Results: We included 231 MS patients. Patients starting vitamine D within the first three years from onset had a significantly lower mean EDSS score at the end of follow-up and a lower risk to reach an EDSS score of 3.5 (HR 0.86; CI 0.75-1.00; p= 0.05). Trends were similar dividing patients according to quartiles of vitamine D distribution at baseline. Patients had a lower probability to develop new MRI lesions when they started vitD earlier (p= 0.01) but we did not find a significant relationship with the probability to have Gad+ MRI scans at follow-up.
Conclusions: Our study suggests that a time window opportunity should be considered also for vitD supplementation in MS patients. If confirmed, these results would add relevant information about the time and use of vitD among MS patients.

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EP1358

A descriptive study of switching patterns among MS patients who started on Glatopa therapy: a claims database analysis

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Background: Glatopa 20 mg/mL was introduced in April 2015 as a follow-on glatiramer acetate (FOGA) therapy for patients with MS. However, little is known about patterns of Glatopa 20 mg/mL (FOGA) use since becoming commercially available.
Objectives: To describe the demographic characteristics and switching patterns of MS patients with FOGA use from a large US claims database.
Methods: The study sample included adult Medicare Advantage enrollees with Part D coverage (MAPD) meeting the following inclusion criteria: ≥1 pharmacy claim for FOGA between 01JUN2015 and 31JUN2016 (identification period). Index date was the date of the first pharmacy claim for FOGA during the identification period. Patients had continuous enrollment in a

single health plan at least 6 months prior to index date and at least 3 months following index date. Discontinuation of FOGA was defined as a gap in therapy (ie, days without the medication) of at least 30 days. Therapies used by patients after discontinuation were also analyzed.

Results: A total of 95 subjects were included in the analysis (76% female, average age 61 years, average 428 days of follow-up). Eighty-four patients (88%) had a fill for Copaxone 20 mg/mL (branded glatiramer acetate [GA]) once-daily at some time prior to index date. Fifty-five patients (58%) were non-persistent on FOGA, either discontinuing with no evidence of another therapy or switching to another therapy. Overall, thirty-one patients (33%) switched to branded GA 20 mg/mL once-daily, and 9 (9.5%) switched to branded GA 40 mg/mL three-times-weekly. Seventeen patients (18%) restarted FOGA after discontinuation or switch. The average length of FOGA persistence before switch or discontinuation was 112 days.

Conclusions: Although the study sample was small, and the exact reasons for switch need to be further investigated, this study highlights the importance of understanding patient persistence and switching behaviors when they start on a new MS therapy. Further studies are needed to confirm and further investigate these findings.

Disclosure

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EP1359

The OFSEP high definition cohort: to prognosticate the evolution of multiple sclerosis at clinical key steps of the disease

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Context: For neurologists and patients with MS, one major unmet need is to better appreciate the causal factors of disease progression and to obtain reliable predictive tools that could apply on the individual level and at different key moments in the disease course (landmarks). Taking advantage of the existing network of neurologists collecting data in daily practice, the French MS registry (OFSEP) initiated a "high-definition" (HD) cohort. Its overarching objective is to determine, at specific landmarks over the disease course, the prognostic factors of the evolution of disability in MS and the care practices that can modify this predicted evolution in real-life settings.

Objective: To describe the OFSEP HD Cohort.

Methods: Patients with a diagnosis of MS and an EDSS score $\leq$ 7.0 followed in French expert centres will be included. Collection of data will include OFSEP core minimal clinical data (disability, neurological episode, treatment…), MFSC (T25FW, 9-HPT, CSCT), brain MRI, comorbidities, quality of life (EQ-5D, SF12, MusiQoL), socioeconomic indicators, alcohol and tobacco consumption, in addition to serum neurofilament light chains and biocollection at T0. Four landmarks will be studied: 1) the first visit when the diagnosis of MS is set; 2) the first visit when the diagnosis of progression (either primary or secondary) is set; 3) any visit with recent disease activity, defined by the occurrence of a relapse and/or MRI activity in the past 3 months; 4) any visit with absence of disease activity in the past 5 years. Patients will be followed annually and at the time of occurrence of a landmark of interest. Collected outcomes will be disability, MSFC, relapse, progression, death, lesion load, cerebral atrophy, patient-reported outcomes and combined outcomes including activity and progression, NEDA or OFSEP specific indicators.

Results: Inclusions will start in June 2018. We expect to include 5,000 patients up to 2020. The analyses will begin in 2020. The scientific program aims to deliver 1/ predictive tools that could identify subgroups of patients with a maximum expected disease progression free survival with good quality of life and 2/ economic assessments in a cost-of-illness and cost-effectiveness approach.

Discussion: For the first time in Europe a large cohort of MS patients with annual or targeted systematic extended collection of data will be open to researchers to improve knowledge on the disease.

Disclosure

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Jonathan EPSTEIN has no financial disclosure related to this project to declare.

Yohann FOUCHER has no financial disclosure related to this project to declare.

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EP1360

Use of anxiety and depression treatment in Hispanic multiple sclerosis patients of San Juan MS Center

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Introduction: Anxiety and depression are common psychiatric conditions in patients with Multiple Sclerosis (MS). Several studies have reported high rates of depression in MS patients with a lifetime prevalence of ∼50% and annual prevalence of 20%. Studies have shown that neuroinflammation is associated with anxiety and depression in patients with relapsing-remitting MS. In Puerto Rico there are no studies of prevalence of depression and anxiety in MS. It is common to find that patients are using multiple antidepressants, mood stabilizers and anxiolytics. Many patients are not followed by mental health specialists, are in long term drugs, and receiving a prescription from their primary care provider. Studying these comorbidities is of great importance due to their association with low quality of life in this population.
Aims: Our study aims to determine the use of common anxiety and depression drugs in MS patients of San Juan MS Centre (SJMSC), evaluate their frequency and natural progression**,** describe the medications pattern use, active symptoms, and use of specialized and alternative treatments for emotional conditions.
Methods: Medical records of patients from SJMSC were reviewed to determine the use of selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and other drugs for anxiety and depression. The State/Trait Anxiety Inventory and the Beck Depression Inventory - 2 will be collected to identify active symptoms and severity. Data will be analysed using descriptive statistical analysis, comorbidities transition states will be modelled by Markov chains (MC).
Results: From a total of 1,397 MS patients 54% were using drugs for psychiatric conditions. Among these, 44% were using antidepressants, 27% anxiolytics, 14% for both anxiety and depression, and 15% were using other types on their most recent visit. Patients receiving only antidepressants at a specific visit reported, in their subsequent visits, treatment for the same comorbidity in 55% of the cases and among those who reported changes in comorbidity 30% received only anxiolytics, 4% anxiolytics and antidepressants, and 11% other type of drugs.
Conclusions: There is a high prevalence of anxiety and depression treatment use in SJMSC patients. Among them, about 50% had changed their treatments in a subsequent visit. Further investigations are needed to describe the effect of medication change in patients.

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EP1361

Characteristics of multiple sclerosis patients treated with disease-modifying therapies in Puerto Rico

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Introduction: Reported incidence rates of MS in Puerto Rico have been higher than those observed in other countries in Latin America and the Caribbean, but lower than those in countries at higher latitudes. Data on the use of disease-modifying therapies (DMTs) among patients with MS in Puerto Rico are limited.
Aims: To describe the characteristics of patients with MS who received DMTs via the largest specialty pharmacy provider in Puerto Rico.
Methods: Retrospective, observational study using data collected between January 1, 2010 and December 31, 2016 from the Special Care Pharmacy Services (SCPS) database. SCPS is a longitudinal database serving approximately 65% of the overall DMT prescriptions for MS in Puerto Rico, and contains information on patient demographics (age, gender, and region), insurance coverage, and type of DMT (oral, injectable, infusible). Inclusion criteria were MS diagnosis and DMT prescriptions via the SCPS during the study period. Patient characteristics were assessed at the time of the most recent prescription of DMT, which could have been received anytime during the study period.
Results: 2070 patients with MS had received ≥1 DMT during the study period; 1566 (75.7%) were female; mean age was 43.6 years. Of these, 782 (37.8%) were covered by government insurance, 623 (30.1%) through commercial insurance, and 663 (32.0%) through Medicare. Mean duration on current DMT was 16.7 months, with 44.3% of patients remaining on injectable DMTs, compared to 28.1% and 27.6% remaining on infusible or oral DMTs, respectively. The municipality with the largest number of MS patients was San Juan (11.6% of the analysis population), followed by the Bayamon (7.8%), and Carolina (5.3%) municipalities.
Conclusion: Despite the launch of novel therapies of increased convenience and/or higher efficacy, the majority of patients with MS in Puerto Rico remained on injectable medications, possibly due to formulary restrictions implemented by various payers. The number of patients with MS correlated with the general population densities within Puerto Rico municipalities. Our findings may serve as a useful resource for further MS research, since this

study describes a patient population that may be of interest to other regions with substantial Hispanic populations.

Disclosure

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EP1362

Female to male ratio trend of multiple sclerosis in Tehran, Iran

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Background: Female to male ratio, incidence and prevalence of MS have been reported to have a general increasing trend worldwide. Our goal is to evaluate sex-specific changes of incidence and prevalence and overall trend and enlightening the patterns.
Method: This is a cross-sectional population-based study founded by Iranian MS Society data from 1999 to 2017. We design a questionnaire to evaluate most important epidemiologic data including female to male ratio in different subgroups of MS patients containing pediatric MS, late-onset MS, familial history of MS in different degrees of relatives and general population via Joinpoint regression analysis. Chi-square test analysis was used for indicating significance of gender frequency difference among subgroups with STATA v.14.
Results: Among 16980 MS patients, 24.8% were males and 75.19% were females. The female to male ratios were 3.03:1 in general population, 3.82:1 in patients with pediatric MS, 2:28:1 in late onset MS, 2.78:1, 3:06:1 in positive familial history of MS and negative familial history of MS, respectively. In general, female to male ratio showed an insignificant decreasing trend.
The decreasing pattern was observed in all of the mentioned subgroups except late-onset MS patients and was only significant in patient with positive familial history of MS. Gender frequencies were significantly different among pediatric and non-pediatric patients, late-onset and non-late-onset patients, and nearly significant among patients with and without familial history of MS.
Conclusion: Unlike the general pattern of the increasing female to male ratio worldwide, we observed decreasing pattern which could be due to a more rapid increase in the incidence of MS in male patients, caused by earlier diagnosis or an actual increase based on relevant genetic and environmental factors.

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EP1363

The role of heavy metals in genesis of multiple sclerosis in the population of various districts of Tashkent city

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Purpose: Study the influence of environmental pollution of heavy metals(HM) on the development of multiple sclerosis in the population of various districts of Tashkent. The research tasks included the study of the content of TM in the urban environment, as well as their determination in biosubstrates of MS patients.
Materials and methods: Studies were conducted in medical institutions in Tashkent between 2014 and 2017. At the first stage, the primary medical documentation was reviewed for visiting district clinics and city hospitals, using information from journals for recording neurological patients, and materials from statistical offices. For the second stage of the study, 400 patients with MS whose mean age was 37.03 years were selected. Inclusion in the study was carried out in accordance with the diagnostic criteria McDonald et al., 2010., i.e. in the course of the examination, characteristic clinical manifestations of MS in the form of symptoms of multifocal lesion of the central nervous system of various degrees were revealed. At the third stage, a survey of the urban environment was conducted, both in the zone of location of large operating enterprises and in the residential areas of the city. The quality of soil, atmospheric air was analyzed. The content of cadmium and nickel in environmental objects and biosubstrates was determined by atomic absorption spectrometry (AAS).
Results: The obtained results testified to the presence of stable high, by cadmium in 3-5.5 times, over nickel in 1.5-2 times exceeding MAC values of atmospheric and soil content in the Almazar and Mirabad districts of the city. Similarly high was the content of HM in the blood and urine of MS patients. So the concentration of cadmium in the blood of patients was from 0.065 ± 0.05 μg / l to 0.071 ± 0.04 μg / l, which exceeded the reference values. Similar results were obtained with respect to serum levels of patients with MS of nickel, which was 0.34 ± 0.09 - μg / l (at a nickel toxicity level> 50 μg / l). Even more obvious was the presence of a high level of nickel in the urine, which was revealed by us in the examined MS patients living in the Almazar and Mirabad regions, equal to 1.8 ± 0, 1 and 1.5 ± 0.09 μg / l ($P < 0$, respectively, 05).
Conclusions: Thus, high concentrations of cadmium and nickel in the studied biosubstrates of the MS patients correlated with their high content in the environment of the Almazar and Mirabad regions.

Disclosure

"Gulshanbonu: nothing to disclose"

MS and gender

EP1364

The study of the gender value of the degree of asthenic syndrome according to the test "SAM" in patients with multiple sclerosis

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Intraduction: In recent years there has been a significant increase in the number of patients with psychosomatic pathology. More often depressive and anxious depressive steels are often observed in patients with multiple sclerosis
Objective: To study the gender value of the degree of asthenic syndrome in the "SAM" test in patients with multiple sclerosis.
Aims and methods: To study the degree of asthenic syndrome in patients with MS, a study was conducted in 35 patients,13 (55%) women,12 (50%) men,aged from 22 to 46 years.And it was also subdivided according to age categories: from 22-30, 32-35 and 35 or more. The "SAM" test was used to determine the asthenic syndrome.
Results: To study was conducted in 35 patients with MS, 13 (55%) women, 12 (50%) men, prevalence from 22 to 46 years. At the same time, the results on sex and age differences were singled out. The "S" the state of health in 23 patients (65%) of them 15 men (65%), women 8 (35%) was worsened and averaged 32.6 points for men, 36.4 points for women (in the normal amount points should be 50 points or more) - the patients noted symptoms like weakness, rapid fatigue, lethargy, weakness.The activity level "A" in 28 (80%) patients, men 17 (61%), women 11 (39%) was reduced and averaged 31.3 points in men-35.1 points in women (in Norm the sum of points should be 55 points or more) - lack of mobility, inactivity and indifference in the events around, slowness, fatigue was revealed.The "M" was in the mood for 32 (91%) of the male patients 19 (60%), for women 13 (40%) with PC was lowered and averaged 37 points in men, in women 32 points should be 54 points or more).Patients with MS in the 22-30 age group "S" at 36, the score, "A"33p.s., the "M"was 40.In the age group 31-35 years, "C" at 30p., "A"35p.s.,"M"31p.s.In the age group of 35 years and older, "C" -sensitivity was estimated at 38p.s, "A"was 36 points, "H" - the mood was 49 points.
Conclusions: 1. Summing up, it can be argued that in patients of a younger age they have disorders in the psychoemotional sphere, asthenia of the autonomic nervous system of varying degrees.2. Women in comparison with men proved to be more resistant to different stressful and conflict situations, their asthenia was less pronounced than in men. Patients in the age groups of 22-30 years had marked abnormalities than patients in the age group of 31-35 and 35 and over 7.

Disclosure

nothing to disclose"

EP1365

Exclusive breastfeeding does not affect postpartum exacerbations

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Introduction: There are quite contradictory data on protective role of exclusive breastfeeding. When deciding to continue breastfeeding, the main therapy of MS will be postponed. This can negatively affect on the activity of disease.
Objective: to evaluate role of breastfeeding on postpartum relapses.
Methods: A retrospective analysis from 2011 to 2017 of SPbMS Center registry was performed. For the analysis, the data were selected during observation for 1 year after delivery and without the use of 2-line drugs during pregnancy and the first months after childbirth. Various characteristics of the impact of the cardinal exacerbations were assessed: gynecological history, fertility, anesthesia, gestational age, MRI data before and after pregnancy, pre-pregnancy therapy, total lactation duration, and duration of exclusive breastfeeding. Statistical analysis was performed with the program GraphPad Prism v7.0.
Results: 127 women (133 births) were enrolled in the study. In 43% of cases there were exacerbations in the first year after birth with a median at 2.5 months/There was a weak negative correlation with the age of onset ($p = 0.0039$), age of diagnosis of MS ($p = 0.0011$) and the probability of exacerbations after childbirth. When assessing gynecological history data, none of the correlation parameters was obtained (the presence of abortions, prior births, cesarean section or the use of anesthesia during labor). Also, there was no correlation with the gestational age of infants. The presence of lactation and the duration of exclusive breastfeeding did not correlate with the likelihood of exacerbations. Most patients with exacerbations (90.5%) and without exacerbations after childbirth (95.6%) started breastfeeding. The duration of exclusive breastfeeding was approximately the same in the two groups, but there was a difference in the total lactation time ($p = 0.013$). There was no correlation of exacerbations after childbirth with the duration MS treatment and any MS injectable medicine (interferons and glatiramera acetate).
Conclusion: Exclusive breastfeeding did not reduce the frequency of exacerbations after childbirth ($p = 0.249$).

Disclosure

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EP1366

Rebound in disease activity after fingolimod suspension for pregnancy planning: predictor factors

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Introduction: Rebound of disease activity beyond pretreatment levels has been associated with discontinuation of highly-effective multiple sclerosis (MS) therapies, especially natalizumab, but also after stopping fingolimod. This fact is important especially for pregnancy planning due to that most MS therapies must be discontinued to avoid potential fetal risks.

Objectives: To (1) describe the frequency of rebound activity, clinical features and outcome, after cessation of fingolimod for childbearing desire, and (2) analyze the contributor factors associated with early activity reappearance.

Methods: Clinical and radiological data of 7 MS women from our center who discontinued fingolimod from May 2012 to March 2018 for pregnancy planning.

Results: Three of the 7 (42.8%) patients had a rebound of the disease after stopping fingolimod, and all of them became pregnant. The median time to pregnancy was 76 days (range, 0-263). Before pregnancy only one patient had a relapse (214 days after discontinuation). During pregnancy, the 3 patients had a mean (standard deviation, SD) of 5.3 (1.3) relapses, and 13 of the 16 relapses were treated with intravenous steroids and/or immunoglobulins. They had a median increase of the Expanded Disability Status Scale of 3 points (range, 2-4), and a median increase of 27 (range, 9-40) new gadolinium-enhancing lesions and 38 (range, 21-70) of new T2 lesions seen on a magnetic resonance imaging performed within the first three weeks after delivery. The 3 pregnancies resulted in delivery of healthy babies with low birth weight in two of them. A strong correlation was found between the lymphocyte count at fingolimod onset and the annualized relapse rate in the period without therapy (r= -0.84, p=0.005). The time to first relapse was shorter in those patients who had < 300/µl lymphocytes in the 3 first months of fingolimod onset (median time 46 vs 426 days, p=0.010).

Conclusions: Fingolimod rebound represents a severe long-lasting inflammatory syndrome that may affect up to 40% of the MS women who discontinuing fingolimod to attempt pregnancy. Lymphopenia < 300/µl within the first 3 months from fingolimod onset may predispose to suffer early and higher MS activity after cessation. It takes priority to determine the best discontinuing fingolimod strategy in MS women with childbearing potential to diminish the risk for this syndrome.

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EP1367

Cesarean section in women with MS: a choice or a need?

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Introduction: Management of pregnancy related issue in women affected by Multiple Sclerosis, requires a multidisciplinary approach. Labour represents a critical moment for both the woman and the newborn, therefore a delicate choice has to be made in agreement with both treating physicians, gynaecologist and neurologist. Several aspects related to pregnancy have been investigated in MS, however little attention has been devoted to the modality of delivery.

Objectives: To investigate whether the diagnosis of MS influences delivery modality.

Methods: We retrospectively analysed data from a cohort of full ambulatory women attending the MS centre of Sant'Andrea Hospital in Rome. Data on reproductive history, pregnancy, miscarriages and pregnancy interruption were collected by the means of a questionnaire with the supervision of an obstetrician. Data on disease history were collected from patient's clinical record. To serve as control, data on delivery of healthy subjects (HS) were collected from clinical registry of Fabia Mater clinic in Rome.

Results: We collected data on pregnancy from 250 HS and 157 patients (mean age 33±5.8; 30±5.8 years respectively); 76 patients (mean age 32,7±5) presented a diagnosis before pregnancy (MSpre). Considering all patients with MS, gestational weeks and birth weight were lower compared with HS (38,4 ±1,7 *vs*39,3±1,3 weeks p =0,001 and 3092±519 *vs* 3290±446 g p< 0,001 respectively). Compared with HS, the MSpre group showed a lower frequency of natural delivery and a higher frequency of both planned and urgency caesarean section (39,3%*vs*66%; 32,7%*vs*22.4% and 24,5% *vs* 9,2%respectively, p< 0,001).

Conclusions: Women with a diagnosis of MS are more subject to cesarean section. This can recognize two possible causes: an aprioristic choice of the gynaecologist and complication during natural delivery.

Disclosure

Federici S, De Luca F, Ianniello A,D'Errico MA, De Angelis C declare no conflict of interest
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Ruggieri S has received fee as speaking honoraria from Teva,Merck Serono, Biogen; travel grant from Biogen, Merck Serono; fee as advisory board consultant from Merck Serono and Novartis.
Borriello G received speaking onorariaand travel grant from Almirall, Biogen, Genzyme, Merck, Novartis, Roche, Teva,
Pozzilli C received consulting and lecture fees and research founding and travel grant from Almirall, Bayer, Biogen, Genzyme, Merck Serono, Novartis, Roche and Teva.

EP1368

The presence of MR-activity before and after pregnancy is associated with the probability of postpartum exacerbations

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Introduction: It is known that exacerbations in the first year after childbirth are associated with the progression of the disease. However, data on the evaluation of various factors on the postpartum relapse's risk is not enough.
Objective: to evaluate MRI data before and after pregnancy.
Methods: A retrospective analysis from 2011 to 2017 of SPbMS Center registry was performed. For the analysis, the data were selected during observation for 1 year after delivery and without the use of 2-line drugs during pregnancy and the first months after childbirth. MRI data before pregnancy (n=92) and 1-3 mo after delivery (n=94) were assessed. Statistical analysis was performed with the program GraphPad Prism v7.0
Results: 127 women (133 births) were enrolled in the study. In the patient milestones there was a relapsing-remitting MS. AAR during pregnancy significantly decreased to 0.08 ($p < 0.0001$) and returned to the previous level 0.5 after delivery ($p < 0.0001$). When registering contrast lesions (Gd +) before pregnancy, the probability of exacerbations after childbirth is increased by 2.2 times (95% CI 1.08-4.9, $p = 0.048$). The existence of Gd+ immediately after delivery increased the probability of exacerbation by 5.8 times (95% CI: 2.83, 9.93, $p < 0.0001$). AUC was 0.76 ± 0.05 (95% CI: 0.65, 0.86, $p < 0.0001$).
Conclusion: MRI-monitoring of disease activity would be helpful for assessment the risk of pospartum relapse in routine practice and can help to decide on the timing of the resumption of therapy. The presence of contrast enhancing lesions first months after birth increased the probability of relapse by 5.8 times (95% CI: 2,8; 9,9, $p < 0.0001$; sensitivity 63,4 %, specificity 88 %).

Disclosure

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EP1369

Effects of sex-related factors on probability of disability in women with multiple sclerosis

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It has been reported that estrogen may affect the level of Th-1 / Th-2 lymphocytes and ratio of Th-1 and Th-2 that play an important role in immunopathogenesis in multiple sclerosis (MS). Therefore hormonal changes during transitional periods such as pregnancy and menopause may affect the activity of the disease at different phases of the menstrual cycle.
The aim of this study is to determine the association of women with MS with variables such as menarche age, menstrual order and menopausal age and disease-related factors such as disability level and a number of attacks.
This descriptive study enrolled 281 person with MS (pwMS). The participants were evaluated by a simple and short survey by the researchers. Expanded Disability Status Scale (EDSS) score, number of attacks and disease duration evaluated by a neurologist.
Sixty-seven (23.8%) of total 281 patients entered menopause. There is no significant difference in the terms of EDSS score of pwMS with or without menopause ($p>0.05$). Sixty patients (21.4%) had children after MS. There is no significant difference between pre-post child and number of attacks, post child and current EDSS scores of these pwMS ($p>0.05$). It was found that 80.4% of the patients had a regular menstrual cycle while 19.6% patients were irregular. The EDSS score was significantly higher in women with irregular menstruation cycle than women with regular menstruation cycle ($p< 0.05$). There is a significant difference between the average age of Turkey menarche (13.3) and the average age of menarche of women with MS (13.07) ($p< 0.05$).
This study has suggested that menopause and childbearing may not affect disability level or a number of attacks women with MS. On the other hand, women with MS has an earlier age of menarche and this could be linked with an increased risk of MS or with an earlier age at MS symptom onset.

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EP1370

Pregnancy outcomes in Chilean MS patients receiving interferon beta or glatiramer acetate: a longitudinal 8 year study

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Introduction: Since 2010, we've recommended patients in child-bearing age to discontinue glatiramer acetate (GA) or interferon (IFN) only after confirmed pregnancy (Pg), avoiding wash-out periods or disease activity while they desire to become Pg. Real world information about perinatal outcomes are needed.
Objective: To explore the effect of exposure to GA or IFN on Pg outcomes in Chilean patients.
Methods: A retrospective cohort of patients controlled in the Programa de Esclerosis Múltiple UC between 2010-2018 was carried out. The outcomes of women exposed to GA or IFN during Pg were compared with the registry of the anthropometric growth curves of Chilean newborns. Data was collected from clinical records and a standardized telephonic questionnaire was also performed.
Results: By May 2018, from a total of 663 MS patients, 433 women, 215 were exposed to GA and IFN. From this sample, we only found 26 Pg from patients effectively receiving treatment with GA (n=8) or IFN (n=18) by the time of conception. During Pg, none of the patients presented with relapses. There were 12 vaginal births, 7 elective c-sections, and 4 emergency c-sections (2 placental abruption, 1 failed forceps and 1 failed induction). One patient required in-vitro fertilization. One first trimester spontaneous abortion (IFN), one ectopic Pg (IFN), and one ongoing Pg were also observed. There were 5 preterm newborns, two at 36w, two at 32w (twins), and one at 25w. Mean gestational age was 37±3.4w (median 38, range 25-40). When comparing weight and height according to gestational age, mean values were within the estimate for the Chilean population with a confidence interval of 95%; at 37w 3340±640g, size 49.25±1.3cm, at 38w weight 3272±471g, size 49.3±1.3cm, and at 39w weight 3164±159g, size 49.5±0.8cm; 3 newborns were outside the range, 1 small for gestational age (40cm, 36w), 1 overweight (3980g, 37w) and 1 with low birth weight (2570g, 38w). Mean exclusive breastfeeding time was 4.5±2.9 months. During breastfeeding, 3 patients had a relapse, at 3rd (brainstem), 5th (myelitis), and 7th (optic neuritis) months, suspending breastfeeding and re-starting DMT. By the time of this analysis, no congenital malformations were reported.
Conclusions: Pg outcomes from patients who discontinued GA or IFN only after confirmed Pg seem comparable to epidemiological data of Chilean newborns, with no congenital malformations reported to date, supporting the safety of continuing GA of IFN until confirmed Pg.

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MS symptoms

EP1371

Workplace difficulties, health-related quality of life and perception of stigma in people with multiple sclerosis with low physical disability

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Introduction: In multiple sclerosis (MS), unemployment occurs even at levels of disability, which are not typically associated with overt physical impairment.
Objective: To assess the impact of MS in people with low levels of physical disability.
Methods: A multicenter, non-interventional, cross-sectional study in adult subjects with relapsing-remitting MS (RRMS) or primary progressive MS (PPMS) according to McDonald 2010 criteria was conducted. The 23-item Multiple Sclerosis Work Difficulties Questionnaire (MSWDQ-23), 29-item Multiple Sclerosis Impact Scale (MSIS-29), 8-item Stigma Scale for Chronic Illness (SSCI-8), and Beck Depression Inventory-Fast Screen (BDI-FS) were used to assess working performance, health-related quality of life, perception of stigma and depressive mood, respectively.
Results: A total of 199 subjects were studied (mean age: 43.9 ± 10.5 years, 60.8% female, 86.4% with RRMS). Mean time from diagnosis was 9.6 ± 7.2 years, median EDSS score 2.0 (interquartile range: 1.0-3.5). Employment rate was 47.2% (n=94). Mean physical and psychological MSIS-29 impact sub-scores were 40.38 ± 17.1 and 20.24 ± 7.8, respectively. Forty patients (20.2%) had at least one SSCI-8 item on 4 or 5, suggesting presence of stigma "often" or "always". Eighty-one patients (40.7%) were depressed, 25 (12.6%) had moderate-to-severe depression. Employed people showed less perception of stigma than unemployed ($p=0.001$). Patients with higher perception of stigma showed higher physical and psychological impact on health-related quality of life (rho=0.61 and 0.55, respectively; $p< 0.001$) and more difficulties at work (rho=0.60, $p< 0.001$). Presence of depressive symptoms was related to working status: pensioner or incapacitated patients had more symptoms of depression ($p< 0.001$). Moreover, severity of depressive symptoms correlated directly with MSWDQ-23 score, indicating work-related problems influence mood status (rho=0.64, $p< 0.001$).
Conclusion: Work-related problems, stigma and poor quality of life outcomes are common in people with low physical disability. Using MS-specific patient-reported questionnaires may be a useful complementary strategy to detect early symptoms in clinical practice.

Disclosure

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EP1372

Autonomic nervous system dysfunction is an independent contributor to multiple sclerosis related fatigue

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Background and aims: The aim of this study was to investigate possible association between autonomic dysfunction and fatigue in patients with MS (pwMS).
Design/Methods: 70 pwMS were enrolled (51 females, mean age 33.8±9.1). Testing of the autonomic nervous system (ANS) consisted of Quantitative Sudomotor Axon Reflex Test (QSART), testing of the cardiovascular reflexes (heart rate and blood pressure responses to Valsalva maneuver and heart rate response to deep breathing) and the tilt table test. Composite Autonomic Scoring Scale (CASS) was utilized to quantify the autonomic dysfunction. Participants completed the Composite Autonomic System Score-31 (COMPASS-31), Modified Fatigue Impact Scale (MFIS), Beck depression scale (BDI-2) and Epworth Sleepiness Scale (ESS). Clinically relevant BDI-2 result was considered if the score was >18. Cut-off scores of ≥38 or ≥45 on the MFIS were used to stratify patients into a fatigued subgroup (N=17 and N=9, respectively) and a non-fatigued subgroup (N=53 and N=61, respectively).
Results: Fatigued patients, as defined by either MFIS cut-off values, were older and scored significantly worse on BDI-2 and COMPASS-31. There was a clear trend of lower sweating outputs on QSART at all measured sites, reaching statistical significance for distal leg (MFIS≥45) and foot (MFIS≥38). We found significant correlations between MFIS and age (r_s=0.329, p=0.005), MFIS and Valsalva ratio (r_s =-0.306, p=0.011), MFIS and sweating output on QSART at the forearm, proximal and distal lower leg (r_s =-0.379, p=0.003, r_s =-0.356, p=0.005 and r_s =-0.345, p=0.006, respectively), MFIS and BDI-2 (r_s =0.756, p< 0.001), and MFIS and COMPASS-31 (r_s =0.607, p< 0.001). Multiple regression model showed that COMPASS-31, BDI-2 and ESS were independent predictors of fatigue (B=0.492, p=0.002, B=17.068, p=0.02 and B=1.122, p=0.009, respectively).
Conclusion: These results suggest an association between autonomic dysfunction and fatigue in MS patients.

Disclosure

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EP1373

Persons with MS are at increased risk of osteopenia and osteoporosis. A ten-year longitudinal study

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Several studies have shown that bone mineral density (BMD) at the femoral neck decreases with increasing physical handicap in MS patients. BMD measurements in an unselected group of 80 fully ambulatory persons with MS aged 19-50 years revealed osteopenia in 12 and osteoporosis in two participants in 2008. We report findings at ten-year follow-up in 2018.
Methods: Examinations performed in February and March 2018 included BMD, measures of physical functioning, and serum 25(OH) vitamin D measurements.
Results: Of 78 persons still alive, 70 participated (73 % women). The number of patients with normal BMD both at the hip (mean total hip) and in the lumbar spine (L1-L4) decreased from 56 (80 %) to 50 (71 %). The number of persons with osteoporosis increased from 2 to 6 (t-score ≤ -2,5 one or both sites), and the number of individuals with osteopenia from 12 to 14 (t-score -1,5 to -2,49 one or both sites) (Pearson Chi-Square < 0.001[KM1]).
Reduced ambulatory function was associated with osteopenia and osteoporosis (Pearson Chi-Square 0.005).
From 2008 to 2018 the proportion of participants with optimal 25(OH) vitamin D values (≥ 75 nmol/L) at the end of winter increased from 14 to 50%, and the proportion with insufficient levels (< 50 nmol/L) decreased from 36 to 19%.
Conclusions: Preliminary analyses show a statistically significant increase in the proportion of persons with osteopenia and osteoporosis over a 10-year period. Linear regression analysis will be applied to estimate the effects of known predictors of BMD. The proportion of patients with vitamin D levels considered optimal for persons with MS and bone health has increased.
Persons with MS should be routinely screened for osteoporosis.

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Sexual dysfunction in patients with multiple sclerosis: association with disability, anxiety, depression and fatigue

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Background: Sexual dysfunction (SD) has been reported in patients with multiple sclerosis (pwMS). However, in clinical practice SD is commonly underdiagnosed. The frequency of SD in pwMS, and its association with disability, anxiety, depression and fatigue has not been studied in Argentina so far. We aimed to assess SD frequency in pwMS and to investigate its association as possible associated risk factors.
Methods: A cross-sectional study (MS = 202 and healthy volunteers (HV) = 200, matched for sex and age) based on self-administered questionnaires such as Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19), The Hospital Anxiety and Depression Scale, Fatigue Severity Scale and Expanded Disability Status Scale (EDSS) was performed in pwMS. In addition, Female Sexual Function Index (FSFI) in women and International Index of Erectile Function (IIEF) in men were evaluated. Thus, we assessed the frequency of SD in pwMS and risk factors associated with SD in pwMS compared with HV.
Results: The frequency of primary, secondary and tertiary SD in pwMS was 81%, 87.3% and 75.2%, respectively. Both erectile dysfunction and female SD were significantly higher in pwMS than in HV (89% vs. 26% and 54% vs. 21%, respectively). Both males and females reported similar symptoms of SD. In addition, fatigue, anxiety and depression were significantly associated with pwMS in comparison with HV. Thirty (14%) pwMS had no sex at last 12 months. Only 45 (22.2%) pwMS had a discussion about sexual issues with their neurologist and 33 (16.3%) pwMS had counselling about sexual issues. Total MSISQ-19 scores were correlated significantly with fatigue (r 0.46), anxiety (r = 0.36), depression (r = 0.50), EDSS (r = 0.44), FSFI (r = - 0.57) and IIEF (r = - 0. 65).
Conclusion: SD frequency was very common among pwMS in Argentina. Physical and psychological factors previously mentioned have a negative impact on the sexual function. Therefore, an effective diagnosis and management for SD should be done in order to take actions to improve the quality of life of these patients.

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Quality of life and SR-fampridine in multiple sclerosis patients

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Background: Sustained-release fampridine (SR-fampridine), a potassium channel blocker, has been approved to improve walking in multiple sclerosis (MS) patients but also the performance of activities of daily living. Few data are available about its effects on quality of life (QoL) in MS patients.
Objective: To analyze the effect of SR-fampridine on quality of life in real-world setting in MS patients, its evolution and the influence of different clinical parameters.
Method: We performed an observational, prospective study of consecutive patients with MS that need SR-fampridine. Time 25 foot walk (T25FW) and MS walking scale-12 (MSWS-12) were done before and 14 days after the start of treatement. Quality of life of responders was evaluated by TLS-QoL10 at baseline, 1, 3 and 6 months after start of SR-fampridine. Clinical parameters like sex, age, EDSS, disease form and duration and walking time were collected and their impact on TLS-QoL10 score evolution was searched.
Result: We included 123 MS patients, 104 (84.55%) of which were responders and TLS-Qol 10 data were available in 92 responders (88.46%). In the responders group, 59.78% (55/92) of patients were women, 34.78% had a relapsing-remitting form of MS, 65.22% a progressive form (39.13% secondary and 26.08% primary). Mean EDSS of this group was 5.2 (+/-1.11) and mean disease duration was 194.84 months (+/-121.07). We observed a significant increase of QoL score over time of the study, due to an early increase as the first month of treatment (4.1 at baseline vs 5.4 at 1st month, p< 0.001), which remained at 6 months (6.2 at M3 and 6.4 at M6). This increase of TLS-QoL10 score was influenced by sex (women were more responder than men), age (increase was earlier in younger than older patients), disease form (patients with relapsing-remitting and secondary progressive form were more responder than those with primary progressive form). EDSS and improvement of walking time between baseline and J14 had no effect on TLS-QoL10 score.
Conclusion: The results of this study suggested that SR-fampridine may have an early positive effect on quality of life. These results were independent of the effect on walking scales.

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EP1376

Evolution of afferent trigeminal system involvement in patients with clinically isolated syndrome over two-year follow-up

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Introduction: It has been shown that the tongue somatosensory evoked potentials (tSSEP) are able to detect afferent trigeminal system involvement in people with clinically isolated syndrome (pwCIS), regardless of the MRI results. The aim of this study was to investigate the evolution of trigeminal afferent system involvement, measured by tSSEP, in pwCIS over the two-year follow-up.
Methods: 115 pwCIS (80 females, mean age 32.12±8.62, median EDSS 1 (0 - 3.5)) performed tSSEP at baseline and 75 after two-year follow-up. Latency of the component P1 and amplitude P1_N1 were analyzed. The tSSEP score was calculated from the raw tSSEP data according to cut-off values for absent response and prolonged latency of the main component, P1 (0 = normal response, 1 = prolonged latency, 2 = irregular morphology, 3 = absent response). It was calculated separately for the left (left tSSEP) and the right side (right tSSEP) and the two values were summed.
Results: Baseline median tSSEP score was 1 (range 0-6) (median left tSSEP score 0 (0-3) and median right tSSEP score 0 (0-3)). After two years, median tSSEP score was 3 (range 0-6) (median left tSSEP score 2 (0-3) and median right tSSEP score 2 (0-3)). This worsening of tSSEP score (including both right and left tSSEP score) after two-year follow-up was statistically significant, $p < 0.001$ ($p=0.004$ and $p=0.001$, respectively). Out of 75 patients with all data available for analysis, conduction block was present in 6 patients at baseline and 20 patients after two years on the right side ($p=0.004$), and 11 patients at baseline and 26 patients after two years on the left side ($p=0.003$).
Conclusion: Substantial proportion of pwCIS experience worsening of tSSEP over 24 months of follow-up.

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EP1377

Association between cognitive functions, balance, and walking in persons with multiple sclerosis with minimal disability

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Background: Balance and cognitive impairments are serious health concerns for persons with multiple sclerosis (MS, pwMS). Since majority of the studies have included pwMS with overt disability, association between cognition and balance in minimally disabled pwMS is not clear.
Aims: The aim was to investigate the association between cognitive functions and balance, fall risk, walking ability, balance confidence, depression and quality of life in pwMS with minimal disability using well-established measures and compare them with healthy controls (HC).
Methods: This study included 35 pwMS with the Expanded Disability Status Scale (EDSS) ≤ 3.0 and 39 HC. Cognitive functions were assessed using Brief International Cognitive Assessment for MS (BICAMS) that measures processing speed (Symbol Digit Modalities Test, SDMT), verbal (California Verbal Learning Test-2, CVLT2) and visuospatial (Brief Visuospatial Memory Test-Revised, BVMT-R) memory. Limits of stability (LOS- forward, backward, right, left, overall, test time), postural stability (PS- mediolateral, anteroposterior, overall) and fall risk (FR) were assessed with a posturography. The Brief-Balance Evaluation Systems Test (Brief-BESTest), Timed 25-Foot Walk Test (T25FW), 12-Item MS Walking Scale (MSWS-12), Activities-Specific Balance Confidence (ABC) Scale, Beck Depression Inventory (BDI), and MS International Quality of Life (MuSiQol) were also used.
Results: There were significant difference between the MS and HC in all domains of balance, gait and cognitive functions ($p < 0.05$). In MS group, SDMT was significantly correlated with the LOS test time, LOS overall, LOS posterior, PS overall, PS mediolateral, FR, Brief-BESTest, T25FW ($r=-0.370, 0.380, 0.460, -0.350, -0.397, -0.488, 0.463, -0.537$, $p < 0.05$). BVMT-R was significantly correlated with LOS test time, mediolateral PS, FR, Brief-BESTest, T25FW ($r=-0.409, -0.371, -0.494, 0.471, -0.359$, $p < 0.05$). CVLT was only correlated with Brief-BESTest total and biomechanical limitations sub-score ($r=0.389, 0.473$; $p=0.021, 0.004$). EDSS, MSWS-12, ABC, BDI, and MuSiQol were not correlated with BICAMS scores.
Conclusions: İnformation processing speed and visuospatial memory are highly associated with balance in minimally disabled pwMS independently of disability degree. Although Brief-BESTest was correlated with all cognitive domains including processing speed, verbal-auditory and visual memory, posturography was not correlated with the verbal-auditory memory.

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EP1378
Risk factors associated with falls in persons with multiple sclerosis: an observational study

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Falls are one of the common symptoms in persons with multiple sclerosis (pwMS). Since falls may result in decreased activity and participation and increased disability, it is important to determine risk factors, to develop outcome measures and to design fall prevention strategies. The purpose of this study is to identify risk factors for falls in pwMS.
Subjects who were definitely diagnosed with MS were included in the study. The outcome measures comprised Timed Up and Go Test (TUG) and TUG cognitive form, Single Leg Stance Test (SLST), the Timed 25-Foot Walk (T25FW), Six Minute Walk Test (6MWT), 12-Item Multiple Sclerosis Walking Scale (MSWS-12), Activities-Specific Balance Confidence Scale (ABC), Modified Fatigue Impact Scale (MFIS) and Brief International Cognitive Assessment for MS (BICAMS). The number of falls of the participants during the last 3 months was recorded.
In the study, 89 female and 32 male individuals with an average age of 35.29 ± 11.05 and an EDSS average of 1.20 ± 1.24 were included. A total of 118 falls were recorded from 39 participants (%32.23) who experienced falls. The duration of SLST, MSWS-12, MFIS and ABC were found to be significantly different between fallers and non-fallers ($p < 0.05$). Correlation was stated between SLST, 6MWT, MFIS, ABC and number of falls ($rs = -0.235$-0.388, $p > 0.05$).
Decrease in walking quality and balance confidence, balance impairments and increase in fatigue are risk factors associated with falls in pwMS. Approaches to these symptoms may be effective in reducing the rate and number of falls.

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EP1380
Physician- and patient-derived sources of error estimating prevalence of pseudobulbar affect in an academic multiple sclerosis referral center

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Introduction: Pseudobulbar affect (PBA) denotes involuntary laughter or crying disconnected from or incongruent with experienced emotion. In multiple sclerosis (MS), PBA results from disrupted limbic and paralimbic networks modulated by the cerebellum. Increased PBA recognition and available pharmacotherapeutics raise expectations that clinicians diagnose and treat PBA. However, prevalence estimates ranging from 3.0 to 46.2% suggest widespread ascertainment error.
Objectives: Determine prevalence of PBA in an academic MS center.
Methods: Consecutive patients with >6 months of MS followed in the University of Alabama MS clinic from 1 June through 30 September 2017 completed a one-time survey. PBA was

ascertained by physician impression and the subject-completed Center for Neurologic Study-Lability Scale (CNS-LS). Depression was determined by physician impression and the Patient Health Questionnaire-9 (PHQ9). Published cut-offs for scales dichotomized presence or absence of PBA and depression.
Prevalence rates of PBA and depression were calculated by physician impression and cut-offs for CNS-LS (>=13, 17, and 21) and PHQ9 (>=10). Correlations between diagnostic methods were assessed with chi-square, and associations between diagnoses, demographics, and MS disease characteristics were tested using chi-square or t-tests, as appropriate. All statistical analyses were performed using JMP 13.0.
Results: Seventy-four subjects completed surveys. Clinicians identified PBA in 2 subjects (2.7%) and depression in 33 (45.2%). Using the CNS-LS, PBA prevalence decreased with increasing cutoff score (>= 13: 39.2%; >= 17: 27.0%; >=21: 13.5%).
The PHQ9 identified depression in 28 subjects (39.2%). Agreement between clinician-perceived depression and PHQ9-criterion depression was 48.5%, while agreement between subject experienced depression and PHQ9 was higher at 58.6%. When subjects with depression by PHQ9 were excluded, PBA prevalence fell across all CNS-LS cutoffs (>=13: 18.9%; >=17: 9.5%; >=21: 5.4%).
Conclusions: Despite published criteria for PBA, consistent methods to recognize PBA remain elusive. Physicians diagnosed very little PBA in this cohort, possibly due to under-recognition, over-estimation by the CNS-LS, or greater attention paid to depression or other factors. Symptom overlap between PBA and depression may increase misdiagnosis. Communication with patients and contextual interpretation of scales are essential for diagnosing affective disorders in MS.

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EP1381

Reverse takotsubo cardiomyopathy in the setting of active multiple sclerosis lesion involving the medulla oblongata

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Background: Takotsubo cardiomyopathy (TTC) has been sporadically related to multiple sclerosis (MS) relapses involving the medulla oblongata. From a pathophysiological point of view, it is believed that the demyelinating brainstem lesions involve bulbar autonomic regulatory areas and lead to acute sympathetic pathway overactivation and subsequent massive release of catecholamines, triggering a transient myocardial stunning. The underlying mechanism remains however incompletely understood. To date, only 11 well-documented cases of TTC during MS exacerbations have been described.
Objective: To describe the case of a reverse TTC, a variant of classic TTC phenomenon, in the setting of acute brainstem MS relapse.
Results: A 30-year-old woman was diagnosed with relapsing-remitting MS in the beginning of March 2018 after she had a second clinical event requiring intravenous corticosteroids. Three weeks later, she presented to the *emergency department* with acute chest pain, palpitations and shortness of breath. She had hypoxemia and hypotension. Electrocardiogram showed repolarization abnormalities and atrial fibrillation with rapid ventricular response (150/min) but there was no ST-segment modification. Blood tests showed elevated serum troponin levels (peak value 6,71 ng/mL; N < 0,12). Echocardiography revealed a severe left ventricular dysfunction with decreased ejection fraction (20%; normal > 50%). Cardiac angiography demonstrated normal coronary arteries, but left ventriculography showed basal and midventricular akinesia with apical hyperkinesia, suggesting reverse TTC. Intensive care management was required. Extensive serologic workup for myocarditis was negative and urine catecholamine levels were normal. Neurological examination showed vertical nystagmus and cerebellar ataxia. Brain magnetic resonance imaging was performed and showed a newly formed acute MS lesion in the medulla oblongata with gadolinium-enhancement and also revealed 2 new left cerebellar lesions. The patient completed a seven-day course of high-dose intravenous corticosteroids (1000 mg/day). Cardiac dysfunction fully recovered in less than 3 weeks. The patient was tested negative for anti-JC virus antibodies and natalizumab was started.
Conclusion: Acute brainstem MS relapse should be considered in patients presenting with TTC, especially in the absence of other identifiable cause of acute heart failure occurring in young patients.

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EP1382

Management of multiple sclerosis - related trigeminal neuralgia in Italian centres

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Background: The prevalence of trigeminal neuralgia (TN) in the Multiple Sclerosis (MS) population has been reported to be between 1 and 6%, which is 20-fold higher than in the general population. To date, there is a lack of robust scientific evidence on the optimal medical/surgical treatment of patients.
Objective: Aim of the present Italian, cross-sectional, multicentre survey was to gather information on the current treatment modalities and options of MS-related TN across Italian MS centres.
Methods and Materials: Neurologists members of the RIREMS (Rising Researchers in MS) group were asked to fill out a questionnaire on the management of MS-related TN at their MS centre. Collected data included: medications prescribed at any time and as a first choice, availability of surgical options, number of patients with TN seen in the previous two years and proportion of these who had undergone surgery.
Results: Twenty-two MS centres completed the questionnaire. The median number of patients with TN per centre was 11 (interquartile range: 7-20), equal to 1.2% (0.8-2.8%) of all patients seen in the preceding two years. The most frequent first-choice symptomatic treatments were opioids (in 27% of centres), intravenous (27%) and oral (27%) steroids. First-choice preventive treatments were carbamazepine (in 77% of centres) and oxcarbazepine (23%). Carbamazepine was prescribed at least once by all centers, followed by pregabalin (96% of centres), gabapentin (91%) and oxcarbazepine (77%). A median of 24% (13-33%) of patients per center had undergone at least one surgical procedure and, of these, 27% underwent at least one repeat surgical procedure. Microvascular decompression was the most commonly available procedure (in 59% of centres), followed by percutaneous balloon compression (27%), glycerol rhizotomy (27%), radiofrequency thermocoagulation (27%) and gamma knife stereotactic radiosurgery (23%). Surgical procedures were unavailable in six centres (27%). TN pain exacerbations were considered MS relapses and treated with intravenous steroids by 52% of centres. Two centres (9%) use a visual analog scale to assess response to treatment.
Conclusion: Medical treatment approach to MS-related TN was fairly homogeneous throughout Italian centres, while the frequency and types of available surgical procedures, which were unavailable in almost one third of centers, varied considerably. None of the centers use pain scoring questionnaires to assess response to treatment.

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EP1383
Cognitive function as measured by SDMT is associated with employment status in an Australian MS cohort

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Background: A high proportion of MS patients display cognitive impairment impacting on their socioeconomic well-being. However, the direct relationship between cognitive status and quality of life and overall work productivity in MS still remains unclear. The objective of our study was to test for an association between cognitive function and employment status, work productivity and quality of life.
Methods: 52 MS participants (42 RRMS, 10 SPMS) and 49 age, sex and education matched, healthy controls (HC) were included. Cognitive status was evaluated using BICAMS battery and Audio Recorded Cognitive Screen (ARCS). Quality of life was assessed by applying the MSQOL-54 questionnaire and employment status and self-rated assessment of work productivity was determined using the WPAI general health questionnaire. Independent samples T tests were used to compare cognitive status, QOL physical and mental parameters, and for individuals currently employed, WPAI indices of work activity, absenteeism and presenteeism between MS and HC groups. The chi-square test was applied to determine differences in employment status between groups. Correlations between cognitive and employment status, work productivity and QOL test scores were then explored using Pearson's r tests.
Results: MS patients were 82% female, aged 49$\pm$2 years, with 53% reaching at least senior high school. MS patients had a mean EDSS 2.7$\pm$0.3 and disease duration of 11.3$\pm$1.3 years. Compared to the HC group, the MS cohort had significantly lower total ARCS, memory, fluency and attention scores and reduced performance on all BICAMS battery assessments ($p \leq 0.01$). Quality of life physical and mental status were lower in the MS group ($p \leq 0.0001$) by 24.5% and 20.2% respectively. The proportion of individuals employed in the MS group (57.1%) was lower than in HCs (79.6%) ($p=0.03$). Of those employed, work activity impairment, presenteeism and overall work impairment was increased by 2.4, 7.4 and 6.7 fold respectively, in the MS group ($p \leq 0.05$). While age was a predictor for employment status for both HC and MS, SDMT was the only predictor for employment status in the MS cohort, once all other factors were accounted for.
Conclusions: Despite an overall low EDSS, MS patients display a lower cognitive performance and quality of life than matched controls. Employment status seems to be linked to cognitive performance. Monitoring SDMT in MS patients is essential, as it predicts the ability to remain in the work force.

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EP1384
Factors related to restless leg syndrome in multiple sclerosis

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Restless Leg Syndrome (RLS) has been reported in people with multiple sclerosis (MS, pwMS) ranging from 12.12% to 57.5%. This ratio is 4 times higher than general populations. Dopaminergic dysfunction and spinal cord lesions may play a role in the presence of more RLS in pwMS. Patients with central dopaminergic dysfunction have difficulties in performing or initiating alternative movements.
The aim of this study is to evaluate the gait function, balance and MRI findings in MS with RLS.
In total, 299 pwMS were enrolled in this study. The diagnosis of RLS used the criteria defined by the International Restless Legs Syndrome Study Group. Walking function was assessed with 12-Item Multiple Sclerosis Walking Scale (MSWS-12), Timed 25-Foot Walk (T25FW), Timed Up and Go Test (TUG) and the 6 Minute Walk Test (6MWT), balance was assessed with Activity-Specific Balance Confidence Scale (ABC) and One Leg Stand Test (OLST). The presence of spinal cord lesion was determined by the neurologist.
The RLS was detected in 88 (29.43%) of the 299 pwMS who participated in the study. The MSWS-12 and ABC score was a significantly higher in participants with RLS than without RLS ($p < 0.05$). On the other hand, there was no significant difference between the participants with RLS and without RLS in terms of

performance-based outcome measures such as T25FW, TUG, 6MWT and OLST and presence of spinal cord lesion ($p > 0.05$).
This study has suggested that the pwMS with RLS have less perceived walking and balance ability compared to without RLS. However, the performance of a walking function, balance, and presence of spinal cord lesion was similar compared to pwMS without RLS. Although this lack of perceived does not affect the performance, early assessment and rehabilitation program for the lower extremities are important to prevent possible functional deficits in pwMS with RLS.

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EP1385

Fatigue and related factors in persons with multiple sclerosis

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Fatigue is the most commonly reported symptom in multiple sclerosis (MS) and is observed in 53-97% of people with MS (pwMS). The presence of fatigue lowers the quality of life and pwMS generally regard fatigue as the most disturbing symptom. Disease duration, disability level, number of attacks, sleep quality and depression levels may be associated with fatigue in pwMS.
The aim was to compare the duration of disease, level of disability, number of attacks, sleep quality and depression levels in pwMS with or without fatigue.
In total, 373 pwMS enrolled in this study. The levels of disability, sleepiness and depression were assessed with the Extended Disability Status Scale (EDSS), the Epworth Sleepiness Scale, and the Beck Depression Scale, respectively. The level of fatigue was assessed with the Modified Fatigue Impact Scale (MFIS) and 38 points for fatigue were considered cut-off values.
The fatigue was detected in 242 participants (64.88%).Duration of disease, disability level, number of attacks, daytime somnolence and depression levels were significantly higher in participants with fatigue than participants without fatigue ($p < 0.05$).
This study has suggested that pwMS with fatigue have more disease duration, disability level, number of attacks, daytime sleepiness and depression levels than without fatigue. While the evaluation and rehabilitation programs for fatigue are being organized, the duration of illness, disability level, number of attacks, sleep quality and depression levels should also be considered.

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EP1386

Speech profile of multiple sclerosis patients admitted to a neurorehabilitation unit

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Introduction: the language, voice, speech, breathing and swallowing disorders represents a group of pathologies few addressed in clinical multiple sclerosis (MS) studies.
Aim: To analyze speech disorders profile in a group of patients MS who are admitted to a neurorehabilitation unit (NRU) and its relationship with clinical parameters.
Methods: retrospective analysis of medical records of MS patients admitted into the NRU between 2010-2018. Were recorded: age, gender, EDSS scale, age at the beginning of the MS, years of MS evolution, presence and type of language, voice, speech, breathing and swallowing disorder and Functional Independence Measure (FIM) scale. A descriptive and correlational statistical analysis was performed using SPSS 19.
Results: of 172 MS admissions into the NRU, 64 were referred by the neurologist to speech therapist. 11 of them did not present speech pathology and 53 (30,81 %) had speech pathology. 60.4%, 35.8% and 3.8% were RR, SP and PP respectively; 67.9% women; average age: 46 ± 10 years, EDSS: 5.5 ± 1.5, years of evolution: 13 ± 8 years, age at the beginning of MS: 32 ± 10 years, FIM: 89.5 ± 22.9. Of the 53 evaluations performed (41 patients) the most frequent pathology was language disorder in 68%, followed by swallowing disorders (56.6%). The most frequent type of language disorder was the decrease in verbal fluency (86%). 86, 8% of evaluations showed more than one disorder. We found correlation between the total number of disorder in each patient with EDSS (r: 0.34, $p = 0.046$). We did not find correlation with years of evolution and FIM (r: -0.15, r: 0.14 respectively).
Conclusion: Given the high frequency of speech disorders, will be necessary to perform standardized evaluations to offer a comprehensive treatment to MS patients.

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EP1387

Benign multiple sclerosis patients display increased prevalence of sleep disorders

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Introduction: Benign multiple sclerosis (B-MS) patients display preserved somatic neurological functions but nevertheless other nervous system faculties such as cognitive functions may be impaired.
Objective: Our aim was to explore the status of sleep functions in B-MS.
Methods: Age, gender and disease duration-matched B-MS (EDSS < 3.0 more than 10 years after MS onset) (n=12) and non-benign MS (NB-MS, n=18) patients were recruited for evaluation of sleep functions. All patients were in the remission stage, using immunomodulating medications. None of the patients had received steroid treatment in the last 3 months. Detailed sleep history was obtained, Epworth Sleepiness Score (ESS) and Pittsburgh Sleep Quality Index (PSQI) were employed. Full night polysomnography (PSG) recordings were performed by two blinded sleep specialists. Sleep disorder prevalences were compared with chi-square test and PSG parameters were compared with Mann-Whitney U.
Results: Twenty (67%) MS patients (8 B-MS and 12 NB-MS; p>0.999) displayed multiple sleep disorders including obstructive sleep apnea syndrome (12), periodic limb movement disorder (8), restless legs syndrome (4), REM sleep behavior disorder (1) and insomnia (1). There were no significant differences among B-MS and NB-MS patients by means of ESS and PSQI scores, sleep efficiency index, sleep continuity index, sleep latency, rapid eye movement latency, duration of each sleep stage, oxygen saturation and periodic leg movements in sleep (PLMS) index.
Conclusions: Sleep disorder prevalence of B-MS patients is comparable to that of NB-MS patients, indicating involvement of sleep related brain regions in this MS subtype despite apparent preservation of motor, sensory and visual domains.

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EP1388

Tracking symptom impact in MS patients: longitudinal study of symptoMScreen scores in patients attending two large tertiary MS centers

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Background: Natural history studies in MS largely focused on determining time-to-disability benchmarks. Little is known about changes in MS symptom burden from patient's point of view. SymptoMScreen is an in-house developed and validated patient-reported outcome (PRO) tool for assessing symptom severity in 12 domains commonly affected by MS - walking, dexterity, spasticity, bodily pain, sensory, bladder, fatigue, vision, dizziness, cognitive, depression and anxiety. SymptoMScreen is collected on all patients at each visit in our MS Centers and can be used to track disease impact as perceived by the patient.
Objective: To report on longitudinal changes in total and domain SymptoMScreen scores in MS patients attending two tertiary MS centres.
Methods: SymptoMScreen is collected on all patients attending NYU or Barnabas MS Care Centers as part of routine clinical care. We retroactively analysed responses in our patients who were age 18 or older, had clinician-diagnosed MS (McDonald criteria) and fully completed 2 or more SyMS questionnaires over a period of ≥12 months.
Results: 594 MS patients (72.3% women) satisfied our inclusion criteria. At baseline, mean age was 44.1 (±12.3) and disease duration was 10.8 (±9.1). Follow up period was 16.7 (±3.7) months (range 12-38). Average disability at baseline, assessed by Patient-Determined Disease Steps (PDDS) was 1.9 (±2.0) (range 0 to 7; scores of 3 or more correspond to worsening ambulatory dysfunction and motor disability). PDDS at last follow up was 2.0 (±2.1) (range 0-7), an increase of 0.1 points, paired t-test p=0.012. Mean total SymptoMScreen score at baseline was 17.3 (±14.3), and at last follow up - 18.1 (±14.9), an increase of 0.7, paired t-test p=0.034. Domain SymptoMScreen significantly increased in bladder p< 0.001, hand p=0.044 and dizziness p=0.050 domains and did not significantly increase in the other domains. In a multivariable regression analysis with age, gender, time between assessments and baseline symptoMScreen, only baseline total SymptoMScreen was a significant predictor of the final total SymptoMScreen score.
Conclusions: Overall symptoms botheration, as assessed with multi-dimensional SymptoMScreen, has increased modestly but significantly over the period of observation of ~16 months, in parallel with increase in patient-rated disability score. Changes in SymptoMScreen domain scores varied across symptoms and were significant in bladder, dexterity and dizziness domains.

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EP1389

The effect of spasticity on the walking speed and quality of life in patients with multiple sclerosis

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Background: Spasticity is a common symptom in multiple sclerosis (MS) that limits the mobility of patients and worsens their quality of life. The aim of our study was to assess the effect of spasticity on the walking speed and quality of life of patients with MS.
Methods: The study was carried out at the Department of Neurology, University of Szeged.
The walking ability of consecutive MS patients at the MS Outpatient Unit of the Department was assessed with the Timed 25-Foot Walk Test (T25FWT) and the time needed to walk 500 meters (500MW), or the maximum possible distance with or without a walking aid was recorded. The validated Hungarian version of the Multiple Sclerosis Quality of Life Instrument (MSQoL-54) was given to the patients. Based on the neurological examination the EDSS and Asworth scores were determined and clinical and demographic data of the patients were collected. Those patients who were considered to have spasticity were additionally given the validated Hungarian version of the Multiple Sclerosis Spasticity Scale (MSSS-88) as well. Statistical analysis was performed with the SPSS 22.0 statistical software.
Results: 97 patients were tested. 77% are female, the mean age is 47.6±11.6 years, the mean duration of the disease is 11.8±6.8 years, the mean EDSS is 3.0±2.0. 90% have relapsing-remitting clinical form. 30 patients (31%) had any degree of spasticity. There was a significant negative correlation between MSQoL-54 overall quality of life and T25FWT (r= -0.226; p=0.037) and 500MW (r= -0.287; p=0.010): patients with higher walking speed had better quality of life. More spastic patients (as assessed by the limb with maximal Asworth point) walked more slowly both at the T25FWT (r=0.613; p< 0.001) and the 500MW (r=0.312; p=0.002). There was a significant negative correlation between spasticity and the overall quality of life: patients with higher Asworth points had worse quality of life (r= -0.313; p=0.007). When corrected with the EDSS points spastic patients still walked significantly slower than patients without spasticity: 25FWT 16.5±12.7 sec vs 7.1±2.1 sec (p=0.003), 500MW 538.2±230.6 sec vs 367.5±103,4 sec (p=0.027).
Conclusions: Spasticity slows down the walking speed of MS patients and has a negative effect on their quality of life. Therefore adequate assessment and treatment of spasticity should be a priority in daily clinical practice.

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EP1390

Predictors of long term disability progression in patients with relapsing remitting multiple sclerosis

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Introduction: Multiple sclerosis (MS) is a disease with complex and not fully understood etiology and pathogenesis. Regardless of the new trends in MS research over the past decade, the clinical parameters remain crucial for diagnosis, physical disability assessment, follow up and prognosis of the disease progression.
Aim: to find predictors of increased physical disability and secondary progression in patients with relapsing remitting MS (RRMS).
Material and methods: 75 patients with RRMS were followed for 10 years period after diagnosis of MS. All subjects were on immunomodulatory therapy. The sample included 50 women and 25 men, aged 32 ± 8.7 years during the onset of the disease. The patient´s demographic characteristics, the presence of co-morbidity, the type of symptoms during the first and second attack (afferent, efferent and combined), the presence of mono- and polysymptomatic manifestations, the intervals between the first symptoms and the MS diagnosis, as well as between first and second attack, were analyzed.
Results: The baseline EDSS was 1.5±0.48. Within the 10-year period, 31 of the patients reached EDSS≥ 4 and 45% of them experienced secondary progression (EDSS 6). Based on the decision tree, we defined categorical variables (gender, mono/polysymtomatic manifestation, afferent/efferent symptoms during 1-rst and 2-nd relapse) and continuous variables (age at MS onset, the above mentioned time intervals) as predictors of obtaining EDSS ≥4. Through calculation of the predictive parameters we established a prognostic score for physical disability progression. The established score had specificity 82%, sensitivity 65%, positive predictive value 71% and negative predictive value 77%.

Conclusion: our study showed that the course of MS can be predicted with good accuracy based on early clinical signs, age at the disease onset and patient's gender. The introduced score could help reaching the individual therapeutic approach by providing directions for choosing appropriate immunomodulatory therapy.

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EP1391

The effect of the decrease in walking distance and speed on the quality of life and activities of daily living in patients with multiple sclerosis

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Background: Walking impairment is an important clinical outcome measure for multiple sclerosis (MS). While the EDSS score is dependent on the maximum walking distance and the use of walking aids, it fails to consider the importance of walking speed. The aim of this study was to assess the effect of walking speed and distance on the activities of daily living (ADLs) and the quality of life of MS patients by using a newly developed Hungarian language ADL questionnaire for MS.
Methods: The study was carried out at the Department of Neurology, University of Szeged. The walking ability of consecutive MS patients at the MS Outpatient Unit of the Department was assessed with the Timed 25-Foot Walk Test (T25FWT) and the time needed to walk 500 meters (500MW), or the maximum possible distance with or without a walking aid was recorded. The validated Hungarian version of the Multiple Sclerosis Quality of Life Instrument (MSQoL-54) was given to the patients. We developed a questionnaire specifically for assessing the impact of MS on walking ability and speed and the effects of walking impairments on ADLs. We translated and adopted to Hungarian some of the questions from previously existing English language instruments. We also wrote additional questions. The resulting questionnaire includes 11 questions rated on a scale with five answer options and 7 questions requiring a 'Yes/No' response. Based on the neurological examination the EDSS scores were determined and clinical and demographic data of the patients were collected. Statistical analysis was performed with the SPSS 22.0 statistical software.
Results: 97 patients were tested. 77% are female, the mean age is 47.6±11.6 years, the mean disease duration is 11.8±6.8 years, the mean EDSS is 3.0±2.0. 90% have relapsing-remitting clinical form. There was a significant negative correlation between MSQoL-54 overall quality of life and T25FWT ($p=0.037$) and 500MW ($p=0.010$): patients with higher walking speed had better quality of life. Patients who walk slower had higher ADL scores (having more problems with ADLs): T25FWT ($r=0.432$, $p< 0.001$) and 500MW ($r=0.501$, $p< 0.001$). Patients who experience more problems with ADLs have worse quality of life: ADL and MSQoL-54 correlation ($r=-0.583$, $p< 0.001$).
Conclusions: There is a good correlation between the walking speed and the ADLs of patients with MS. By measuring the walking speed we have a quick method to evaluate the amount of problems they may have in their ADLs.

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EP1392

Sleep disorders sub-estimated during multiple sclerosis - study of a series of Algerian patients

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Introduction: Multiple sclerosis (MS) is an inflammatory autoimmune disease, a degenerative disorder of the central nervous system. In the literature, there are few original studies on sleep disorders and MS that rely on small groups of patients.
Objectives: To evaluate the prevalence of sleep disorders
Identify the most common disorders
Patients and methods: Our study is prospective .The data collected: demographic, clinical form, current disability appreciated by EDSS, current treatment (interferon) .The Epworth Sleepiness Scale Sleep Scale (ESS) was used to assess daytime sleepiness. .A questionnaire: for nocturnal sleep disorders
* 1st component: appreciated the difficulties to fall asleep (initial insomnia), waking up during the night (average insomnia), nightmares and behavioral problems during sleep, waking up early in the morning without falling asleep again (terminal insomnia)
* the second part included the symptoms of MS that affect sleep
Patients excluded from the study are those who are undergoing treatment or who are taking corticosteroid
Results: 254 patient patients were included in the study. Prevalence sleep disorders 52.7% .Avoid night-time sleep disorders terminal insomnia is more common (50.7%), followed by average insomnia (33%) and initial insomnia (28%) Epworth sleeping scale (ESS) sleep results of less than 8 in 84%, between 9 and 15 in 15%, greater than 15 in 0.7% Table III: No relationship between demographic variables The signs of MS that influenced sleep were pain (21%), spasticity (18%), and bladder disorders (11%).
Discussion: More than 50% of our patients complained of sleep disorders, a result similar to the data from the literature.

-The results of the Epworth Scale, lower and higher values have been noted by other authors.We did not find any relationship between sleep disorders and demographic factors. Some authors have suggested a higher prevalence among women.
-On our patients, sleep disorders did not depend on disability or clinical form.The majority of authors have not found such relationships. Signs of MS that influenced sleep are consistent with other studies. We found a lower prevalence of NST in patients treated with interferons. These problems are described among the side effects of the treatment.
Conclusion: Sleep disorders are a serious problem and deserve more attention in patients with MS. Polysomnography would be important to detect these long-unknown disorders

Disclosure
nothing to disclose

EP1393
Translation in "Arab" and "Moroccan dialect" adaptation and validation of the modified fatigue impact scale during multiple sclerosis

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Introduction: Fatigue is one of the symptoms not to be overlooked in multiple sclerosis (MS), it is now an integral part of management, although it remains poorly understood by the patient'sfamily and even medical professionals. Modified Fatigue Impact Scale (MFIS) is the most appropriate tool for assessing fatigue during MS. In our Arab and Moroccan socio-cultural context, the use of such a scale remains difficult or even impossible for the majority of patients in routine consultation and therefore results in an incomplete evaluation of the main complaint.
Study aims:
- Proposing a tool for evaluating fatigue during MS, translated, adapted and validated tothe Arab and Moroccan population.
- Assessing the prevalence of fatigue during MS in a Moroccan cohort.
Methods: Prospective cross-sectional study of patients followed since 1998 for MS according to the 2010 revised Mc Donald´s criteria. All patients < 60 years of age and exhibiting cognitive impairment or psychiatric disorders were excluded.
The MFIS was translated into Moroccan Arabic dialect by a representative commission of all ethnics. The understanding of the scale was evaluated by a simple questionnaire after each interview.
A statistical analysis will be done in correlation with the depression status of the patients, the degree of disability and disease progression.
Results: The preliminary results of this study are:
192 patients were evaluated among about 250 patients followed.
Mean age: 36.7 [23-70] with a sex ratio F/H of 1.8
RRMS: 63%; PR 30.9%; PP 6.2%
Average Expanded Disability Status Scale at 4.6;
Level of studies: illiterate 8.5% - primary education 18.3% - secondary education 35.2% - post graduate education38%.
Fatigue is present in 49.1% of cases and depression is present in 28.6%.
Conclusion: The authors offer, by this study, a translated, adapted and validated version of the MFISin the Moroccan population. This practical tool could improve the assessment of Arab and Moroccan MS patients.

Disclosure
Nothing to disclose

Clinical assessment tools

EP1394
Short-term effects of inpatient multidisciplinary rehabilitation in multiple sclerosis: clinical predictors from a large-scale, single-center study

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Background: Multidisciplinary rehabilitation (MDR) can be effective in improving functional recovery and quality of life (QoL) in persons with multiple sclerosis (pwMS). The identification of possible predictors of inpatient MDR efficacy on the short-term is important to optimize the access priority and to assess the cost/benefit profile of this intervention.
Materials and methods: We retrieved clinical charts of pwMS admitted to our Neurorehabilitation Unit from July,1st, 2011 to June, 30th, 2016. Subjects' demographics, disease duration, disease phenotype, modified Barthel Index (mBI), Expanded Disability Status Scale (EDSS), pain numerical rating score (NRS), types of intervention administered (motor, occupational, speech/swallowing, respiratory, cognitive, psychological) were collected in a single database. All clinical scales were rated at admission and discharge. Using a multivariate logistic regression analysis, we assessed whether clinical and demographics at baseline, as well as the number of interventions, were predictors of MDR effects. Improvement at discharge was defined as follows: for mBI an increase of at least 5 points, for EDSS a 1.0 decrease for baseline score ≤5.5 and 0.5 for baseline scores >5.5; for pain NRS any decrease.
Results: We collected data from 653 pwMS, with a median disease duration of 15 years. Most of pwMS had a progressive (52.5% secondary (SP) and 17.5% primary (PP)) and 30% had a relapsing-remitting (RR) disease course. At admission, median EDSS was 6.5 and mBI 63. At discharge, 65% and 22% of patients improved for mBI and EDSS, respectively, NRS decreased in 89% of them. mBI improvement was significantly associated with a disease duration shorter than 15 years and with access to psychological

counseling. EDSS improvement was associated with baseline EDSS scores higher than 6.5, disease duration shorter than 15 years, RR course, female gender and longer duration of the admission period. Pain NRS improvement was associated with higher scores at admission and psychological counseling.

Conclusions: Inpatient MDR improved autonomy in activities of daily living in the majority of admitted pwMS. The effect seems to be more pronounced in female subjects with shorter disease duration. More comprehensive scales and measures reflecting QoL changes are needed to capture the actual effectiveness of inpatient MDR.

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EP1395
Treatment burden in multiple sclerosis

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Background: Treatment burden refers to the workload healthcare imposes on patients. It can affect treatment adherence, quality of life (QoL) and reported outcomes. The Treatment Burden Questionnaire (TBQ) aims to assess TB for different medical conditions and under varying treatment contexts. The objective of this study was to assess treatment burden in Multiple Sclerosis (MS) patients.

Methods: A group of 33 MS patients completed the following questionnaires and scales: TBQ total and TBQ13, Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) , Symbol Digit Modalities Test (SDMT), Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Multiple Sclerosis International Quality of Life Questionnaire (MuSiQoL), Fatigue Severity Scale (FSS), MOS social support scale, Beck Depression Inventory (BDI), Moriski Medication adherence scale-4 (MMAS-4) and the Hospital Anxiety and Depression Scale (HADS). Agreement levels between patients and physicians were studied.

Results: 33 patients (20 females), aged 43.6+12 years, were evaluated. Patients with different clinical forms of MS (52.9 % RRMS, 17.6% SPMS, 23.5 % PPMS, 5.9 % CIS),and varying degrees of: disease duration (10+9.3 years); neurological status (EDSS mean 2.1 range 0-8) and/or type of disease-modifying treatment (injectable 26.5%, oral 26.4%, monoclonal antibodies 14.7% or none 32.4%) were included. Total number of pills/ injections (including symptomatic treatments) used per patient per day was 3.69+2.32. Presence of comorbidities was also assessed (11.8% were smokers, 15.2% had a BMI >30 and 41.1 % had at least one other vascular risk factor). Mean total TBQ was 38.7+26.2 and TBQ13 was 33+22.6. TBQ showed positive correlation with fatigue (TBQ total r=0.467, p 0.006) (TBQ13 r=0.512, p 0.002) and negative correlation with QoL (TBQtotal r=- 0.480, p 0.005) (TBQ13 r =-0.483, p 0.004). No correlation was observed with EDSS or any other scale.

Conclusions: In this preliminary study, the TBQ showed adequate correlation with QoL scales in MS patients. Although further validation is needed, TBQs may therefore be used as a patient report outcome, and thus contribute to more tailored drug prescription by physicians, taking into account not only efficacy and safety of available treatment modalities, but also degree of treatment burden associated to adherence.

Disclosure

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Dr Correale is a board member of Merck-Serono Argentina, Novartis Argentina, Genzyme LATAM, Genzyme global, Biogen-Idec LATAM, and Merck-Serono LATAM. He is part of the Steering Committee for the clinical trials of Ofatumumab (Novartis Global). Dr. Correale has received reimbursement for developing educational presentations for Merck-Serono Argentina, Merck-Serono LATAM, Biogen-Idec Argentina, Genzyme Argentina, Novartis Argentina, Novartis LATAM, Novartis Global, and TEVA Argentina as well as professional travel/accommodations stipends

EP1396
SCOPOUSEP: a predictive model for scoring the severity of relapses in multiple sclerosis

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Background: In multiple sclerosis (MS), severity and symptoms of relapses are highly variable and the residual disability is difficult to predict.
We aimed to develop a clinical-based model for predicting the risk of disease progression at six months post-relapse in MS patients.
Methods: For learning and internal validation, we used data of the COPOUSEP (« Corticothérapie Orale dans les Poussées de Sclérose en Plaques ») study. It consisted in 186 patients, aged 18 to 55, respecting the 2005 McDonald criteria and having an EDSS ≤ 5 at inclusion. The predictive outcome was defined as an increase of ≥1 point of EDSS six months after relapse. We studied the following prognostic factors: gender, age, disease duration and disease modifying therapy at relapse time, EDSS before and during the relapse, and symptoms of the relapse (motor, sensory dysfunction, visual or cerebellar impairment, cranial nerve dysfunction, bladder/bowels disorders, or cognitive impairment). We used a logistic regression with LASSO penalization to construct the model and Bootstrap Cross-validation for internal validation. The model was externally validated by using a cohort constituted by 174 patients followed in Bordeaux University Hospital.
Results: Patients experienced mostly sensory disturbances (74%) and motor dysfunction (39%). Six factors were retained to construct the SCOPOUSEP model ("SCOring des POUssées de Sclérose en Plaques"): age > 40 yo, an increase of EDSS at relapse time higher than 1.5 points, disease duration, EDSS higher to or equal than 1 point before relapse, proprioceptive ataxia and subjective sensory disorders. The model presented acceptable discriminative capacities for both the internal (AUC=0.82, CI95% from 0.72 to 0.91) and external (AUC=0.71, CI95% from 0.61 to 0.79) validations.
Conclusion: We developed and validated a simple predictive model to help neurologists to evaluate the severity of a relapse in daily practice as defined by the risk of progression 6 months after the relapse.

Disclosure

All : Nothing to disclose

EP1397

Validation study of the MS-COG-e scale at 60 seconds cut-off point. A new electronic and brief neuropsychological scale to detect cognitive impairment (CI) in patients with multiple sclerosis (MS)

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Introduction: Although CI is common in MS patients it is difficult to detect in clinical practice, and high sensitivity and specificity cognitive tests for diagnosis such as the Brief Repeatable Battery of Neuropsychological test (BRB-N), require the intervention of neuropsychologists or trained personnel. The MS-COG-e consisted of electronically-matched 10 pairs of pictograms and was developed as an easy-to-administer CI screening tool. The MS-COG-e assesses memory, speed of information processing, attention and frontal executive functions.
Objective: To validate an electronic and brief screening scale (MS-COG-e) for CI among MS patients.
Methods: Cross-sectional, observational study that included adult patients, diagnosed with MS (McDonald 2010), Expanded Disability Status Scale (EDSS) score ≤ 6.5, no relapses/corticosteroid treatment within last 2 months and no depression symptoms (according to the Beck Depression Inventory[BDI-II]). Patients completed on the same day (among others) the BRB-N ("gold-standard" for MS patients) and MS-COG-e (higher scores more CI): pictogram-score (0-10 matchings) and pictogram-time (0-600 seconds). The MS-COG-e feasibility, reliability test-retest (coefficient of intraclass correlation [IC]) and predictivity (receiver operating characteristic [ROC] curve) were assessed.
Results: 194 patients (59% female) were included from 3 Spanish centres: mean (standard deviation) age of 42(9) years, mean MS evolution of 10(7) years, 90% had relapsing-remitting MS, 86% had disease-modifying treatment and median (interquartile range) EDSS of 2.0 (1.0-3.5). According to BRB-N, 27% of patients had CI. All patients did the pictogram with pictogram-time ceiling effects only in CI patients. The IC and ROC curve were 0.09 and 0.57 for pictogram-score, and 0.48 and 0.71 for pictogram-time. At cut-off point ≥ 60 seconds reaches a sensitivity=0.75 and a specificity=0.51.
Conclusions: The MS-COG-e showed good psychometric properties and time to complete the pictogram had an acceptable diagnostic accuracy in patients with low disability (median EDSS=2). This easy and quick tool can help neurologists to identify CI in MS patients that should be further assessed by neuropsychologists to confirm CI diagnosis.

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ECG: Nothing to disclose in the elaboration of this study.
RHC: Nothing to disclose in the elaboration of this study.
EGM: Nothing to disclose in the elaboration of this study.
MCS: Nothing to disclose in the elaboration of this study.
ECA: Nothing to disclose in the elaboration of this study.
IC: Nothing to disclose in the elaboration of this study.
ASB: Nothing to disclose in the elaboration of this study.
TCT: Nothing to disclose in the elaboration of this study.
JMCM: Nothing to disclose in the elaboration of this study.
LFR: Nothing to disclose in the elaboration of this study.
JOU: Nothing to disclose in the elaboration of this study.

EP1398

Longitudinal assessment of upper limb function by an engineered glove reveals a deterioration not captured by the EDSS over 7 years in patients with multiple sclerosis

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Introduction: An engineered glove (Hand Test System, HTS) has been previously used to quantitatively measure impairment in finger movements in a cohort of patients with MS (pwMS), showing good cross-sectional correlations of upper limb impairment with clinical measures (EDSS and SDMT).
Objectives: To evaluate whether the HTS is able to detect a deterioration in upper limb function over a follow up period of 7 years in a group of patients with stable EDSS.
Methods: We re-evaluated the finger motor function in 17 pwMS with stable EDSS and 17 age-matched healthy controls (HC) after a mean follow up of 6.7 years (range 5.9-8.3 years). All the subjects performed 60-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),the inter-hand interval (IHI), and the number of correct sequences for each task. All the patients had a baseline clinical assessment by EDSS, Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT) and PASAT. Mann Whitney U test was used to compare HTS parameters changes between HC and pwMS and the Spearman correlation coefficient to assess correlations of baseline disease status with HTS parameters changes.
Results: The EDSS was stable over the follow up for all the included patients (mean age 43 years, disease duration 12 years, EDSS 2.3). As compared to HC pwMS had a decrease over follow up in the number of correct sequences when performing the task at maximal velocity (mean change: -1.5 in pwMS vs +4.0 in HC, p=0.038) and bimanually paced by a metronome (mean change: -3.5 in pwMS vs +4.1 in HC, p=0.002). There was no significantly different change between pwMS and HC in the RATE and in the IHI. In pwMS the change in the number of correct sequences obtained at maximal velocity significantly correlated with baseline EDSS (r=-0.60, p=0.01), while the change in the number of correct sequences obtained bimanually paced by a metronome correlated with baseline PASAT (r=0.47, p=0.05).
Conclusions: The sensor-engineered glove is a simple and quantitative device to assess upper limb function and it was able to detect a decline in upper limb function in patients with stable EDSS over a 7 years follow up period; this tool can represent a promising method to enrich the disability progression assessment in pwMS.

Disclosure

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Conflicts of Interest:
CL: received honoraria for travel expenses for attending meetings from Roche.
AS: received teaching honoraria from Novartis
LB, LN, FB: have nothing to disclose.
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EP1399

Social functioning with regard to impact of the disease in the patients with multiple sclerosis

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Disability due to multiple sclerosis (MS) may influence the patients´ psychosocial condition. The aim of the study was to assess social functioning of MS patients with regard to the disease-related variables.
The study comprised 200 MS patients (140 females, 60 males, aged 24-69 years), followed-up at the Department of Neurology. The data on MS course, current treatment and degree of disability (Expanded Disability Status Scale - EDSS) were obtained from medical records. The World Health Organization Disability Assessment Schedule (WHODAS) was used to assess disability impact upon social functioning; Beck Depression Inventory (BDI) - to evaluate depression. Self-administered questionnaire on demographics, major complaints and patients´ perception of treatment

was also applied. The results were statistically analyzed using general linear models.
Mean MS duration was 10.1 years, mean EDSS score - 3.15, 174 patients received disease-modifying treatment. Total WHODAS results for 32.8% of patients were between 75 and 90 ‰ and for 27.4% above 90 ‰ compared to the population norms. 34.8% of respondents had highest scores in "participation in society", 13.4% -"understanding and communicating" and 3.9% - "getting along with people" categories of WHODAS. According to BDI, 14.4% of patients had mild depression and 17.3% - moderate to severe one. Mobility problems, fatigue and visual deficit were most frequently reported as major complaints (39.8%, 23.9% and 17.4%, respectively).
Total or partial results of WHODAS did not show significant relationships with age, gender, MS duration, EDSS or treatment.
Total WHODAS result correlated significantly with BDI score ($p< 0.001$; β 0.73) and mobility problems as the major complaint ($p< 0.001$; β 0.25). WHODAS score in "participation in society" correlated with BDI score ($p< 0.001$, β 0.65) and mobility problems or headache and vertigo as major complaints ($p< 0.001$, β 0.26; $p=0.02$, β 0.13, respectively). WHODAS score in "understanding and communicating" correlated with BDI score ($p< 0.001$, β 0.56) and visual deficit and fatigue as major complaints ($p=0.006$, β 0.16, $p=0.017$, β 0.14, respectively)
The impact of MS substantially affects the patients´ social functioning, which is associated with increased risk for depression. Specific symptoms of neurological deficit influence social functioning more than general disease-related variables. These aspects deserve attention during individualized follow-up of the MS patients.

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EP1400
Validity and potential added value of multi-domain computerized cognitive assessment for patients with multiple sclerosis

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Background: The Minimal Assessment of Cognitive Function in MS (MACFIMS) is recommended for neuropsychological assessment of people with multiple sclerosis (PwMS). The need for a trained test supervisor and the difficult process to obtain normalized scores, are among the many obstacles for its widespread implementation.
Aim: To assess the construct, criterion and predictive validity of a computerized, multi-domain cognitive assessment battery (CAB, NeuroTrax) in MS.
Methods: Principle component factor analysis was used to assess construct validity. For criterion validity analysis the gold standard definition of cognitive impairment was a score of >=1.5SD below average on at least one cognitive domain, according to MACFIMS normative data. Logistic regression models were used to explore whether computerized cognitive scores can predict vocational disability among PwMS.
Results: 81 patients with MS (Age: 45 ± 8.1, Female: 59 (73%), EDSS: 4 ± 1.7) and 15 healthy controls (HC) completed both MACFIMS and CAB-NeuroTrax on the same day. Computerized cognitive scores of MS patients were significantly lower than those of HC for the memory, information processing speed (IPS), working memory, executive function, attention, visual spatial and motor domains. Traditional and computerized tests of memory, IPS, visual spatial and executive function converged by factor analysis. Computerized tests could detect cognitive impairment, as defined by MACFIMS, with 80% sensitivity and 73% specificity. PwMS with cognitive impairment detected only by the computerized battery had significantly slower reaction times and significantly higher rate of unemployment compared with those who were found normal by both batteries. Computerized tests predicted unemployment among PwMS, independent of depression and EDSS.
Conclusion: This specific computerized assessment battery is valid for cognitive screening of people with MS. PwMS with normal cognitive function by MACFIMS, but impaired by the computerized battery, had increased risk for unemployment and had slower reaction times, implying for improved sensitivity rather than poor specificity of the computerized battery. Multi-dimensional cognitive screening analysis has value in routine MS care.

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All authors have nothing to disclose

EP1401
Factors associated with falls in multiple sclerosis

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Background: Falls are common in patients with multiple sclerosis and cause injuries, affect self-confidence and mobility. It is important to recognize main risk factors and causes that could predict future falls.
Objective: to investigate demographic and clinical factors predisposing falls of the patients with multiple sclerosis and to compare these parameters in the fallers and non-fallers groups.

Methods: It was a prospective study of the patients with relapsing-remitting multiple sclerosis in remission with the disease modifying treatment and the Expanded Disability Status Scale (EDSS) < 6.5. Patients were asked to fill the original questionnaire about falls, numeric severity of fatigue scale; Hospital Anxiety and Depression Scale (HAD); Symbol Digit Modalities Test (SDMT). Patients were divided to fallers and non-fallers groups according to number of falls past 6 months. Demographic and clinical parameters were compared in these groups.
Results: We analyzed data from 69 patients. 21 (30,4%) of them fell one or more times past 6 months and were included in the fallers group, 48 (69,6%) haven't fell and were included to non-fallers group. Groups were similar by age (p= 0,469), gender (p=0,378) and disease duration (p=0,527). Mean of falls was 3,57±0,62. Falls were severe for 9 patients (42,9% of fallers) with trauma (bruises, fractures, sprains). Significant higher disability status was found for the fallers (EDSS for the fallers 3,6±1,45, the non-fallers 2,37±1,13 (p=0,001)). Self-reported numeric severity of fatigue scale difference was not found (p=0,692). Significantly higher HAD score was found in the fallers group (anxiety for the fallers 11,05±11,36, the non-fallers 6±3,82; p=0,005; depression for the fallers 8,24±12,27, the non-fallers 3,58±3,16, p=0,006). Cognitive status using SDMT didn't differ (p=0,097). We found significant odds ratio (OR) for falls using binary logistic regression, considering to variables significantly predicting falls in one-dimentional analysis (HAD depression score >4,5 OR 5,394[1,313-22,157], EDSS>2,25 OR 5,265[1,603-17,29]; Anxiety score >7,5 OR 4,64 [1,42-15,14], EDSS>2,25, OR 6,78 [1,66-27,67])
Conclusion: More than one quarter of patient suffered falls past 6 months. We found significant difference in disability status, anxiety and depression levels that could increase risk of falls.

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EP1402

Upper limb function in MS: correlation between instrumental and clinical scale

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Background: Unlike lower limb dysfunction in MS, there are no validated, self-administered scale and normative data, that assess different dimensions for upper limb functions.
Materials and methods: The main aim of this study is to create a set normative data for both objective and subjective scores; correlate upper limb function scales' scores with subjective scales' score.
183 patients has been enrolled: 125 F/58 M; mean age: 47,18 years; mean EDSS: 4.05; mean disease duration: 14,12 years; 117 RRMS, 47 SPMS, 18 PPMS. They were evaluated using: Hand grip strength; 9 HOLE PEG TEST (HPT); Box and block (BB); MAM-36; DASH.
Results: The results obtained has been (mean): MAM36 (0-100): 72.77; DASH (0-100): 28.52; MFIS (Physical): 16.76; MFIS (Cognitive): 11.61; MFIS (Psychosocial): 3.09; MFIS (Total): 31.46; HAND-GRIP (r): 39.86; HAND-GRIP (l): 36.86; BB(r): 45.75 BB(l): 44.93; 9HPT (right): 27.93; 9HPT (left): 30.88.
Correlation between upper-extremity function tests (* p< .05 ** p< .01**)** BBleft vs right: 0.88**; 9HPT(Right) vs BB(right): -.47**; 9HPT(Right) vs BB(left): -.38**; 9HPT(left) vs BB(right): -.35**; 9HPT(left) vs BB(left): -.41**; 9HPT(left) vs BB(right): .63**; HAND-GRIP (Right) vs BB(Right): .09; HAND-GRIP (Right) vs BB(left) -.01; HAND-GRIP (Right) vs 9 HPT(Right): -.06; HAND-GRIP (Right) vs 9 HPT(Left): 0.01; HAND-GRIP (Left) vs BB(Right): 0.01; HAND-GRIP (Left) vs BB(Left): .03; 9 HPT(Right) vs HAND-GRIP (Left): .04; HAND-GRIP (Left) vs 9 HPT(Left): -.06; HAND-GRIP (Left) vs HAND-GRIP (Right): .85**.
Discussion and conclusion: In conclusion, we found:
- A strong inter-correlation between right and left hand scores for BB, 9HPT and hand-grip
- A moderate negative correlation between BB and 9HPT, but not a correlation with Hand-grip score.
- A strong negative correlation between MAM-36 and DASH scores: both scores shows moderate-to-strong correlations with MFIS variables
- A moderate correlation between DASH and MAM36 with BB and 9HPT, while correlation with hand-grip was small

Disclosure

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EP1403

Pilot Study of Telemedicine in multiple sclerosis to evaluate the effectiveness of a telecommunication system for the detection of the clinical activity of the disease in the number of relapses with respect to the standard clinical practice. TELEM

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Introduction: Telemedicine is a method to provide health care services at a distant site.The objective of this study was to measure the ability of telemedicine to detect relapses in patients with Multiple Sclerosis (MS). The second aim was to observe the difference between patients with cognitive impairment and cognitive preservation.
Methods: 130 patients under treatment with first-line drugs for MS who had the computer skills to access to a web platform created by this study were recruited. The patients had to answer surveys about their clinical status and were randomized in two groups: survey (intervention) and non-survey (control). Also, three visits were made during the study: the basal visit, visit 6 and visit 12 months. All patients fulfilled questionnaires of mood, health, satisfaction with health services and adherence to treatment. They performed the Multiple Sclerosis Functional Composite (MSFC), and the Expanded Disability Status Scale (EDSS). The cognitive status was estimated using two tests for cognitive ability measurement: the Symbol Digit Modalities Test (SDMT) and the Paced Auditory Serial Addition Test (PASAT) and a classification was done: cognitive impairment/ suspected impairment/ cognitive preservation.
Results: The sensitivity of the platform survey was 100% and the specificity 96.5%. Both groups were equivalent in all the analyzed features, with the exception of the EDSS, which was significantly higher in the intervention group than in the control group (mean 0 vs. 1). There were no more relapses in the survey/intervention group (average 0 vs. 0). Patients with cognitive impairment had a worse mood at the beginning of the study and were less satisfied with the health services received than the cognitively preserved, but they showed the same adherence as them.
Conclusions: Telemedicine can be a useful tool in detecting relapses in MS patients and cognition is an important factor in health and mood of patients with multiple sclerosis.

Disclosure

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EP1404

Coping in multiple sclerosis: qualitative analysis of themes

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Background: Foundational qualitative work with people with Multiple Sclerosis (pwMS), for the Trajectories of Outcomes in Neurological Conditions study, confirmed the influence of coping on quality of life. Pilot quantitative work used the Coping Orientations to Problems Experienced (COPE60) scale, but cognitive debriefing showed that pwMS felt that the wording of the items lacked validity. MS was perceived as different from any previous challenge they had experienced and to their perception, they were drawing on unfamiliar strategies in order to reduce the stress of living with MS.
Objective: To identify the concepts and domains relevant to coping in MS.
Method: One-to-one interviews were done with a wide range of pwMS, transcribed and subjected to thematic analysis, until no new themes emerged.
Results: Saturation of themes was achieved by 43 interviews. Participants were mostly female (62.8%), age range 20-75 years, illness duration 0.5-45 years, with a range of disability as measured by EDSS; 16 (37%) had relapsing, 13 (30%) primary progressive and 14 (33%) secondary progressive disease.
Participants felt MS posed a unique stressor as it is incurable, long-term and the future course cannot be predicted. Coping required acceptance, whether to unexpected relapses or inexorable progression. PwMS talked about the importance of activity to assist with coping, by continuing normal activities and interests, although that might require pacing, flexibility and a stepwise approach. They sought some aspect of their life they felt they could preserve despite their MS, this might be tangible like a hobby or a personal characteristic like religious belief.
PwMS stressed the importance of maintaining an optimistic, determined and self-reliant attitude. To achieve this, they cited a range of strategies, such as 'looking on the bright side', comparing themselves positively to others with MS, reframing, or remembering past successes to boost confidence. Humour was used to defuse the stress of coping with MS.
In practical terms, some pwMS found social support from family, friends, other pwMS and professionals useful for coping. They occasionally used information-seeking, alternative therapies or meditation.
Conclusion: PwMS feel that MS requires them to develop new coping capacities and they use a range of strategies such as acceptance, activity, and cultivating a positive mindset. These themes are reported by pwMS throughout the disease course.

Disclosure

Young CA, Ando H and Cousins R declare no conflicts of interest for this work. The TONiC study was supported by unrestricted grant support from NIHR, MNDA, Walton Neuroscience Charity, Biogen, Genzyme, Merck, Novartis, Roche, Teva.

EP1405

Fatigue, patient reported outcomes, and sleep apnea in people with multiple sclerosis: perception is insufficient to just sleep on it

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Background: Fatigue is a common and disabling symptom in people with MS (PwMS). Presence and degree of fatigue in PwMS primarily relies on patient self-reported outcomes (PRO). PRO fatigue, sleep disturbance/OSA may be unreliable. Prior studies utilizing polysomnography (PSG) to evaluate fatigue in a population of PwMS are typically limited by the small patient sample size, limiting characterization of the spectrum of sleep disorders. Epworth Sleepiness Scale (ESS) is commonly used to

screen for the presence of sleep disorders (ESS>10) and the FSS has been utilized to screen PwMS for the presence of high fatigue (FSS>36). The presence of OSA is defined by PSG (Apnea-Hypopnea Index (AHI) ≥5). The relationship of these PRO in PwMS with the presence or absence of OSA PwMS who report fatigue has not been explored.
Objective: To explore the relationship of both FSS and ESS in PwMS who report fatigue to PSG identified obstructive sleep apnea (OSA).
Methods: Retrospective analysis of PwMS who reported fatigue, and were not previously diagnosed as having OSA, and who agreed to have overnight PSG studies.
Results: 292 PwMS (average age 47.3 ± 10.7 years, 81.4% female). 61% (n=177) of PwMS had PSG OSA (AHI ≥5). Of these, 55% had ESS≤10 and 45% had ESS>10 (n=95). OSA severity (None: AHI< 4.9, Mild: 5< AHI< 19.9, Moderate: 20< AHI< 39.9, Severe: AHI>40) relationship to ESS score revealed: 24% ESS≤10 and 20% with ESS>10 had no OSA; 46% ESS≤10 and 44% with ESS>10 had mild OSA; 19% ESS≤10 and 17% with ESS>10 had moderate OSA; and 11% ESS≤10 and 20% with ESS>10 had severe OSA. Of the 61% PwMS with OSA: 18% FSS< 36 and 82% had FSS≥36 (n=148). However, when the OSA severity and FSS scores are explored along a continuum: 46% FSS< 36 and 43% with FSS≥36 had no OSA; 29% FSS< 36 and 37% with FSS≥36 had mild OSA; 18% FSS< 36 and 12% with FSS≥36 had moderate OSA, and 7% FSS< 36 and 9% with FSS≥36 had severe OSA.
Conclusions: PRO investigation in PwMS by either/both FSS and ESS are insufficient to predict the presence of PSG documented OSA in PwMS. Overnight PSG is required to identify the presence and degree of OSA in PwMS. Since fatigue related to OSA is treatable, a high index of suspicion for OSA in PwMS who report fatigue should be present regardless of the FSS or ESS scores. Comprehensive evaluation of all factors potentially contributing to fatigue in PwMS, is warranted so that appropriate treatment intervention can be addressed.

Disclosure

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EP1406
Multiple sclerosis and EDSS: a closer inspection of the Walking Scale finds erratic walking

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Background: Disease burden in people with Multiple Sclerosis (PwMS) is traditionally quantified by EDSS. A digital gait-mat (Gaitrite) quantifies multiple gait dimensions including: base of support (BoS), stride length (StrL), step length(StpL), double support(DS), single support(SS), and a global score (Functional Ambulation Profile-FAP). A 20% change in velocity is defined significant despite variability within EDSS groups. Use of comprehensive analytics could identify disability prior to critical progression thresholds being passed. Defining the window of opportunity to intervene prior to the appearance of disability might improve MS care.
Objective: Explore the relationship of objective gait domains for preferred waking speed (PWS) within homologous EDSS groups in PwMS.
Methods: Cross sectional retrospective analysis of PwMS who underwent computerized gait analysis in the course of routine care, EDSS < 6.5. EDSS scores were grouped: 0-2.5 (low). 3-4.5 (medium), and 5-6.5 (high). Mean (M), standard deviation (SD) and percent variability (coefficient of variation) were calculated for each EDSS group for FAP, BoS, StrL, StpL, DS, SS.
Results: 255 PwMS, 72% female, age range 46+/-10 years. Gait domain values and variability within the EDSS were identified: EDSS 0-2.5 *FAP:*94.38M, 8.23SD, 8.73%, EDSS *3-4.5*: FAP:82.53M, 16.75SD, 20.30%, EDSS *5-6.5 FAP:*58.03M, 16.24SD, 28.19%; EDSS 0-2.5 *BoS:*10.76M, 3.74SD, 34.81%, EDSS *3-4.5 BoS:*13.66M, 4.56SD, 33.34%, EDSS *5-.6.5 BoS:*11.93M, 4.67SD, 39.46%; EDSS 0-2.5 *StrL:*130.59M, 18.03SD, 13.81%, EDSS *3-4.5 StrL:*107.98M, 23.41SD, 21.68%, EDSS*5-6.5 StrL:*81.21M, 23.61SD, 29.28%. EDSS 0-2.5 *StpL:* 64.88M, 9.02SD, 13.91%, EDSS *3-4.5 StpL:*53.66M, 11.71SD, 21.82%, EDSS *5-6.5 StpL:*39.90M, 10.89SD, 27.49%; EDSS 0-2.5 SS:36.80M, 2.85SD, 7.74%, EDSS *3-4.5 SS:*34.13M, 2.76SD, 8.07%, EDSS *5-6.5 SS:*28.69M, 9.79SD, 34.37%; EDSS *0-2.5 DS:*26.76M, 5.06SD, 18.90%, EDSS *3-4.5 DS:*31.85M, 5.45SD, 17.13%, and EDSS *5-6.5 DS:*44.83M, 17.13SD, 25.57%.
Conclusion: Quantified gait abnormalities in PwMS demonstrate variability within EDSS groups; the degree of variability in some homologous groups were >20%. The degree of variability increased across EDSS groups, and with increasing disability suggests that groups of "homologous" physical disability within the EDSS are not homologous. Patient centric quantified analysis of disease impact/change might improve choice/timing of treatment interventions.

Disclosure

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EP1407

Assessment of cognitive function in early stages of multiple sclerosis. Validation of BICAMS in Norway

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Background: Cognitive dysfunction is well-documented in the early stages of multiple sclerosis. The frequency varies between 20 % - 65 % across different studies. In a Norwegian project we aim to validate the Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS) in a sample of MS patients diagnosed in 2014-2016, with onset of symptoms no more than 3 years previous to diagnosis. We aim to establish BICAMS as a screening tool to identify patients in need of intervention and/or adaptation regarding work or school.

Method: Processing speed, verbal and visual memory are cognitive functions known to be affected in MS patients, assessed in BICAMS by Symbol Digit Modality Test (SDMT), the learning part of both California Verbal Learning Test (CVLT-II) and Brief Visuospatial Memory Test-Revised (BVMT-R), respectively. Fatigue, depression and anxiety are assessed by self-reports on the Fatigue Scale for Motor and Cognitive Functions (FSMC) and the Hospital Anxiety and Depression Scale (HADS) prior to testing. In addition, the 9HPT, T25FW and a full neurological exam are performed to evaluate physical symptoms and EDSS-score. Healthy controls are tested with BICAMS and complete the HADS. Demographical data regarding employment and education are reported by the participants.

Results: Altogether 68 patients (44 female, 24 male, mean age 37) and 58 healthy controls (41 female, 17 male, mean age 38) were tested with BICAMS at baseline. A total of 31 healthy controls were randomly selected for retesting after 7-36 days (mean interval 19.5 days) after baseline. Both SDMT and BVMT-R achieved good test-retest reliability with r= 0.79 and r= 0.71, respectively. The CVLT achieved an adequate r-value of 0.67. The MS-patients showed a statistically significant difference compared to controls for CVLT (p=0.003) and BVMT-R (p= 0.022), but not for SDMT (p=0.778). With cognitive deficit defined as a test result lower than 1.5 standard deviations below the mean for the control group, 30.9 % of the patients show signs of cognitive deficit according to CVLT-II. Correspondingly 22.1 % were identified by BVMT-R and 10.3 % by SDMT.

Conclusion: The BICAMS seems to be a reliable test battery for screening cognitive deficit in Norwegian MS-patients. The results regarding the SDMT indicate that this may be the weakest part of this battery in contrast to other studies. Further analysis of data and validation procedures are ongoing.

Disclosure

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- KM. Myhr has participated on scientific advisory, boards for Novartis Norway, Biogen and, Sanofi-Genzyme; received funding for travel from Teva; received speaker honoraria from Sanofi-Genzyme, Novartis, Merck, Biogen and Roche; and received unrestricted research support from, Sanofi-Genzyme, Novartis and Biogen.
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EP1408

A preliminary investigation into the relationship between the Multiple Sclerosis Walking Scale (MSWS-12) and an objective multi-dimensional digital gait analysis

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Objective: Explore the relationship of MSWS-12, a patient-reported outcome (PRO) of walking ability in people with Multiple Sclerosis (PwMS), to an objective multi-dimensional gait analysis.

Background: MS commonly impacts ambulation. Disease impact/progression is commonly measured by PRO, EDSS, adaptive devices or MRI. Quantifying subtle important disease variability not captured by traditional approaches that represent critical thresholds/reserve of progression maybe important to improve clinical decision making to optimize disease modifying therapy choice. Improved objective multi-dimensional metrics could address an unmet need to identify treatment needs contributing to an ability/disability continuum.

Methods: Retrospective analysis of PwMS who completed both MSWS-12 and GAITRite, in the course of routine care, each within 6 months. Multivariate regression modeling was used to analyze the relationships between MSWS-12 and 15 objective digital gait domains (DGD).

Results: 16 PwMS (50% female, average age = 55.7±10.8) completed testing. DGD correlations were: 80% (12/15) high-strength ($r \geq 0.50$) with MSWS-12 including- base of support (r=0.69, p< 0.01), stride-length (right r=0.71, p< 0.01; left r=0.71, p< 0.01) legs, step-length (right r=0.69, P< 0.01; left r=0.73, p< 0.01) legs, % gait-cycle double-support (r=0.66, p< 0.01), % gait-cycle single-leg support (right r=0.54, p< 0.05; left r=0.72, p< 0.01), leg-stance (right r=0.58, p< 0.05; left r=0.55, p< 0.05), cycle-time (r=0.55, p< 0.05), step-time (right r=0.60, p< 0.05; left r=0.57, p< 0.05), step-time differential (r=0.50, p< 0.10), cadence (r=0.50, p< 0.10), mean normalized velocity (r=0.66, p< 0.01), and functional ambulation profile score (r=0.67, p< 0.01); 7% (2/15) medium strength ($0.30 \leq r \leq 0.49$) including- swing-time (right r=0.35, p< 0.20, left r=0.42, p< 0.15) legs; and 7% (2/15) were low strength ($r \leq 0.29$) including- cycle-time differential (r=0.04, p>0.85), step-length differential (r=0.23, p>0.25).

Conclusions: Multiple unique important and quantifiable objective gait domains underlie ambulatory function and defines PRO

centric walking ability/disability. A PRO scale is insufficient to provide such quantitative granular objective patient-centric data as obtained by objective, multi-dimensional approaches to identify/define disease impact/change.

Disclosure

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EP1409

Making precision medicine work at the bedside without a universal health record: the MS BioScreen experience

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Background: There is high enthusiasm for creating precision medicine tools to deliver more effective and personalized care for multiple sclerosis (MS). A plethora of tools and devices (often commercially-driven) are available but with unproven effectiveness. Further challenges, in the USA, include insurance and privacy regulations limiting the integration of these data in healthcare settings. To tackle these challenges, the UCSF MS BioScreen was created in 2014. Since then, technological and regulatory changes and user experience feedback, have substantially refined its scope.
Objective: To qualitatively describe the iterative testing and refinement of an innovative digital health tool within diverse and specific healthcare settings.
Methods: The original tablet-based BioScreen was developed to track, visualize, contextualize, predict and improve MS course. In an iterative process, we (1) tested feasibility and efficacy of deploying this tablet-based tool vs. usual care in 100 UCSF MS Center patient visits; (2) performed >75 interviews with stakeholders (patients, support groups, clinicians, scientists, MS societies, healthcare leaders, pharmaceutical and technology companies) to evaluate use cases; then (3) partnered with healthcare, institutional, governmental and non-profit stakeholders to develop next versions of the BioScreen.
Results: There was strong stakeholder enthusiasm for the BioScreen. Patients and clinicians prioritized integration at the point of care, leading the BioScreen to target three distinct populations. In the diverse N. Californian Sutter Health system, MS-Share launches from the EPIC EMR, and focuses on delivery of comprehensive care. Within the academic UCSF MS Center, the BioScreen launches from EPIC and pulls both EMR data and advanced metrics from research environments. For patients outside these health systems, the Open MS Bioscreen is a free online tool that can function as an MS-specific portable medical chart.
Conclusions: We describe the adaptation of BioScreen to varying clinical settings and unfolding regulatory requirements, illustrating both the challenges and opportunities in deploying precision medicine tools at the point of care. Future studies will focus on the tool's impact on care value.

Disclosure

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AL works for Alan.
CB, JBJ, WFS work for Sutter.
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EP1410

Validation of the Spanish version of the Treatment Burden Questionnaire in multiple sclerosis patients

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Background: Treatment burden (TB) refers to the workload imposed by healthcare on patients and its effect on quality of life (Qol). The Treatment Burden Questionnaire (TBQ) aims to assess TB under varying conditions and treatment contexts. In this study, we evaluated the validity and reliability of a Spanish version of the TBQ for use in MS patients.
Method: The TBQ was translated into Spanish applying a forward-backward translation method. Wording and possible exclusion of items were assessed during a pretest by two focus groups and during semi-structured interviews. A sample including 162 heterogeneous MS patients completed the TBQ. A subgroup of 33 patients also completed the following tests: Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite, Symbol Digit Modalities Test, Brief International Cognitive Assessment for Multiple Sclerosis, Multiple Sclerosis International Quality of Life Questionnaire, Fatigue Severity Scale, MOS social

support scale, Beck Depression Inventory, Moriski Medication adherence scale-4 and Hospital Anxiety and Depression Scale.
Results: A final pretest version of the TBQ was obtained following 2 focus group sessions and 25 interviews including 38 MS patients (25 females), aged 42.7 ± 7.9 years, EDSS 2.1 (range 0-8[1] [2]). After approval by original authors of the questionnaire, a new item was added as a result of uncertainty over complementary study results, which emerged as an additional burden. 162 randomly selected MS patients answered the modified version. Following statistical analysis, items relating to self-monitoring, dietary changes and physical activity were eliminated due to poor factorial load. Results of Confirmatory Factor Analysis supported a 3-factor structure: 1) burden related to pharmacological treatment, 2) comprehensive health assistance; and 3) psycho-social-economic context. Composite reliability was > 0.8 for all factors. Total TBQ and modified TBQ13 results showed positive correlation with fatigue (TBQ total r=0.467, p 0.006) (TBQ13 r=0.512, p 0.002) and negative correlation with Qol (TBQtotal r=- 0.480, p 0.005)(TBQ13 r =-0.483, p 0.004). No correlation with EDSS or other scales was observed.
Conclusions: We found the Spanish language version of the modified TBQ to be a reliable instrument, and provide evidence of its use in assessing treatment burden in Spanish-speaking MS patients.

Disclosure

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Dr Correale is a board member of Merck-Serono Argentina, Novartis Argentina, Genzyme LATAM, Genzyme global, Biogen-Idec LATAM, and Merck-Serono LATAM. He is part of the Steering Committee for the clinical trials of Ofatumumab (Novartis Global). Dr. Correale has received reimbursement for developing educational presentations for Merck-Serono Argentina, Merck-Serono LATAM, Biogen-Idec Argentina, Genzyme Argentina, Novartis Argentina, Novartis LATAM, Novartis Global, and TEVA Argentina as well as professional travel/accommodations stipends

EP1411

Reliability and validity of the activities-specific Balance Confidence scale and Fall Efficacy Scale-International in Iranian patients with multiple sclerosis

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Background: Falls are a prominent problem in people with multiple sclerosis (MS) which involve more than 50 percent of people during any six months period. Balance impairment and fear of falling are two common risk factors for falls. Therefore, there is a need for developing the valid and reliable clinically feasible tools to assess these risk factors and identify individuals at increased risk for falls. The aim of this study was to examine reliability and validity of the Activities-specific Balance Confidence scale (ABC) and Fall Efficacy Scale-International (FES-I) in Iranian patients with MS.
Method: 128 people with MS were enrolled in this study and completed the Persian version of ABC, FES-I, Multiple Sclerosis Walking Scale-12 (MSWS-12), and Berg Balance Scale (BBS) questioners in the test session. To assess the test-retest reliability, 47 people filled out the Persian version of ABC, and FES-I in the retest session with an interval of 2-7 days.
Results: the Intraclass Correlation Coefficients (ICC) for test-retest reliability were 0.96 and 0.92 and Cronbach's alpha coefficient for internal consistency were 0.98 and 0.96 for ABC and FES-I, respectively. Correlation analyses showed a significantly positive correlation (p < 0.001) between ABC and BBS(r=0.55), and FES-I and MSWS-12 (r=0.72). While there were a significantly negative correlation between ABC and MSWS-12 (r=0.70), and FES-I and BBS (r=0.56).
Conclusion: The Persian version of ABC and FES-I are reliable and valid measures to quantify balance confidence and fear of falling in people with MS in both clinical and research setting.
Keywords: Activities-specific Balance Confidence scale (ABC), Fall Efficacy Scale-International (FES-I), Multiple Sclerosis, Reliability, Validity

Disclosure

nothing to disclose

EP1412

Evaluation of changes in cognitive function as assessed by NeuroTrax in patients with multiple sclerosis treated with natalizumab for up to 5 years

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Introduction: Cognitive impairment affects many patients with multiple sclerosis (MS). In a previous analysis using NeuroTrax to assess cognitive changes from baseline to 2 years in

patients initiating natalizumab, patients demonstrated a significant improvement (mean change from baseline in global cognitive score [GCS], 3.4; *P*=0.003; N=52), and 32.7% of patients demonstrated clinically significant improvement in GCS (previously defined as an increase from baseline >1 standard deviation [SD]) at year 2.
Objectives: Evaluate changes in cognitive function assessed using NeuroTrax in patients on natalizumab treatment for up to 5 years.
Methods: This retrospective study included adult MS patients in the United States who received natalizumab for 1-5 years. The primary endpoint was the longitudinal change in NeuroTrax GCS from year 1 to 5; additional endpoints included GCS change from year 1 to year 2, 3, or 4 and changes in the 7 individual cognitive domain scores. All mean changes from year 1 to year 2, 3, 4, or 5 were evaluated in patients with data available in both years.
Results: NeuroTrax GCS data were available for 84 patients at year 1; of these, 51, 40, 45, and 42 patients also had data at years 2, 3, 4, and 5, respectively. Mean (SD) GCS was 97.19 (13.95) at year 1, 100.74 (11.833) at year 2, 98.11 (13.177) at year 3, 100.90 (14.139) at year 4, and 98.32 (17.23) at year 5. Mean change from year 1 to year 5 was 2.48 (95% CI: -0.90-5.86; *P*=0.146; n=42). Mean change in GCS from year 1 to years 2, 3, and 4 were 2.23 (95% CI: 0.21-4.25; *P*=0.031; n=51), 2.71 (95% CI: 0.07-5.35; *P*=0.045; n=40), and 1.66 (95% CI: -0.10-3.41; *P*=0.064; n=45). In the individual cognitive domains, the greatest increases from year 1 to year 5 were observed in the visual, information processing speed, and executive function domains (mean [95% CI] changes from year 1: 7.16 [2.92-11.39], 3.60 [-0.55-7.74], and 3.43 [-0.48-7.34], respectively).
Conclusions: These results provide information on cognitive function during long-term natalizumab treatment (up to 5 years) and extend previous analyses showing clinically significant cognitive function improvement upon natalizumab initiation.

Disclosure

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EP1413
Rapid foot-tapping but not hand-tapping ability distinguishes between multiple sclerosis subtypes

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Background: Over 80% of people with relapsing-remitting or non-progressive multiple sclerosis (MS) transition into progressive multiple sclerosis, but the triggers for this transition in subtypes are unclear, and the diagnosis is made retrospectively. Therefore, there is a need to identify clinical measures that can distinguish non-progressive MS from progressive MS. Rapid successive movements such as tapping are useful markers of central motor function as they require intact corticospinal and cerebellar control. Prior research has shown that foot tapping speed is slowed in MS and other central nervous system disorders.
Objective: We investigated whether rapid hand- or foot-tapping ability can distinguish progressive and non-progressive MS subtypes.
Methods: 31 people with non-progressive MS and with 31 people with progressive MS, as well as 31 age-matched non-MS controls participated in this study. Participants wore extrinsic inertial sensors that measured angular velocity on the foot and the hand. Participants were instructed to tap as fast as possible for 10 seconds. Taps were identified as ascending zero-crossings of angular velocity using a custom MATLAB program. We obtained the average tap count across 6 trials for the right and left extremity for both the foot and the hand.
Results: Average foot tap count was significantly greater in controls than in non-progressive MS ($p< 0.001$, 95% confidence interval (CI) for difference in means =[4.9, 13.1]) and in progressive MS ($p< 0.001$, CI=[12.6, 19.4]). In addition, average foot tap count was significantly greater in non-progressive MS than in progressive MS (p=0.0038, CI=[2.4, 11.6]). The average hand tapping count was significantly greater in controls than in non-progressive MS ($p< 0.001$, CI=[3.9, 11.9]) and in progressive MS ($p< 0.001$, CI=[5.7, 13.5]), but did not differ between the non-progressive and progressive MS-subtypes (p=0.4889, CI=[-3.2, 6.7]).
Conclusions: Average foot tap counts can be used to distinguish between controls and MS groups, as well as between MS subtypes. In contrast, while hand-tapping speed was slower in both MS groups compared to controls, this task did not distinguish the MS subtypes. These results suggest that rapid motor coordination may be affected differently in the upper and lower extremities in MS, and that foot-tapping may be better suited to differentiate between MS subtypes and potentially a useful tool in studies designed to track progression of motor function in MS.

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EP1414

Evolution of dysautonomia in patients with clinically isolated syndrome over two-year follow-up

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Introduction: The Composite Autonomic Scoring Scale (CASS) has been validated for assessment of dysautonomia in people with clinically isolated syndrome (pwCIS). The aim of this study was to investigate the evolution of dysautonomia in pwCIS over two-year follow-up.
Methods: 121 pwCIS (85 females, mean age 32.15±8.74, median EDSS 1 (0 - 3.5)) performed CASS at baseline and 84 after two-year follow-up. The CASS is s further divided into three indices - adrenergic, cardiovagal and sudomotor. Adrenergic index (AI) is calculated from blood pressure responses to the Valsalva maneuver and tilt table test, cardiovagal index (CI) from respiratory sinus arrhythmia (RSA) and Valsavla ratio (VR), and sudomotor index (SI) using quantitative sudomotor axon reflex test (QSART).
Results: Baseline median CASS was 1 (0-6) (AI 0 (0-3), CI 0 (0-2) and SI 0 (0-3)). At M24, median CASS was 1 (0-5) (AI 0 (0-3), CI 0 (0-1) and SI 0 (0-3)). There was no difference in CASS, AI and CI at baseline and after two years (p=0.119, p=0.335 and p=1.000, respectively). However, RSA was significantly lower after two years (23.6±8.1 vs 21.7±8.0, p=0.01), while there was no difference in VR (p=0.467). Significantly more patients developed pathological QSART response after two years on the forearm, distal lower leg and foot (p=0.001, p=0.002 and p=0.001, respectively).
Conclusion: While there is no significant change in sympathetic adrenergic and parasympathetic function in pwCIS, substantial proportion of pwCIS experience worsening of sudomotor function over 24 months of follow-up.

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EP1415

Do you exercise regularly? Psychometric analysis of a single question for assessing physical activity in people with multiple sclerosis

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Although benefits of regular physical activity (PA) in people with multiple sclerosis (pwMS) are well known, evidence suggests that pwMS have inadequate PA levels. For this reason, it is extremely important to measure PA in clinical practice. Although there are many questionnaires and technological approaches to assess PA, these methods are not always practical in a busy practice. The aim was to determine the psychometric properties of a simple single question to assess PA in pwMS.
The data of 355 pwMS were investigated in this retrospective study. Physical disability levels were assessed using the Expanded Disability Status Scale (EDSS). Regular exercise habits were questioned with a single question "Do you exercise regularly?" with response options "Yes" and "No". Additionally, the Godin Leisure-Time Exercise Questionnaire (GLTEQ) was used to assess PA levels. Participants with a GLTEQ score of 24 and above were classified as active, while those below 24 were classified as insufficiently active. Beck Depression Inventory (BDI), Modified Fatigue Impact Scale (MFIS), Timed Up and Go (TUG), Timed 25-Foot Walk (T25FW), and Nine-Hole Peg Test (9HPT) were used in addition to the GLTEQ to assess validity. The specificity and sensitivity of the single question method according to the GLTEQ were also calculated.
There was no significant difference in age, gender, EDSS score and disease duration among the participants who answered "Yes" (28.7%) and "No" (71.3%) in the single question (p>0.05). BDI (p=0.002), MFIS (p< 0.001), TUG (p=0.011), and T25FW (p=0.04) scores of "Yes" responders were significantly better than the "No" responders. There was no significant difference between the scores of dominant and non-dominant 9HPT between the two groups (p=0.862 and 0.597, respectively). According to GLTEQ score, 75.8% of participants had insufficient PA level. The specificity and sensitivity of the single question was calculated as 83.3% (95% Confidence Interval (CI): 78.3-87.5%) and 66.3% (95% CI: 55.3-76.1%), respectively.
The results showed that the single question has adequate concurrent, convergent and discriminant validity to assess PA levels in pwMS. It was also found that the single question has adequate specificity to detect pwMS with insufficient PA level. A single question such as "Do you exercise regularly?" is thought to be a psychometrically adequate measure in intensive clinical practice for referring pwMS to more advanced tests and interventions for PA.

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EP1416

Value of the MoCA test to detect cognitive impairment in MS patients without subjective cognitive complaints

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Background: Although cognitive deficits are frequent in MS, screening for them with tools such as the Montreal Cognitive Assessment (MoCA) test is usually not performed unless there is a subjective complaint. The Multiple Sclerosis Neuropsychological

Questionnaire (MSNQ) is among the instruments most commonly used to assess subjective complaints in MS. Nonetheless, the MSNQ (patient version) does not always accurately reflect cognitive status; many patients with cognitive deficits thus fail to receive appropriate referral for detailed neuropsychological evaluation.
Objective: The objective of this study was to examine the validity of the MoCA test to detect the presence of objective cognitive deficits as assessed by the Minimal Assessment of Cognitive Function in MS (MACFIMS) among MS patients without subjective complaints.
Methods: The MSNQ-P (patient form) was used to select patients without subjective cognitive complaints (score ≤ 24). The sample included 98 patients (80.6% female, mean age 49.6±11.4 years) who completed the MACFIMS, the MoCA test and the MSNQ-P and MSNQ-I (informant form). Failure (z score < -1.5) of two or more tests on the MACFIMS was the criterion used to define the presence of cognitive impairment.
Results: Cognitive impairment was observed in 23.5% of the patients. With a cut-off score of 27, ROC curve analysis (AUC = 0.815; $p < .001$, YJ = 0.550) yielded a sensitivity of 87% and a specificity of 68% for the MoCA test, which supports its validity to discriminate patients that are cognitively impaired from those that are cognitively intact. The MoCA test was significantly correlated with the MSNQ-I ($r = -.246$, $p = .017$), but not with the MSNQ-P ($r = .075$, $p = .462$).
Conclusion: Despite the absence of subjective complaint, MS patients should be screened for cognitive impairment, given its known impact on professional and personal life. The validity of the MoCA test to properly classify non-complaining MS patients with or without cognitive impairment confirmed by the MACFIMS adds to the interest of using this instrument more systematically in clinical practice during follow-up appointments. This rapid screening test could be used to target patients for whom a more detailed neuropsychological assessment would be recommended.

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EP1417

Timely intervention, monitoring and education MATTERS in multiple sclerosis (TIME MATTERS in MS): developing a globally applicable quality improvement tool

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Introduction: The multiple sclerosis (MS) community has widely endorsed the concept that minimizing delays in care pathways maximizes lifelong brain health.[1] Recently, an international group of MS neurologists has agreed global quality standards for timely care.[2] These new benchmarks - formulated as a quality improvement (QI) tool - will enable MS service improvement.
Objectives: To develop a QI tool, based on previously agreed standards, for MS care teams to evaluate their service.
Methods: MS healthcare professionals on the MS Brain Health Steering Committee collaborated with a clinical trial specialist to develop a globally applicable QI tool. The content was derived from the standards for acceptable, good and high-quality brain health-focused MS care.[2] A pilot study is being conducted in selected countries to test clinical usability in different healthcare systems.
Results: The prototype QI tool has worksheets for data input, analysis and report. The data input worksheet requires the inputting of dates of procedures and events in the care pathway, and answers to binary (yes/no) questions. Embedded formulae compute 26 time intervals, compare data to the quality standards (acceptable, good or high), and generate summary reports.
The aim of the initial pilot study is to identify changes needed prior to a larger pilot study of approximately 250 patient records (at representative stages of the care pathway) at several international sites.
Conclusions: We developed a QI tool enabling MS clinics to compare their services against international quality standards for timely, brain health-focused MS care. Future work will focus on testing and refining the tool, before making it available to MS clinics worldwide.

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EP1418

Upper limb function in MS: creation of a normative data set on subjective and objective measures and the construction of an MS-specific assessment tool

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Background: There are no validated, self-administered scale that assess dimensions for upper limb functions. Proximal and distal strength may be rated using a dynamometer, although normative data are not available.

Objectives: Developing: a set of normative data for both objective and subjective measures of upper limb function and a self-administered MS-specific scale.

Methods:

Phase 1

A literature review confirmed that there is no specific measure. The panel identified 4 scales used in other neurological conditions: Manual Ability Measure (MAM-36), Disabilities of The Arm, Shoulder and Hand (DASH), Motor Activity Long (MAL)

Phase 2

Translation and adaptation of scales (MAM-36, DASH, MAL):

- the questionnaire has been fulfilled by 5 MS patients followed by second expert meeting
- the final version has been tested in the final sample

183 patients enrolled: 125 F/58 M; mean age: 47,18 years; mean EDSS: 4.05. They were evaluated using: hand-grip; 9Hole Peg Test (9HPT); Box and Block (BB); MAM-36; DASH.

Results:

Correlation between upper-extremity function tests (* p< .05 ** p< .01**)** BB left vs right: 0.88**; 9HPT(Right) vs BB(right): -.47**; 9HPT(Right) vs BB(left): -.38**; 9HPT(left) vs BB(right): -.35**; 9HPT(left) vs BB(left): -.41**; 9HPT(left) vs BB(right): .63**; HAND-GRIP (Right) vs BB(Right): .09; HAND-GRIP (Right) vs BB(left) -.01; HAND-GRIP (Right) vs 9 HPT(Right): -.06; HAND-GRIP (Right) vs 9 HPT(Left): 0.01; HAND-GRIP (Left) vs BB(Right): 0.01; HAND-GRIP (Left) vs BB(Left): .03; 9 HPT(Right) vs HAND-GRIP (Left): .04; HAND-GRIP (Left) vs 9 HPT(Left): -.06; HAND-GRIP (Left) vs HAND-GRIP (Right): .85**.

Discussion and conclusion: In conclusion, we found:

- A strong inter-correlation between right and left hand scores for BB, 9HPT and hand-grip
- A moderate negative correlation between BB and 9HPT (both hands), but not a correlation with hand-grip score.
- A strong negative correlation between MAM-36 and DASH and a moderate correlation of both with BB and 9HPT

Disclosure

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EP1419

Hope in multiple sclerosis: qualitative analysis of concepts and domains

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Background: The Trajectories of Outcomes in Neurological Conditions study began with qualitative work with people with Multiple Sclerosis (pwMS) to identify factors which they believed influential for quality of life. These interviews and focus groups identified *Hope* as an important factor. However, cognitive debriefing of the Herth Hope Index-12 revealed that it lacked face validity for pwMS. We conducted a thematic analysis of Hope in pwMS as a foundation step to developing an MS-specific Hope Index.

Objective: To identify the concepts and domains relevant to Hope in MS.

Method: One-to-one interviews were done with a wide range of pwMS, transcribed and subjected to thematic analysis, until no new themes emerged. The resulting domains were compared to the literature.

Results: Saturation of themes was achieved by 43 interviews. Participants were mostly female (62.8%), age range 20-75 years, illness duration 0.5-45 years, with a range of disability as measured by EDSS; 16 (37%) had relapsing, 13 (30%) primary progressive and 14 (33%) secondary progressive disease.

Hope was conceptualised as involving a better future state, achieving which involved both motivation and activity. Participants varied considerably in whether they believed they still could aspire to a better future state; this was not reflective of illness duration or disability. The motivation to work towards future goals varied, for some the unpredictability of outcome in MS left them feeling demotivated and fatalistic, whereas others saw the variability of outcome as confirmation that it was worth them trying. PwMS modified their path to the aspired state according to the effects of their MS, and they valued professional advice on their plans.
Conclusion: Hope for pwMS has three components: acknowledging the possibility of a desirable future state (goals), being motivated to aspire to it (agency) and making an action plan (pathways). This is in keeping with earlier work which defined Hope as "a positive motivational state that is based on … successful (a) agency (goal-directed energy), and (b) pathways (planning to meet goals)"[1].
[1] Snyder CR, Irving L, Anderson J (1991). Hope and health: Measuring the will and the ways. In Handbook of Social and Clinical Psychology (p 287).

Disclosure

Young CA, Ando H and Cousins R declare no conflicts of interest for this work. The TONiC study was supported by unrestricted grant support from NIHR, MNDA, Walton Neuroscience Charity, Biogen, Genzyme, Merck, Novartis, Roche, Teva.

EP1420

Multi-domain analysis of cognitive impairment in people with multiple sclerosis (PwMS): relationship of the number of cognitive domains impaired (#CDI) to visual evoked potential latency (VEP-L)

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Background: PwMS frequently experience cognitive impairment and fatigue as well as visual difficulty, all of which can be disabling. Cognitive impairment can result in disability distinct from physical disability. Disease activity is frequently evaluated by reported relapse rate, or identified changes in EDSS or MRI. None of these metrics is sufficient to quantify/track subtle but critical cognitive or visual impact/change in PwMS if not apparent to patient/examiner/MRI. We have previously reported a relationship between the number of cognitive domains impaired (#CDI) and increasing economically important disability (employment, driving, and fall risk) as well as measureable MRI volumetric changes. Cognitive impairment, as measured by individual cognitive domains, and cognitive fatigue have also both noted to track with Visual Evoked Potential Latency (VEP-L). However, individual cognitive domain scores might not reflect multi-domain cognitive network "efficiency" whereas # CDI and VEP-L together might reflect such a link that can be tracked concurrently in routine care. A potential relationship might explain "cognitive fatigue" on the basis of increasing "cognitive network failure".
Objective: To explore the relationship between #CDI to VEP-L (unilaterally, and interocular latency difference).
Methods: PwMS completed standardized validated computerized cognitive testing and underwent VEP-L recording in the course of routine care. Spearman correlations were utilized to examine the relationship of VEP-L (continuous and categorical) with #CDI.
Results: 435 PwMS (age 45.7+/-10.4, 74% female). Sequential average prolongation of each eye (OD, OS) individual VEP-L tracked with an increasing # CDI (0-3+) with a significant Spearman's rank-order correlation ($p < .001$, $p=.002$) while Inter-Ocular VEP-L did not demonstrate a similar significant relationship.
Conclusion: The number of cognitive domains impaired is related to VEP-L but not to inter-ocular latency difference. Accumulation of CDI coupled with concomitant progressive increase in VEP-L might indicate that cognitive fatigue reflects increasing cognitive network failure as the basis for this "fatigue". Multi-dimensional objective monitoring of disease impact/change in PwMS might provide earlier identification of increasing cognitive disability and cognitive fatigue.

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EP1421

Investigation into the relationship between digital brain volume and computerized screening assessment of cognitive function in people with multiple sclerosis: objective analytics to quantify disease impact

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Background: Multiple Sclerosis (MS) impact/progression is traditionally quantified by subjective and objective data including: patient reported outcomes (PRO), reported relapse rate, EDSS and visualized MRI changes. Disability in people with MS (PwMS) can occur by use of delayed/ineffective therapies or other factors. No Evidence of Disease Activity (NEDA) is a treatment desire to maintain ability in PwMS. Use of traditional metrics might be insufficient to provide multidimensional information that is patient centric along a continuum of disability to measure critical milestones of change by current monitoring approaches. Incorporation of both a computerized multidimensional cognitive screening battery (CAB) and analysis of MRI identification of disease impact might provide important information that can impact treatment. The cross-sectional relationship of CAB to digital analysis of brain volume in PwMS has not been established.
Objective: To examine the relationship between digitized brain volume and computerized multi-domain cognitive screening battery in people with MS.
Methods: Retrospective review of PwMS who underwent both a validated multi-domain computerized cognitive screening battery (CAB-NeuroTrax) and MRI digital measurements (Icometrix) of whole brain volume (WBV) and FLAIR white matter (WM) hyper-intensity volume in routine care. CAB-Neurotrax analysis included: memory (Mem), executive function (Exe), attention (Attn), visual spatial (Vis-Spat), verbal function (Ver), and information processing (Inf-Pro), Global Cognitive Summary Score (GCS), as well as the number of Cognitive Domains Impaired #CDI) >1 standard deviation from age/education controls. Linear regression analysis was used to test the significance, which was set at $p< 0.05$.
Results: 127 PwMS, 72.8% female, average age 51.18 +/- 10.6. Significant relationships were identified: WBV and GCS (p=0.0025), Mem (p=0.0087), Exe (p=0.0107), Verb (p=0.0003), and #CDI (p=0.0059). FLAIR WM Hyper-intensity Volume and GCS (p=0.0034), Mem (p=0.0546), Exe (p=0.0404), Vis-Spat (p=0.0454), Ver (p=0.0045), Inf-Pro (0.0215), and #CDI (p=0.0092).
Conclusion: In PwMS digital measures of brain volume are related to computerized screening assessment of multiple cognitive domains. This quantified objective analytic approach adds examiner independent information about disease impact in a way that can supplement/improve the sensitivity of current approaches to evaluation of disease impact/progression.

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WVH- Employee at Icometrix

EP1422

Investigation into the relationship between patient reported disease severity (MSIS-29) and a multi-domain objective computerized screening cognitive analysis aattery in people with multiple sclerosis

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Background: Disease burden/progression in people with Multiple Sclerosis (PwMS) is traditionally measured by reported relapse, EDSS and MRI change. Multiple Sclerosis Impact Scale (MSIS-29) is a patient reported outcome (PRO) that provides patient perspective about disease impact globally, as well as by subscale (physical, cognitive). PwMS frequently experience cognitive impairment but measurements of cognitive impact are not commonly included in routine care. If cognitive impact is usually measured through unidimensional outcome measures, such as SDMT. Use of a multi-domain screening cognitive assessment battery (NeuroTrax, CAB-NT) provides rich quantitative patient centric information. The relationship of the MSIS-29 and CAB-NT in PwMS has not been explored.
Objective: To examine the relationship in PwMS between MSIS-29 scores with CAB-NT outcome measures
Methods: Retrospective cross-sectional review of PwMS who completed both MSIS-29 and CAB-NT in routine care. MSIS-29 scores included: global score, and physical and cognitive subscores. CAB-NT included 7 cognitive domains global cognitive summary score (GCS), memory (Mem), executive function (Exe), attention (Att), information processing speed (Inf), verbal function (Ver) and motor skills (Mot). Multivariate regression analysis was used to analyze these potential relationships. Significance was set at $p< 0.05$.
Results: 244 PwMS, average age 50 +/- 11.7, 47% female. Significant relationships were identified: **MSIS-29 global scores** and GCS (r=0.34, $p< 0.05$), Mem (r=0.19, $p< 0.05$), Exe (r=0.38, $p< 0.05$), Att (r=0.26, $p< 0.05$), Inf (r=0.22, $p< 0.05$), Ver (r=0.21, $p< 0.05$), and Mot (r=0.37, $p< 0.05$); **MSIS-29 physical score** and GCS (r=0.36, $p< 0.05$), Mem (r=0.20, $p< 0.05$), Exe (r=0.41, $p< 0.05$), Att (r=0.29, $p< 0.05$), Inf (r=0.22, $p< 0.05$), Vis (r=0.15, $p< 0.05$), Ver (r=0.23, $p< 0.05$), and Mot (r=0.39, $p< 0.05$): **MSIS-29 cognitive score** and GCS (r=0.26, $p< 0.05$), Mem (r=0.16, $p< 0.05$), Exe (r=0.30, $p< 0.05$), Att (r=0.23, $p< 0.05$), Inf (r=0.21, $p< 0.05$), Ver (r=0.18, $p< 0.05$), and Mot (r=0.30, $p< 0.05$).
Conclusions: Self-reported MSIS-29 scores, whether reflecting global or physical or cognitive sub-scores are related to individual cognitive domain scores in PwMS. Perception of disease impact

in PwMS must be related to objective analysis of disease impact to better understand both their perceptions and the basis of these perceptions so that appropriate/effective treatment choices/changes can be made.

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EP1424

Reliability, validity and responsiveness of the timed 360° turn test in multiple sclerosis

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Introduction: Falls are the one of the most disabling features of Multiple Sclerosis (MS), affecting nearly half of patients and decreasing quality of life. Injuries due to falls during turnings are more commonly shown than during straight forward. Therefore, it is important to understand turning performance in patients with MS to predict the risk of falling.
Objectives: To investigate the concurrent validity, reliability, responsiveness and discriminant ability of the timed 360^0 turn test for patients with MS.
Methods: Forty-three patients with MS (mean age 37.6 years), Expanded Disability Status Scale (EDSS) ≤6.5, were recruited. The test-retest reliability was assessed in 35 patients both more affected and less affected side. Validity was assessed by correlating the timed 360^0 turn test with other outcome measurements EDSS, Berg Balance Scale, Timed Up and Go Test, one-leg stance test and four square step test. Responsiveness calculated using the minimal detectable change (MDC), reflecting actual patient change, not measurement error.
Results: Test-retest reliability of the timed 360° turn test was excellent for more affected and less affected side ($ICC_{2,1}$=0.958, $ICC_{2,1}$=0.966, respectively). The timed 360^0 turn test correlated significantly with other outcome measurements for more affected and less affected side (ranged from 0.721 to 0.855, ranged from 0.770 to 0.865, $p< 0.001$; respectively), indicating good concurrent validity. MDC of 1.53 seconds was found for patients turning toward the more affected side and 0.47 seconds for patients turning toward the less affected side.
Conclusions: The timed 360^0 turn test appears to be a reliable, valid and responsiveness measurement for assessing turning ability in patients with MS. The MDC values may help clinicians and researchers interpret the change scores more accurately.

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EP1425

A new test for the measuring balance in multiple sclerosis: psychometric evaluation of the Static Balance Test

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Introduction: Impaired balance is hallmark and disabling in patients with Multiple Sclerosis (MS). Therefore, quick, inexpensive and not time consuming tests for balance in patients with MS are needed.
Objectives: To evaluate the concurrent validity, reliability, responsiveness and discriminant ability of the Static Balance Test (SBT) for patients with MS.
Methods: Forty-three patients with (MS), (aged 37.6±11.6 years and Expanded Disability Status Scale, EDSS ≤6.5) participated in the study and retest measurement with a one-week interval. Validity was assessed by correlating the SBT with other outcome measures EDSS, Berg Balance Scale, Timed Up and Go Test, one-leg stance test, and functional reach test. Responsiveness calculated using the minimal detectable change (MDC). Ability of the SBT to discriminate between fallers and nonfallers was determined using receiver operating characteristic (ROC) curves.
Results: The SBT was excellent test-retest reliability ($ICC_{2,1}$=0.939). The SBT correlated significantly with other outcome measures (ranged from 0.699 to 0.832, $p< 0.001$), indicating good concurrent validity. Minimal detectable change (MDC_{95}) of the SBT was 1.2 point. The area under the curve was 0.810 (95%Cl 0.68-0.94) for SBT. A discriminative optimal cut-off point between fallers and nonfallers was determined as 17 point (sensitivity 73%, specificity 75%).
Conclusions: The SBT appears to be a reliable, valid and clinically available measurement for assessing balance in patients with MS. Also, it is sensitive for identifying fallers. The MDC score will assist clinicians for assessing changes of balance ability in patients with MS.

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EP1426

MMP-9 activity dynamics in relapsing-remitting multiple sclerosis patients under natalizumab treatment and their relationship to JCV reactivation and T-lymphocyte phenotypes

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Aims: The aim of the study was to assess the modifications of MMP-9 activity in relapsing-remitting multiple sclerosis (RRMS) patients during natalizumab (NTZ) treatment in relation with JCV reactivation and T-lymphocyte phenotypic alterations.
Methods: A total of 116 plasma samples were collected from 34 RRMS patients, enrolled at the Department of Human Neurosciences, Multiple Sclerosis Center of the Sapienza University, Rome. MMP-9 activity was measured by zymography on gelatin-copolymerized gels in plasma samples stratified according to NTZ infusion number (0, 3, 6, 12, 15, 18 and 24). JCV-DNA was detected through quantitative real time PCR in all plasma samples. T-lymphocyte phenotype was assessed with flow cytometry. Statistical analyses were performed using GraphPad Prism.
Results: A positive correlation between MMP-9 activity and Expanded Disability Status Scale was found (p=0.04). MMP-9 activity tended to decrease from 0 up to 12 NTZ infusions, whereas a linear increase was observed from 12 to 24 infusions(p=0.02). Stratifying all samples in JCV-DNA positive (JCV+) or negative (JCV-) an increased MMP-9 activity was found in JCV+ compared to JCV- samples (p=0.01). Moreover, MMP-9 activity resulted directly correlated with JCV viral loads in JCV+ samples (p=0.003).

CD8 immune activation levels were increased in RRMS patients with a longer exposition to NTZ. The CD8 immune activation levels were higher in JCV+ than JCV- samples, although the differences were not statistically significant. A positive correlation between CD8 immune activation levels and JCV viral loads was found (p=0.03). Interestingly, CD4 T-lymphocyte immune senescence and CD8 immune activation levels were positively correlated to MMP-9 activity (p=0.02 and p=0.04, respectively). CD8 effector percentages were positively correlated to MMP-9 activity (p=0.03), whereas CD8 naïve percentages were inversely correlated to MMP-9 activity (p=0.01).
Conclusions: MMP-9 plasma activity resulted increased during the second year of NTZ treatment, when PML risk starts to increase. MMP-9 activity was higher in plasma samples with detectable JCV-DNA and positively correlated with CD8 immune activation. These data suggest a potential pathogenic role of MMP-9 in the development of PML during NTZ treatment. We suggest that in RRMS patients, the combined effect of NTZ treatment and JCV reactivation could enhance MMP-9 activity, thus contributing to CD8 immune activation and blood-brain barrier impairment.

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EP1427

Relationship between upper and lower limb impairments objectively assessed in people with multiple sclerosis

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Aims: To investigate the relationships between UL and LL impairments in pwMS while performing motor tasks relevant for their quality of life, such as walking and "hand-to-mouth" (HTM) movement.
Methods: Twenty-four pwMS (EDSS: 3.8±2.3, range 1-6) underwent a 3D kinematic analysis during gait and HTM movements. The following parameters were computed: for HTM, overall movement duration, velocity, smoothness and adjusting sway (AS, length of the trajectory during mouth localization); for gait, speed, stride time and length and cadence. Correlations between UL and LL parameters and between EDSS and UL/LL parameters were assessed using Spearman´s rank coefficient.
Results: Moderate correlations were found between total HTM duration and stride time (rho=0.56, p< 0.01), and between HTM velocity and gait speed (rho=0.35, p< 0.05). The precision of the HTM movement, expressed by AS, was also found moderately correlated with gait speed (rho=-0.36, p< 0.05) and stride length (rho=-0.34, p< 0.05). The index associated with movement smoothness was found negatively correlated with gait speed (rho=-0.31, p< 0.05). Lastly, EDSS was found weakly correlated with total HTM duration (rho=0.35, p< 0.05) and strongly correlated with gait speed (rho=-0.85, p< 0.01).
Conclusions: UL and LL motor abilities in pwMS appear weakly-moderately correlated, although both worsen as disability increases. This suggests UL and LL impairments should be separately assessed using specific tests to have a whole view of the motor functions in MS. However further studies on a larger set of UL movements are needed to verify if such lack of relationship is confirmed.

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The authors have nothing to disclose

EP1428
Quality of life and some features of social functioning in multiple sclerosis

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Purpose: To study the quality of life and social functioning of MS patients, as well as to determine their motivational orientation and the main stereotypes of emotional response in situations of frustration.
Material and methods: 40 patients with relapsed remission MS were examined: 18 men and 22 women aged 18 to 66 years. The quality of life was assessed using the questionnaire "A brief form of studying the medical summary parameters of MOS SF-36" (SF-36). Clinical-psychopathological and experimental-psychological methods were used (Rosenzweig´s frustration test, a test of humorous phrases). The neurological deficit was determined according to the original scale of assessment of the neurological status . According to the neurological deficit, patients corresponded to the I-II severity of the disease, as the most indicative in terms of functional activity.
Results: In patients with MS, there was a significant reduction in all quality of life measures according to the SF-36 questionnaire. To a greater extent, with RS, role functioning is associated with both physical (RP) and emotional state (RE) of patients. The mental health indicator (MH) also declines to a lesser extent than role-play. At the same time, the overall assessment of the health status (GH) of patients with MS did not differ significantly from the control group. In the study of the emotional response of MS patients in situations of frustration, in 39.7% of the subjects, the subjects exhibited impunitive reactions (reconciling), 33.3% - external accusers, and 27.3% - self-incriminating. For this group, the following types of reaction were characteristic: 45.7% of the reactions "with fixation on self-defense", 28.2% "with fixation on the obstacle", 26% "with fixation on meeting the need". With the help of the test of humorous phrases hypertrophied motifs "human stupidity" were revealed in 50% (10) patients, "aggression" in 40% (8). Frustration with regard to the themes of "money" was noted in 75% of the subjects, "sex relations" - in 50%, "mediocrity in art" - also in 50%, "career" - in 45% of the surveyed.
Conclusions: Thus, with MS, the physical and role functioning of the individual, connected with the physical condition, is significantly impaired. The presence of psychological problems in this category of patients leads to a significant decrease in the quality of life, despite the absence of a pronounced neurological deficit, and requires timely correction.

Disclosure
Gulshanbonu: Nothing to disclose

Economic burden

EP1429
Impact of multiple sclerosis on the occupational status in developing countries. An experience in Argentina

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Introduction: The negative impact of Multiple Sclerosis (MS) on the occupational status of patients is well known. For this reason, there are questionnaires (Q) on the impact of MS on the occupational status of working employees (W).
Objective: a) To develop a Q on the occupational status of MS that is useful for developing countries; and b) To describe the changes that patients must do in order to keep their occupational status.
Method: A structured questionnaire was developed *ad hoc* to compile information on the occupational status of MS patients. The EDSS, the Fatigue Severity Scale, Rao´s Neuropsychological Battery and Beck´s Depression Inventory II were administered as well. The results were compared with a control group with the same basal socio-demographic characteristics.
Results: Out of a total of 60 patients with MS, the mean age 45.1 (± 10.6), mean school education 14.4 years (± 3.6), EDSS 2.5 (± 2), 33.3% had full-time jobs, 29.4% had part-time jobs, 5.9% were housekeepers, 2% were retired, 15.7% had retired early, 7.8% were under sick leave, 2% were under sick leave for other causes, and 3.9% were unemployed. Unemployee Causes: 76% had impaired locomotion, 38% had impaired hand motility, 46% had urinary incontinence, 61% had fatigue, 46% had pain, and 7% cognitive impairments. No housekeeper mentioned MS as a cause of their occupational status. Of working patients, 46.6% had made changes in their work in order to keep it: 5 did simplified tasks, 7 did tasks with lower physical involvement, 2 worked from home, 4 cut down their working hours, 7 spent more time in developing tasks, 9 took more frequent rests, and 3 changed their working hours. Out of the respondents who had one or more managers or colleagues, 17% answered that they had been rejected due to their MS; while 71% answered that they had received their support.
Discussion: The Q developed recorded the occupational status of patients and showed how the disease affected them. Understanding these issues allows setting interventions to prevent the loss of job and to reduce the impact of MS on the occupational status of patients.

Disclosure
The authors have nothing to disclose

EP1430
The value of multiple sclerosis caregiver burden scale. An Argentinean population

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Introduction: The caregivers of patients with Multiple Sclerosis (MS) may present with the so-called caregiver burden syndrome. The Zarit Scale has been applied in prior studies. However, this scale was designed for caregivers of patients with dementia, and patients with MS constitute a population with different symptoms.
Objective: To analyze the psychometric properties of a version of the Zarit Scale tailored for the caregivers of patients with Multiple Sclerosis.
Method: We drafted 10 questions related to symptoms specific to Multiple Sclerosis that may lead to discomfort in caregivers, which were incorporated into the Zarit Scale. This version was administered to 40 informal caregivers of patients with Multiple Sclerosis along with the Neuropsychiatric Inventory (NPI), the Beck Depression Inventory (BDI-II), the Stait Trait Anxiety Inventory, and an actual patient dependency scale.
Results: Caregivers had a mean age of 52.1 years (SD = 18); 58% were women. The modified Zarit Scale had a Cronbach´s Alpha of .97; Guttman´s split-half was .95, and all item-total correlations were >.50. Positive Pearson´s correlations >.60 were found between the scale and total NPI, the NPI of caregiver burden, and the actual dependency scale and BDI-II. An abridged version with 16 questions comprising the items with the highest discrimination power had a Cronbach´s Alpha of .95, and similar correlations as the ones found with the full version, with NPI of the caregiver, dependency and BDI-II.
Discussion: Although the study population is small, the data suggest that both the full and the abridged versions of the scale are adequate to measure the burden of the caregivers of patients with MS, showing adequate reliability and convergent validity rates. Conducting further studies with this population will provide a better understanding of the psycho-social issues that trigger caregiver stress in this population.

Disclosure

The authors have nothing to disclose

EP1431

Development of the adaptive, bilingual multiple sclerosis Health Resource Survey (MS-HRS)

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Background: Chronic diseases like multiple sclerosis regularly come along with a live long need for care, monitoring and medication. Besides direct health-related costs, there are necessary resources that result in indirect costs of the disease. Regardless of which treatment is indicated, the economic burden of MS is always an important topic to patients, relatives, healthcare providers and agents of the healthcare system. There is no standard instrument available that comprises all MS-related costs, provides a detailed picture and a comparable sum with one take. Most health-economic studies for MS rely on system-wide estimations but miss the direct assessment of costs.
Goals: To develop a holistic but easy to administer survey (Multiple Sclerosis Health Resource Survey, MS-HRS) covering all relevant MS-related costs and required resources
Methods: An expert group consisting of neurologists, healthcare administrators, psychologists and MS nurses at the Multiple Sclerosis Centre, University Hospital Dresden developed the item pool in German between 2011 and 2014. The first version of the MS-HRS was created as addition to register-like non-interventional studies that were emerging at the time. After incorporating the feedback from patients, nurses and physicians, a second version was built in 2016 that aimed to be more time-efficient. The adaptive version of the MS-HRS in its German and translated English version is the result of the third round of development.
Results: From the original item pool with 140 cost-related questions, the first non-adaptive version of the MS-HRS was created with a total of 118 items. The time for completion ranged from 15 to 20 minutes. After an optimization with respect to cost models for MS and national healthcare regulations, the second version consisted of 68 items. After integrating the MS-HRS in an adaptive eForm in the Multiple Sclerosis Documentation System 3D, the minimal number of question needed to be answered has dropped to 23 items and the timely effort decreased to 5 to 10 minutes. All tangible costs, which had an impact on the healthcare system, were included.
Conclusions: An efficient tool to assess MS-related costs will be a valuable contribution to almost all kind of treatment-related investigations. The MS-HRS is a promising option to measure costs precisely instead of estimating them or using surrogates. In future studies, external validity will be demonstrated and country-wise cost-weights will be introduced.

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EP1432

Work related and quality of life consequences of early multiple sclerosis

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Background: Multiple Sclerosis causes a large spectrum of symptoms including motor, sensitive, cognitive and neuro-psychiatric difficulties. MS affects young and middle aged adults in the most productive and active stage of their life causing serious negative effects on work related issues and thus causing significant socioeconomic burden. However, the impact of the disease on workplace has not been studied at the initial stages of the disease, when motor deficits are not present.
Objectives: To study the work status, the perceived workplace difficulties and cognitive performance of patients with early MS and their impact on quality of life.
Methods: Patients were recruited from the outpatient MS clinic at the Raul Carrea Institute for Neurological Research (FLENI) by attending neurologists. Thirty-four relapsing-remitting MS patients, fulfilling 2017 McDonald criteria, with ≤ 2 years disease duration and scores ≤2 on EDSS, were included. Thirty subjects matched for age, gender, and educational level, recruited from a local volunteer group, served as controls. Both groups underwent complete neuropsychological evaluation (Rao BRB).Work Status was inquired (employed/unemployed), work place difficulties were assessed using the Multiple Sclerosis Work Difficulties Questionnaire (MSWD-23) and Quality of Life was assessed by the MusiQuol.
Results: Groups did not differ significantly in age, sex, educational level or in the neuropsychiatric scales that assessed depression, anxiety and apathy. Patients showed significant deficits in cognitive tests of verbal memory, executive functions and language (Rao BRB). Groups did not differ in their employment status (p=0.58). However, patients had greater work difficulties than controls reflected by the MSWDQ-23 total score (p = 0.002), the Psychological Barriers subscale (p=0.032), the Physical Barriers subscale (p=0.001), and the External Barriers subscale (p=0.009). Furthermore strong correlations were observed between the MSWDQ-23 and the evaluation of the quality of life (Musiquol) (r=0.75, p=0.000).
Conclusions: Patients with early MS present work related difficulties even when working status is still stable. These difficulties impact on patients quality of life and are probably the source of unemployment problems present in later stages of the disease. Early detection of work related difficulties may contribute to the design of employment protection policies for these patients.

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EP1433

Impact of socioeconomic level on the employment status of people with multiple sclerosis

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Background: In recent years the socioeconomic situation has worsened in several countries with consequences that may differ between countries and between the population groups that make them up. People with Multiple Sclerosis (MS) are more vulnerable to unwanted changes in professional status due to their disabilities and uncertain prognosis. Socioeconomic status (SES) can be an indirect indicator of limited employment opportunities.
Objectives: 1) To examine the SES of a population with MS; 2) To study the relationship between the SES and the characteristics of employment (employed, professional self-employed and non-professional self-employed); 3) To analyze the relationship between the SES and the type of working area: specialized (which requires formal education) versus non-specialized (which requires experience or training).
Methods: The sample included 61 patients with MS (93.2% Relapsing-remitting, 1.7% Secondary-progressive and 5.1% Primary-progressive). 59% were women; average age: 38.89 ± 10.38 years; education: 14.18 ± 2.57 years; EDSS: 2.74 ± 2.01; evolution of the disease 11.64 ± 7.57. Outcome measures: Argentinian adaptation of the Buffalo Vocational Monitoring Survey; Socioeconomic Level index (SLI) that are organized in five different degrees: high level (ABC1), medium level (C2), medium-low level (C3), low level (D1), low-low level (D2-E).
Results: The SES of the studied population is distributed: 19.67% ABC1, 21.31% C2, 27.86% C3, 16.39% D1, 6.5% D2-E. An association was found between the SES (Group 1: ABC1-C2 and Group 2: C3-D1-D2E) and the types of employment relationship (employed, professional self-employed and non-professional self-employed) ($\chi 2 = 7.73$, $p = .001$). An association was found between SES (ABC1, C2, C3, D1, D2-E) and employment areas ($\chi 2 = 18.63$, $p = .001$).
Conclusion: 50% of the analyzed population in this study has a socioeconomic level of medium-low to low, which directly impacts on job opportunities. Their relationship becomes more relevant nowadays due to the worsening socioeconomic conditions of some countries.

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EP1434

Decreasing emergency department utilization in a multiple sclerosis patient-centered specialty practice: an advanced multimodal approach

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Multiple sclerosis (MS) is a chronic, inflammatory and neurodegenerative central nervous system (CNS) disease characterized by recurrent relapses and disability progression. Patients may seek care with an emergency department (ED) for treatment of relapse, which can result in inappropriate visits, and overuse of the ED. A National Committee for Quality Assurance (NCQA) recognized Patient-Centered Specialty Practice (PCSP) is well suited for MS management because of its essential elements: 1) timely access to comprehensive care, 2) enhanced communication between patients and providers, 3) continuous coordination and provision of care, and 4) intensive focus on quality and safety.

Evaluate the effectiveness of patient-centered care improvements to access and quality of care within the MS PCSP's impact on healthcare resource utilization (HRU), specifically ED utilization.

ED utilization by MS patients at the MedStar Georgetown University Hospital (MGUH) was measured for 2016 Q4. In June 2017 the practice instituted patient-centered approaches aimed at improving access and quality of care. The new multimodal approach included establishment of a Nurse Practitioner (NP) urgent care clinic within the Georgetown MS Center to provide same-day appointment access, daily pre-visit planning with care team discussions of patient-specific needs, and increased frequency of patients visits with their clinician and between-visit calls for high-risk patients. ED utilization and NP urgent care clinic visits 2017 Q4 and 2018 Q1 were measured and compared.

In 2016 Q4 prior to transformation, there were 40 ED visits. After transformation, ED utilization decreased by 35%, 2017 Q4 (N=26) compared to 2018 Q1 (N=17), while NP urgent care clinic utilization increased 37% quarter over quarter, 2017 Q4 (N=43) and 2018 Q1 (N=59). Observed ED utilization showed a continual decrease from pre-intervention utilization (2016 Q4; N=40) to post-intervention utilization (2018 Q1; N=17), resulting in a total decrease of 58%.

When patient-centered approaches to care for MS patients were instituted within the MS center including establishment of a NP urgent care clinic there was a decrease in ED utilization. This preliminary data suggests that increasing patient access and quality of care at a MS PCSP decreases utilization of the ED leading to reduced heath care costs and improved patient care.

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EP1435

Reduced sick leave in multiple sclerosis after switch from first-line disease-modifying drugs (interferon beta or glatirameracetat) to fingolimod

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Introduction: Fingolimod is an oral disease-modifying drug in MS and has shown to be highly efficient in reducing MS inflammation, but its impact on work ability has so far not been studied.

Objectives: To assess sick leave (short-term absence), disability pension (long-term absence) and unemployment before and after start of treatment with fingolimod.

Method: Patients in working age (n=105) who were switched from first-line treatments to fingolimod during October 2011 to March 2013 were selected from the Swedish Multiple Sclerosis Registry, a nationwide registry with 78% cover. For each patient 2 matched controls on first-line drugs were selected from the same registry. The match was based on age, sex and disease duration. For each patient data from 10 matched non-MS controls of the general population in the same region was collected. The outcome variables; level of sick leave and disability pension (both part- and full-time), were collected from the Social Insurance Agency and unemployment from the Swedish Public Employment Service. The variables were measured for each quarter, 2 years before and 3 years after index. The index was defined as the time point when the fingolimod patients switch from the first-line treatment to fingolimod.

Result: The final sample comprised 105 patients on fingolimod, 210 patients on first-line drugs and 525 controls from the general population (mean age 41 years; 61% female). Median level of Expanded Disability Status Scale for the fingolimod patients was 2.5 and 1.5 for the first-line patients. The mean prevalence of sick leave ranged from 24% 3 months before index (start with fingolimod) to 13% 3 years after index among fingolimod patients, 8% to 6% among first-line patients controls and 6% to 7% among general population controls. Corresponding estimates for disability pension were 32% to 38% for fingolimod patients and 23% to 27% for first line controls and 4% to 4% for the general population controls. Baseline levels of unemployment was highest

among the fingolimod patients, with a peak one year after start and subsequent reduction the following two years ending below baseline.
Conclusion: The results in this study indicate that MS patients switching from first line treatments to fingolimod can benefit regarding their work productivity. The rate of sick leave was reduced within 1 year after start of fingolimod and lasts at least 3 years. The reduction also lasts after adjustment for disability pension and unemployment.

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EP1436

Driving continuous improvement of MS care quality - initial launch experience from the first continuous quality improvement research learning health system in multiple sclerosis-The Multiple Sclerosis Continuous Quality Improvement (MS-CQI)

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Background: The Multiple Sclerosis Continuous Quality Improvement (MS-CQI) Collaborative is the first learning health system for quality improvement research in multiple sclerosis (MS) in the United States. It aims to leverage continuous quality improvement (QI) methods to improve MS care quality by benchmarking system-level performance indicators and testing QI interventions across MS centers. Four centers are currently participating (N=5,600) and four additional U.S. centers are currently in the process of joining (estimated new minimum N=10,000).
Objective: To report initial patient reported outcomes (PRO) and electronic health record (EHR) based outcomes from the MS-CQI study to date.
Design/Methods: This is a three year, randomized controlled study utilizing a step wedge design. Measures include real-time PRO, administrative data, and EHR data. PRO, administrative, and EHR data will be merged in analyses. First year data will be used to establish a baseline for benchmarking analyses. In year 2, two centers will be randomized to QI intervention. In Year 3, two additional centers will be randomized to the QI intervention.
Results: The collaborative has completed the second quarter of the first year of the study. 4,503 baseline PROs have been reported in the first three study quarters, by 203 of 243 active study participants (15% male, 94% white). Nineteen PRO measures are being collected, including (mean, SD): Patient Health Questionnaire-9 (PHQ-9) (7, +/-5), Quality of Life in Neurological Disorders (Neuro-QoL) Cognitive Scale (31, +/− 7), Patient Determined Disease Steps (PDDS) (2, +/− 2), NIH PROMIS Fatigue$_{MS}$ (22, +/-8). Total EHR n=1162, including Disease Modifying Therapy (DMT) (n=842) and MRI utilization (n= 758). Overall collaborative proportion on DMT= 72.3% (range: 64.1-88.7%). Overall collaborative proportion receiving a MRI in past year= 65.2% (range: 58.6-78.5%). Full Year 1 (baseline) results will be reported at ECTRIMS.
Conclusion: MS-CQI has demonstrated initial feasibility, acceptability, and functional data analytic pathways. Ongoing investigation of system-level variation and the effect of improvement interventions on system and population level clinical, patient experience, and functional health outcomes is a new area of investigation in MS that has great potential to improve MS care.

Disclosure

Summary: MS-CQI is funded by Biogen through a Sponsored Research Agreement (SRA). MS-CQI is an investigator initiated study independently designed by the principal investigator and independently conducted. MS-CQI features an independent data analytics center separate from Biogen access or control and is overseen and advised by a research improvement advisory committee (RIAC) comprised of patients, quality improvement experts, multiple sclerosis clinicians and researchers. Biogen representatives participate in reviews of manuscripts but content, authors, analyses, and conclusions are independently determined and finalized by the principal investigator and MS-CQI Collaborative research team.Author disclosures:
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EP1437

Burden of multiple sclerosis in Brazil

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Introduction: In Brazil, although disease-modifying drugs (DMTs) are reimbursed since 2010, comprehensive cost-of-illness information is limited.
Objectives: The objective of this study was to estimate costs to society and patients' quality of life (QoL) at all levels of disease severity (measured with the Expanded Disability Status Scale, EDSS).

Methods: The study was part of an international, cross-sectional burden-of-illness study carried out in collaboration with national MS patient organizations. All information was collected directly from patients using a validated questionnaire. Direct costs were estimated both from societal and payer perspectives, while total costs are presented as societal costs.
Results: The survey included 694 patients (response rate 21%; mean age 40.8 years). 95% of patients were of working age, and around half were working. The mean EDSS score was 3.2 (62.5% of patients with EDSS < 3). Relapses were reported by 18.9% of patients. Fatigue affected almost all patients (94%) regardless of EDSS level, and cognitive difficulties were reported by 69.1% of patients. Mean utility ranged from 0.77 at EDSS 0 to negative values at EDSS 9, with a mean score of 0.58; utility was affected by relapses.
Total mean annual cost was R$33,900 (€ 8,000) per patient in the societal perspective, with direct costs representing 81% (R$ 27,350, € 6,500). Direct costs for the payer amounted to R$ 16,800 (€ 4,500) per patient.
Conclusions: This study included a population with relatively mild and early disease, with a majority of patients with relapsing disease and thus on DMT treatment. It is not possible to conclude directly on the total cost of MS in Brazil. Nevertheless, resource quantities used, QoL and MS symptoms are very similar to what was seen in the European survey.

Disclosure

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Remaining authors: no financial disclosures.

EP1438

Employment status in patients with multiple sclerosis: a cross-sectional study in Argentina

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Introduction: Multiple sclerosis (MS) is associated with both high unemployment rate and burden of disease, especially during critical years of work life. Among 24-80% of MS patients are unemployed and this has been associated with worse quality of life. The aim was to investigate the employment status among patients with MS (PwMS) and to assess factors associated with unemployment.
Methods: A cross-sectional study based on a self-administered questionnaire was carried out from August to December 2017 in Argentina. We included 219 PwMS who were assessed by their employment status. We also evaluated demographic, disease course, disability status, comorbidities, level of education, current treatment, health insurance and burden of MS characteristics, within the last 12 months. These data were compared among PwMS employed vs. unemployed.
Results: Of the 219 PwMS, 185 (84.5%) were employed (full-time: 59%), 34 (15.5%) were currently unemployed and 15 (6.8%) retired by MS. Ages at disease onset, gender, disease duration, disease course, comorbidities, pension for MS disease and both neurological visit and neuro-images frequency in the last year were similar in both groups. Moderate level of disability was significantly associated with unemployment ($p = 0.04$). In addition, both low level of education and current use of MS medication were significantly associated with unemployment ($p = 0.01$, $p = 0.04$, respectively). Twenty-four (71%) PwMS in the unemployed group had certified disability retirement/ disability benefits ($p < 0.01$) and 14 (41.1%) state-run health coverage. On the employed group, 26 (18%) PwMS had licenses due to MS disease and they also had reduction of both working hours (28%) and salary (18%).
Conclusions: The rate of unemployment in this cohort was 15.5%. In addition, these findings support that PwMS employed have reduction of working hours and salary as well as work licenses and certified disability retirement due to MS disease.

Disclosure

None of the authors has any potential financial conflict of interest related to this poster

EP1439

New oral treatments decrease the switch to second-line therapies in multiple sclerosis. A 9-years retrospective, clinical and budget impact study

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Introduction: In the last decade we have increased our therapeutic arsenal (DMTs) for multiple sclerosis (MS). In our country, natalizumab was authorised in the mid 2007, fingolimod in dec-2011, alemtuzumab, teriflunomide, and dimethyl-fumarate, in may-2015. Budget impact (BI) has progressively grown along this period.
Objective: To analyze persistence of DMTs along the three different stages marked by the introduction of new DMTs, and reasons for switch to sencond-line therapies. Description of costs related to these drugs was included.
Methods: This is a 9-years retrospective, uni-center study. Prescription and dispensing were digitally registered from january 2009. We defined first stage corresponding to jan-2009 to dec-2011, second stage from dec-2011 to may-2015, and third sage from may-2015 to feb-2018
Statistics: Chi2, Kaplan-Meyer curve (log-rank method for comparison) and non-parametric comparison of medians were used.
Results: Along this 9-y period, we prescribed 535 treatments (142, 179, and 214 respectively to each stage) in a total of 338 patients. A total of 290 patients are still on treatment. Most interferons (IFN) were suspended along this 9y period, independently of the stage (86.5% of first stage, 63.3% of sencond stage, and 70.6% of third stage), mainly for inefficacy. From the first stage, only 13 IFN remain active, but 6 (33.3%) of AG, and 8 (32%) of NTZ remain active. In the third stage, more than 80% DMTs remain active, except for DMF (68.9%) and IFN1A (29.4%).
Contrary to that expected, 17%, 23.91% and 35.3%, respectively of DMTs prescribed in the first, second or third stage were switched to new oral therapies. Switches from first to second line therapies decreased along this 9y period from 37.32% in the first stage, 12.29% in the second stage, and 8.87% in the third stage. The evolution of spending on these drugs has been linearly increasing during the first 7 y by 20%, afterwards it reduced to 15% in the last 2 y. Kaplan-Meyer curves demostrated that oral therapies were more persistent than injectables (log-rank p=0.001).
Conclusions: We have found that oral and second line therapies were associated with longer persistance on treatment. The use of IFN, was associated with higher probability to switch to second-line therapies.
The more persistent new oral treatments could be related to the reduction in the evolution of BI due to these drugs because of decreased switch to more expensive second-line therapies.

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Neuro-ophthalmology

EP1440

The neuro-opthalmological evaluation of multiple sclerosis' and neuromyelitis optica's optic neuritis: analysis of 238 cases

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Background: Optic Neuritis (ON) is the most frequent sign in multiple sclerosis (MS) and neuromyelitis optica/spectrum diseases (NMO/SD). It is observed in the beginning of the disease or during its course. It is characterized by acute or subacute onset with painful visual loss in either one eye or both eyes simultaneously. However, when the clinical picture appears as isolated ON, how it would evolve clinically and in terms of the visual function is one of the main problems in neurology. Detailed evaluation of large series has the capacity of clarifying many questions. Our study was performed with the aim of scrutinizing this problem and some of these questions. In this study, clinical neuro-ophthalmologic evaluations were performed on 238 ON patients (194 MS-ON and 44 NMOSD-ON.) The findings were compared with the literature, the differences were discussed, and the visual prognoses were evaluated.
Results: 238 cases were evaluated and the following figures were found: mean age = 34.22, female / male ratio= 1.96. Acute ON (45.8%), chronic ON (54.2%), unilateral (68%) and bilateral (32%) involvement, recurrent ON (29.71%), visual loss (93.75%), visual field (GA) abnormality (45.15%), pupillary anisocoria (26%), afferent pupillary defect (79.43%), optical disc abnormality (63.43%). Differences between MS-ON and NMOSD-ON characteristics (severity of visual loss, color vision, contrast sensitivity and visual fields defects) were determined ($p < 0.001$).
Conclusion: The findings show that visual loss is in high rates in both MS-ON and NMOSD-ON, though it is relatively moderate in MS while heavier in NMO. The most sensitive test to detect visual loss was determined to be the "Sloan letter" contrast sensitivity test, and it is suggested that contrast sensitivity tests should absolutely be used in assessing visual loss. In addition, the pupillary anisocoria, which, according to classical literature, is reported to be infrequent in ON, was detected not to be so. This finding requires further research.

Disclosure

Nothing to disclose

EP1441

Evaluation of pupillary response characteristics measured by pupillometry in differentiating MS from NMOSD with the machine-learning approach: a potential pupillary pattern recognition method

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Introduction: Pupillometry measures dynamic changes in pupillary diameter in response to light stimuli, providing a functional assessment of RGC axonal pathways in the Inflammatory Demyelinating Diseases of the Central Nervous System.
Aims: This study aimed to use machine learning technique to determine if a subset of Multiple Sclerosis (MS) patients with different disease course and Neuromyelitis Optica spectrum disorders (NMOSD) may have any distinguishing pupillary characteristics.
Methods: We analyzed Pupillometry data 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 232 patients (169RRMS-29SPMS-21PPMS-13NMOSD).In this Cohort pupillometry parameters of 90 percent of each group is used as train and 10 remaining percent is used as a test in 10 fold cross validation for predicting the type of patients.
We have used nine base learners including Linear SVM, Poly SVM, Radial SVM, random forest, decision tree, Cart tree, K Nearest Neighbors, Naïve Bayes and RPART. Majority voting on the base learners' decisions has been used to make the final decision about each sample. This ensemble learning method achieved the total accuracy of 0.75.
Results: Among all pupillary response features Latency, Constriction Velocity (CV), Maximum of Constriction Velocity (MCV), Dilation Velocity (DV) and the discrepancy between two eyes in neurological pupil index (Npi) were more discriminative than other features according to the calculated feature importance.
Conclusions: We observed that applying machine learning technique to pupillometry data has potential to yield better discrimination of group differences. Our results may help to identify a pattern of alterations in specific pupillary parameters between MS patients with different disease course and NMOSD and may assist in clinical method planning in studies targeting pupillary light reflex pathway.

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EP1442

Characteristics of optic neuropathy in Behcet´s disease

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Objective: Behcet´s disease (BD) could occasionally present a differential diagnosis challenge in patients with optic neuropathy, which has rarely been reported in BD. Multicenter study presented here was aimed to show clinical profile, features and neuro-imaging findings of BD patients with ON.
Methods: Data from five different university hospitals were reviewed retrospectively, and patients with BD and ON were evaluated. Patients with secondary optic nerve damage were excluded. The cohort was divided into 2 groups and their findings were compared; (1) those already diagnosed with BD when ON developed (BD>ON group) and (2) those diagnosed with BD in further evaluation ON (ON>BD group).
Results: There were 25 BD patients with ON (13 males). Among these, 13 had ON>BD (6 males), and 12 had BD>ON (7 males). 17 patients had unilateral ON, and 7 patients had recurrent ON. BD>ON patients were significantly older. Disc edema was seen more in ON>BD patients (10 vs 3). 14 patients also had uveitis. There was other neurological involvement in 8 patients; in BD>ON group all 4 had MS-like neurological presentation. However, in ON>BD group, 3 had typical parenchymal involvement, and one had MS-like neurological presentation. All patients except one received immunsuppressive medications or corticosteroids or both. Prognosis was favourable in most: vision improved in 20 patients, more often in those receiving combined therapies.
Conclusion: BD may be diagnosed earlier if it is considered and investigated during the assessment of ON. Prognosis of ON related with BD seem to be favourable. Immunsuppressants should be given along with corticosteroids. MS-like presentations should also be kept in mind in patients with BD and ON. Further larger multi-center studies are needed to confirm these observations.

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Comorbidity

EP1443

Developmental venous anomalies are more common in patients with multiple sclerosis & clinically isolated syndrome: co-incidence or clinically relevant?

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Background: Developmental venous anomalies (DVAs) are congenital malformations of veins that drain the brain parenchyma. Their incidence has been reported to be 2.58% by a previous autopsy study, while magnetic resonance imaging (MRI) based studies reported a frequency of up to 9.3% in the healthy population.
Objective: Our aim was to determine the prevalence of DVAs in patients with clinically isolated syndrome (CIS) and early multiple sclerosis (MS) and to assess, whether DVAs are related to altered clinical, MRI and laboratory measures.
Methods: All 93 patients (39 CIS, 54 MS) underwent routine neurological- and MRI examination in a single center. DVAs were identified by two raters on post-contrast T1 weighted images. In addition, conventional measures such as clinical disability (n=93) and T2 lesion load (n=90), brain atrophy (n=89), as well as cerebrospinal fluid (CSF) parameters (n=< 82) were determined.
Results: 29 DVAs were detected in 25 patients (25/93; 26.9%); 10 out of 39 CIS patients and 15 out 54 MS patients had DVAs. The prevalence of DVAs did not differ between CIS and MS (p=0.819). In the total cohort of patients, clinical, MRI and laboratory parameters did not differ significantly between patients with and without DVAs, with the exception that a higher frequency of hypointense lesions on fluid-attenuated inversion recovery (FLAIR) sequences in patients with DVAs has been found (percentage of hypointense FLAIR lesions in patients with vs. without DVAs: 44% vs. 28.3%; p=0.037). CIS patients with DVAs had significantly less total ventricle volume (p=0.030) at baseline and showed higher CSF-levels of albumin (p=0.004), immunoglobulin G (p=0.021) and immunoglobulin A (p=0.017). Nethertheless, DVAs were not associated with higher conversion rates from CIS to MS at 1-year (p=0.411) or 2-year follow-up (p=0.281), respectively.
Conclusion: We have detected DVAs in patients with CIS or early MS at a higher frequency than published before. The percentage of DVAs in CIS and MS patients was 10 times higher than the prevalence reported in the healthy population. Patients with DVAs did not have significantly altered clinical outcomes, brain atrophy rates and disease progression. Accordingly, CIS Patients with DVAs do not seem to be at higher risk for converting to MS.

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EP1444

Comorbidities and safety of use of MD1003 in a cohort of patients with progressive multiple sclerosis

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Introduction: MD1003 is prescribed under a temporary authorization for use in progressive MS with good safety. More frequent comorbidities in this population may influence treatment results and should be taken into account.

Objectives: Identify side effects and comorbidities in a cohort of patients with progressive non-active form of MS treated with MD1003 for 12 months.
Methods: 109 patients (mean age 55 +/- 9.4 yrs, median EDSS 6.5, mean duration of illness 18.8 +/-9 yrs) with a progressive non-active form of MS worsening in the last 2 years have been followed for 12 months. Comorbidities likely to disturb the results of treatment evaluation are collected before introduction. At each visit (3, 6, 12 months) are noted sides effects and any undercurrent medical events related to the associated comorbidities or not. MRI results at baseline and at 12 months are also included.
Results: 55 patients have comorbidities: orthopaedic, metabolic and cardiorespiratory disorders. 15 patients discontinued treatment for inefficacy, adverse events and aggravation. 20 patients presented adverse events described in the characteristic summary produced. A sensorimotor relapse has been reported. One-third of patients suffered from an undercurrent medical event. Only one MRI showed an increase in the lesion load with two active lesions and two MRIs increased in isolated lesion load.
Conclusion: Comorbidities are frequent according to the different publications and responsible for undercurrent events that may distort the therapeutic evaluation. Side effects are uncommon and comparable to those previously described. The risk of relapse remains low and corresponds to the risk described by Bonenfant in 2017 for progressive MS. MRI remains stable and may differ from other studies. MD1003 is a well-tolerated treatment and the evaluation of its effectiveness should take into account the more frequent associated comorbidities in this population.

Disclosure

nothing to disclose

EP1445

Prevalence of cancer and the relationship to disease-modifying treatments in a cohort of multiple sclerosis patients over 50 years of age

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Introduction: The relationship between multiple sclerosis (MS) and cancer, has long been investigated but results have been not conclusive yet and a higher risk has been associated only with the previous use of immunosuppressants. The estimated prevalence rate (EPR) of cancer in MS patients is 4.39% and there is no estimated data in those over 50. Since the arrival of new and more effective immunomodulatory treatments and its use in increasingly older patients, a possible higher prevalence of cancer is expected. The aim of this study is to clarify the prevalence of cancer in older MS patients and to evaluate the effect of exposure to disease modifying-treatments (DMTs)
Material and methods: We assessed the prevalence of cancer in a cohort of 155 MS patients older than 50 years. Demographic and clinical data were collected retrospectively from the database of Puerta de Hierro University Hospital. Clinical and radiological isolated syndromes were excluded. We carried out a descriptive and multivariate analysis using a logistic regression model to assess the relationships between the use of DMTs adjusted to exposure time and the prevalence of cancer
Results: No differences in gender, clinical activity or type of MS were found in patients with cancer compared to the whole sample. A total of 11 neoplasms were detected in 10 patients (7.1%), a little higher than expected predominantly in >65 years (EPR: 98 for 50-55 years, 128 for 55-64 years and 138 for >65 years). A complete remission was observed in 8 of them. Only one death ascribed to cancer was reported. The more frequent cancer was non-melanoma skin cancer and melanoma (18.2% for each). The percentage of melanoma in this study was 4 times higher than expected. The mean number of previous DMTs was greater in patients with cancer (2.3+/-0.8 vs 1.5+/-1.2) and a positive correlation was found between cancer occurrence and the number of previous DMTs (OR=1.4 95%IC:2.2-0.6 p=0.001) without a direct relationship with any specific DMT. As expected age was positively correlated to cancer occurrence (OR=0.07 95%IC:1.4-0.03 p=0.04) and negatively to disease remission (OR=-0.1 95%IC:0.3-0.01 p=0.03)
Conclusions: Our findings indicate that in patients older than 50 years, the prevalence of cancer is higher than expected and the use of a higher number of DMTs seems to be a risk factor. Further study is needed to assess possible associations between long-term exposure to the novel DMTs in MS and rate of cancer

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EP1446
Double jeopardy of multiple sclerosis and idiopathic Parkinson's disease: three new case reports

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Method/Results (Case Series Report): The first patient presented aged 64 with a 5 year history of tremor in her right hand, worst at rest. She was found to have cog wheeling and bradykinesia, with reduced arm swing. She had an MRI brain which showed involutional changes, with nonspecific T2 changes in bilateral white matter sparing bilateral basal ganglia. She was subsequently treated with increasing dopaminergic treatment with good clinical response. Her extrapyramidal features fulfilled criteria for diagnosis of idiopathic Parkinson's disease as per UK Brain Bank criteria. DATscan showed changes consistent with idiopathic Parkinson's disease. 4 years later, she began developing progressive right sided upper motor neurone signs. Repeat MRI showed progressive T2 white matter changes withT3/T4 cord lesion suspicious of demyelination. Subsequent CSF was positive for oligoclonal bands(OCB) with negative screening tests for secondary neuroinflammation.
The second patient presented aged 61 with a three-year history of progressive limb weakness, numbness over her arms and urinary incontinence. She had a MRI brain which showed features suggestive of demyelination with positive OCB in her CSF. Eleven years after her diagnosis of progressive MS she was found to have reduced arms swing and bradykinesia. She was trialled on co-careldopa with positive response. Her extrapyramidal features were further improved following up titration of her L-dopa to 300mg/day.
The third patient presented aged 51 with a clinically isolated syndrome of diplopia. 6 years later he had another relapse with diplopia and right sided paraesthesia. MRI, CSF, evoked potential and neuroinflammation screen confirmed MS and he was started on interferon. A year later, he developed extrapyramidal features fulfilling UK Brain Bank diagnosis of IPD. He had positive DATscan. Over the last 6 years, his IPD showed sustained positive response to levodopa.
Conclusion: To date, there are 42 cases of simultaneous Parkinsonism and Multiple Sclerosis in English literature. The majority are attributed to Multiple Sclerosis and Parkinsonism, as opposed to Idiopathic Parkinson's Disease. Furthermore, many have featured patients with early onset Parkinsonism. There are very few cases of Idiopathic Parkinson's Disease and Multiple Sclerosis in patients over 60. More research is needed to decide if the relationship between the two diseases is coincidental or one unifying pathogenesis.

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EP1447
The relationship between migraine and multiple sclerosis therapies

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The objectives of this study was to study the relationship between migraine and MS therapies. 782 MS patients were consecutively admitted. All patients filled out a detailed headache questionnaire and 754 patients were included. Of the total population of 754 MS patients recruited in our center, 515 (68%) reported headaches. Based on headache characteristics on evaluation, 202 (27%) were diagnosed with migraine [128 (17%) patients with migraine without aura, 52 (6.9%) patients with migraine with aura, 17 (2.3%) patients with probable migraine without aura, 5 (% 0.7) patients with chronic migraine]. One hundred and three patients (17%) gave a history of tension-type of headache and 198 (26.3%) patients described to have medical overuse headache. There were 12 (1.6%) patients with unclassified headache. During our study 558 MS patients (74%) were treated with interferon beta therapy/glatiramer acetate. 115 patients (15.3%) received fingolimod. 48 MS patients (6.4%) were treated with teriflunamide, and 33 MS patients (4.4%) received natalizumab. There was no statistical difference between medications and migraine. The mean age of onset of specific treatment for MS was 29.4 and there was a significant association between migraine and the age of onset of MS therapies. The mean age of onset of headaches was 27.4 years. When all headache groups were compared, the age of onset of headache was the earliest in the patients with migraine (mean 25,2). As regards the possible relationships between duration of the history of medication use and headaches, the incidence of migraine was higher in all headache patients. According to this result, the shorter duration of medication use the higher incidence of migraine. The mean value of total duration of medication use until migraine occurrence was 1.82 years. In migraine patients, the duration of medication use until the headache onset was the longest when compared to other headache groups. There was a statistically significant difference between migraine and concomitant symptoms (nausea, vomiting, phonophobia, and photophobia). The consultation rates for migraine in our MS patients were not rare and 78% of patients with migraine were seen by physicians due to headache complaints. In this study, migraine was more common than other headaches and the association between migraine and the age of onset of MS therapies, and also duration of medication use were significant.

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nothing to disclose

EP1448
Pain in AQP4-ab-positive and MOG-ab-positive neuromyelitis optica spectrum disorders

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Background: Pain is a frequent symptom in aquaporin-4-IgG-positive and antibody-negative neuromyelitis optica spectrum disorders (AQP4-NMOSD/ ABneg-NMOSD). Data on pain in MOG-IgG associated neuromyelitis optica spectrum disorders (MOG-NMOSD) are scarce.
Objective: To investigate pain in MOG-NMOSD in comparison to AQP4- and ABnegNMOSD.
Methods: Forty-nine patients with MOG- (n=14), AQP4- (n=29), and ABneg- (n=6) NMOSD were included in this cross-sectional analysis from an ongoing observational study of patients with NMOSD and related disorders. We identified spinal cord lesions in MRI, assessed pain by PainDETECT and McGill Pain Questionnaire, quality of life by Short Form Health Survey, and depression by Beck's Depression Inventory.
Results: Twelve MOG-NMOSD patients (86%), 24 AQP4-NMOSD patients (83%), and all ABneg-NMOSD patients (100%) suffered from pain. MOG-NMOSD patients had mostly neuropathic pain and headache; AQP4- and ABneg-NMOSD patients had mostly neuropathic pain. A history of myelitis was less frequent in MOG-NMOSD than in AQP4-NMOSD patients. Pain influenced quality of life in all patients. Thirty-six percent of patients with pain received pain medication; none of them were free of pain.
Conclusions: Pain is a frequent symptom of patients with MOG-NMOSD and as important as in AQP4- and ABneg-NMOSD. Despite its impact on quality-of-life, pain is insufficiently alleviated by medication.

Disclosure

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EP1449
Multiple sclerosis related headaches. Prevalence and classification

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Background: High prevalence of migraine in patients with multiple sclerosis (pwMS) has been supported by abundant controlled and uncontrolled studies. Yet; the temporal association, headache semiology and MS characteristics of those patients remain to be determined.
Objectives: To investigate the prevalence and characteristics of headaches in MS sample *vs*. control healthy subjects and to compare the MS-headache group (MS-H) with headache-free MS (MS-NH) patients with respect to MS type, symptoms and disease-modifying drugs (DMD) intake.
Methods: A cross sectional, case-control study that included 486 MS patients (non-probability convenient sampling method). The control subjects (n=486) were selected among patients' accompanying friends with age and gender matching. All participants were screened for the presence of headache in the last year (1-year prevalence) using a validated Arabic-language headache questionnaire and migraine severity was assessed using the Migraine Disability Assessment (MIDAS).
Results: We detected 309 (63.58%) pwMS and 245 (50.72%) controls had ''headache within the past year''. Headache was more in secondary progressive (SPMS) than in relapsing remitting (RRMS) patients (71.29% vs 51.02%; p=0.03) and was associated with higher EDSS scores (p=0.04). The migraine frequency was higher in pwMS (45.11 vs 21.67%; prevalence ration (PR): 2.08, p=0.02). Unclassified headache (according to International Headache Society criteria) was more in pwMS (23.71% vs 11.56%; PR: 2.05). Migraine without aura was more frequent in pwMS than migraine with aura but disability (assessed with MIDAS) did not differ between pwMS and controls. According to temporal relationship of headache onset and MS milestones; headaches were classified into; (1) headache preceding MS (n=191/309; 61.81%), (2) headache associated with initial presentations of MS (n=33; 10.68%); (3) headaches developed within the course of MS (whether first presented in relationship to attacks or not) in 46 (14.89%) and (4) headache started after initiation of DMD (n=39; 12.62%). Of our patients, 365/486 (75.10%) were on DMD; which had variable effects on headaches: headache de novo (10.68%) improvement (27.67%), worsening (26.03 %) and remained unchanged (35.62%).
Conclusion: Headache is more common in MS patients than in controls. Patients with MS-H can be classified according to its

temporal relations of MS onset, which may help in resolving the underlying mechanism(s) of this association.

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Pathology

EP1450

Multiple sclerosis clinical trials: how to encourage patients participation? Results from an observational study conducted via Carenity, a worldwide online patient community

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In a worldwide context of competitive multiple sclerosis clinical research, patient engagement is key to optimize medical research and increase participation rates.
An online questionnaire has been submitted from August 2017 to October 2017 to Carenity's French members affected with multiple sclerosis. The aim of this study was to identify patients' motivations and hindrances to join a trial in order to increase participation rates by implementing tailored services and information.
152 patients affected with multiple sclerosis participated in the study (mean age = 49 y/o, 74% of women). 18% already participated in a clinical trial. Reimbursing the expenses related to the clinical trial can improve non-participant motivation (median weight on participants' motivation to join their trial = 10/10), leveraging the trial's healthcare center notoriety (7.0/10) or the trial's doctor notoriety (7.0/10) would entice them to enter a trial. Communication should also aim at reassuring patients about side effects (median weight on participants' reluctance to join their trial = 8.0/10), potential risks for their health (8.0/10) or a change in their doctor / place of care (6.0/10).
Implementing tailored services and clarifying information would be an efficient way to reassure patients and increase their willingness to participate. Non-participants would be enticed to participate if they had access to participant testimonials (75%), to a 24/7 medical helpline (71%) or to transportation services (69%). Spreading and clarifying information before the trial is also critical: 17% of participants did not understand clearly if they will have out-of-pocket costs. Meanwhile, it is a heavily weighted point in the patient's decision to participate. Informing patients via convenient channels is also key: 81% of participants and non-participants think that an online patient community is a relevant medium to convey information about clinical trials.
This observational study allowed to identify concrete levers to reassure patients affected with multiple sclerosis about the benefits/constraints balance and to clarify information at each stage of the trial (before, during, after), which is essential to accelerate clinical trial recruitment.

Disclosure

Name: nothing to disclose

EP1451

Monocyte-derived tissue transglutaminase in multiple sclerosis patients: reflecting an anti-inflammatory status of the cells?

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Neuropathological characteristics of multiple sclerosis (MS) are alterations in blood-brain barrier function, perivascular infiltration and migration of leukocytes, activation of local glial cells, demyelination and axonal loss.
Tissue Transglutaminase (TG2) is a multifunctional enzyme, well known for its role in cross-linking of proteins. In addition, TG2 acts as a co-receptor for β-integrins to enhance fibronectin binding. In this way TG2 is considered to facilitate cell adhesion and migration. In a previous study we observed the appearance of TG2 in MHCII positive cells in active MS lesions[1]. Moreover, in an experimental animal model for MS, TG2 mediated the infiltration of monocytes into the CNS[1]. These data prompted us to study TG2 in monocytes from MS patients with ongoing disease. Thus, in the present study we questioned whether TG2 expression is altered in monocytes from MS patients compared to control subjects? Moreover, we determined the inflammatory status of the TG2 expression cells and whether TG2 can functionally contribute to human monocyte adhesion/migration processes.
From 15 MS patients and 10 healthy control subjects, blood was drawn by vena puncture. After isolation of peripheral blood mononuclear cells, monocytes were derived by using anti-CD14 beads. RNA was isolated from the monocytes and cDNA synthesized. By using q-PCR, we observed that TG2 mRNA levels were significantly higher in monocytes derived from MS patients compared to control subjects. In addition, correlation analyses indicated that TG2-expressing cells from MS patients display a more anti-inflammatory, migratory profile. Using the human THP1 monocyte cell-line, we observed that interleukin-4 (IL-4) was a major trigger of TG2 expression in this cell type. Furthermore, knock-down of TG2 expression by lentiviral transduction of the monocytes with TG2 shRNA led to enhanced IL-1β and TNFα expression, and reduced adhesion/migration after IL-4 treatment. We suggest that TG2 is an important mediator of the IL-4-induced anti-inflammatory properties of monocytes. We propose that in monocytes of MS patients the enhanced expression of TG2 can

drive them into an anti-inflammatory status. Functionally, TG2 could, at least partly, mediate the enhanced adhesion of anti-inflammatory monocytes to the CNS endothelium of MS patients. In general, this could reflect a potential protective mechanism.
[1]Van Strien ME et al., Brain Behaviour and Immunity 50:141-154, 2015
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Disclosure
C. Sestito declares that she has no conflict of interest. J.J.P. Brevé declares that he has no conflict of interest. J. Killestein has accepted speaker and consultancy fees from Merck, Biogen, Teva, Genzyme, Roche and Novartis. C.E. Teunissen declares that she has no conflict of interest. M.M.M. Wilhelmus declares that he has no conflict of interest. B. Drukarch declares that he has no conflict of interest. J.P. van den Elsen declares that he has no conflict of interest. A-M. van Dam declares that she has no conflict of interest.

Experimental models

EP1452
RGC-32 regulates TGF-β-induced reactive astrogliosis in a mouse model of multiple sclerosis

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Introduction: Extracellular matrix (ECM) deposition in multiple sclerosis (MS) lesions may impede axonal regeneration and can modify immune reactions. RGC-32 plays an important role in the mediation of TGF-β effects, but its role in astrogliosis has not been investigated.
Objectives: We are proposing to investigate RGC-32 involvement in the expression of TGF-β-induced ECM components collagen type I, type IV, type V, fibronectin and reactive astrocyte markers α-smooth muscle actin (α-SMA) and nestin, together with the molecular mechanisms underlying RGC-32 expression and function. We also investigate the effect of lack of RGC-32 on astrocyte phenotype during experimental autoimmune encephalomyelitis (EAE).
Aims: Our aim is to evaluate the role of RGC-32 in astrogliosis.
Methods: We purified neonatal astrocytes from wild type (WT) and RGC-32 knock-out (KO) mice. The expression of ECM components and reactive astrocytic markers was assessed by Real time PCR and Western blotting. We also investigated the physical interaction between RGC-32 and Smad proteins, as well as the effect of Smad3 on RGC-32 nuclear localization. Immunohistochemistry for glial fibrillary acidic protein (GFAP) was performed on spinal cords from WT and RGC-32 KO mice with EAE.
Results: Collagens I, IV and V, fibronectin, α-SMA and nestin were induced by TGF-β stimulation and siRNA-mediated RGC-32 silencing resulted in a significant reduction in their expression. We also found that the expression of TGF-β-induced collagens I, IV and V, fibronectin and α-SMA was significantly reduced in RGC-32 KO mice astrocytes when compared with WT mice**.** Co-immunoprecipitation assays showed that Smad3 physically interacts with RGC-32 in astrocytes. SIS3, an inhibitor of Smad3 phosphorylation significantly reduced RGC-32 nuclear translocation and TGF-β-induced collagen I expression. Y27632, a selective ROCK inhibitor was also able to significantly inhibit RGC-32 nuclear translocation, while the Smad3 nuclear translocation was unaffected. In addition, during EAE, RGC-32 KO mouse astrocytes displayed an elongated, bipolar phenotype, resembling immature astrocytes and glial progenitors whereas those from WT mice had a reactive, hypertrophied phenotype.
Conclusions: Our data demonstrate that RGC-32 plays an important role in mediating TGF-β-induced reactive astrogliosis during EAE. Therefore, RGC-32 may represent a new target for therapeutic intervention in chronic MS.

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EP1453
IL-18 improves the activation of encephalytogenic cells and the induction of adoptively transferred experimental autoimmune encephalomyelitis

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Background: Adoptively transferred experimental autoimmune encephalomyelitis (at-EAE) is an animal model that allows for a better delineation of the effector phase of EAE, regardless of the inductor. There is no consensus about an ideal protocol in the existing literature.
Objectives: In order to develop a more severe animal model of at-EAE, encephalytogenic cells were tested *in vitro* to study different conditions of stimulation before they were transferred to recipient animals.

Methods: Splenocytes and lymph nodes from C57BL/6mice with actively induced EAE were cultured in different conditions with MOG_{35-55} (25 or 50μg/ml), IL-12 (25ng/ml) and with or without IL-18 (25ng/ml) at 0, 60, 72 and 96 hours. Differential activation of the encephalytogenic cells was studied by detecting the following markers: CD69, IL-2 and IFN-γ by flow cytometry.
An *in vivo* experiment was conducted in C57BL/6 mice, using the two experimental conditions that produced more cell activation. The animals were evaluated for clinical scores, and the expression of axonal damage (SMI32), demyelination (MBP), astroglial response (GFAP) and microglia activation(Iba1), were determined in spinal cords by confocal microscopy.
Results: Concentration of MOG_{35-55}, cytokine combination and time of culture were decisive in activation/cell death. The optimal condition of culture was 25μg/ml MOG + 25ng/ml IL-12 + 25ng/ml IL-18 during 72 hours. In this condition, coculture of IL-18 and Il-12 induced higher levels of IFN-γ, compared with IL-12 alone . At 96 hours, the activation was greater, but also the death of the cells, as it was the case using 50 μg/ml $MOG_{35-55.}$
In the *in vivo* experiment, the progress of clinical signs was homogeneous, they started at the same time and reached a higher score in the IL-18 group.
Axonal damage and demyelination were increased in spinal cords of mice when IL-18 was added in at-EAE induction. No differences were found in astroglial response and microglial activation.
Conclusions: IL-18 increases the clinical severity of at-EAE. An optimal boosting of encephalytogenic cells *in vitro* might be achieved with the combination of IL-12 and IL-18, which induces a significant secretion of IFN-γ.

Disclosure

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EP1454

Comparative study of reverse transcriptase polymerase chain reaction and fluorescence-activated cell sorting for quantitating B cells after anti-CD20 monoclonal antibody therapy

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Background: Anti-B-cell therapies, such as fully human anti-CD20 monoclonal antibody (Ab) ofatumumab, currently studied in Phase III clinical trials in remitting multiple sclerosis, have strong preclinical and clinical evidence of efficacy. As depletion of B cells may serve as a pharmacodynamic biomarker, we explored two methods in parallel, reverse transcriptase polymerase chain reaction (RT-PCR) and fluorescence-activated cell sorting (FACS), to compare their sensitivity for their quantification.
Objective: To compare the detection threshold of B-cell depletion in blood, as measured by the current standard method (FACS) with that of RT-PCR. Second, to evaluate whether RT-PCR is suitable to quantify anti-CD20 induced B-cell depletion in peripheral lymphoid organs.
Methods: C57BL/6 female mice (n=10; 7 weeks old) were treated with anti-CD20 mAb (20 μg or 200 μg) to induce B-cell depletion. Blood, spleen, and inguinal lymph nodes (LN) were collected and samples were split for FACS and RT-PCR analysis. Single lymphocyte suspensions were stained with anti-CD19-APC/Cy7, anti-CD3-APC, and SYTOX Blue for analysis using a Fortessa flow cytometer and FlowJo software. Total RNA was extracted by RNeasy Protect Animal Blood kit (blood) or RNeasy mini/micro (cell suspensions). A duplex TaqMan assay with either CD19-FAM or CD20-FAM probes, and endogenous control probe GAPDH-VIC was run in triplicates after reverse transcription.
Results: At 7 days after anti-CD20 treatment, a strong depletion of total B cells was observed in blood, regardless of the dose. Both FACS and RT-PCR methods showed that B-cell depletion was dose-dependent. Relative quantification of CD19 mRNA and CD20 mRNA showed nearly identical values. B-cell depletion was quantifiable in LN and spleen by RT-PCR. In spleen, B-cell depletion measured by RT-PCR displayed a larger spread, probably indicating higher sensitivity of detection that will be further explored by absolute quantification using digital RT-PCR.
Conclusions: Quantification of total B cells under anti-CD20 mAb treatment can be performed by both FACS and RT-PCR analysis, as shown here in experimental mice. RT-PCR allows measurement of B-cell depletion in blood and solid tissue. It requires significantly less specimen material, and simpler sample logistics. Moreover, RT-PCR can measure CD20 directly that is not possible by FACS. RT-PCR may be of potential advantage for application in a clinical setting.

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EP1455

A2AR antagonism in acute EAE model leads to early and more severe EAE

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Objective: Adenosine 2a receptors (A2AR) are ubiquitous receptors in the human body. Their activation and inactivation readily regulates inflammation within the brain and the peripheral systems. A2AR antagonism by caffeine has been shown to ameliorate

symptoms of EAE, an animal model of MS. Our aim was to study the effect of adenosine receptor antagonist KW6002 on neuroinflammation in an acute EAE model.
Methods: Ten 5-week-old female SJL/JCrHsd mice were immunized with $PLP_{139-151}$/CFA followed by injection of PTX (kit by Hooke Laboratories). Mice were allocated to two treatment groups. First group (n=5) received daily injections of KW6002 (diluted into 5% DMSO, 5% TWEEN 80, in 0.9% NaCl) i.p. from day 5 post induction for three days at dose 3mg/kg, then for 10 days at 1,5mg/kg i.p. Sham-treated group (n=5) was given daily injections of vehicle. Scoring (0-5, 0=no symptoms, 5=moribund) was done daily. On day 21 post induction mice were euthanized and their brains and spinal cords were collected. Spinal cords were frozen, cut and stained with toluidine blue to visualize any infiltrates. The brains were used for cell sorting by FACS to isolate microglia, macrophages and T cells. RNA was extracted from the sorted cell populations with miRNeasy Micro Kit (Qiagen) and quantitative real-time PCR (qPCR) was performed for the A2AR gene.
Results: A2AR antagonism led to earlier and more severe acute EAE. EAE disease scores were significantly greater in the KW6002-treated group on days 11 (p=0.007) and 12 (p=0.014) post induction compared to sham-treated group. T cells and macrophages retrieved from the EAE brains expressed the A2AR, but negligible A2AR expression was found on microglia. Both treatment groups had similar levels of inflammatory cell infiltrates in their spinal cords.
Conclusions: A2AR antagonism by KW6002 led to more severe disease in an acute model of EAE. This is likely due to an immunostimulatory effect on CNS-infiltrating peripheral immune cells expressing the A2AR, as brain-resident microglial cells did not express the A2AR.

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EP1457
Oleanolic acid protects against gastrointestinal disturbances in the experimental autoimmune encephalomyelitis model of multiple sclerosis

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Background: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the CNS, in which oxidative stress play important roles. Characteristic symptoms include motor and sensory deficits in addition to gastrointestinal (GI) disturbances

which etiology is less understood. The triterpene, oleanolic acid (OA), has proven effective attenuating neurological signs and histopathological features of disease on a MS mice model (experimental autoimmune encephalomyelitis, EAE) via anti-oxidant and immunomodulatory mechanisms. Herein, we investigate GI manifestations associated to EAE as potential therapeutic target of OA.

Aims: To determine the efficacy of OA in the prevention of GI disturbances in EAE, with a focus on oxidative-stress.

Methods: C57/BL6 mice were MOG35-55-inmunized and treated with OA (25 mg/kg/day, i.p). On day 21, in selected sample, we performed s: i) macroscopic intestinal analysis, ii) fecal and cecal evaluation, iii) GI hormone quantification: motilin, and iv) oxidant/antioxidant status analysis: TBARS, FRAP and sestrin-3, a ROS disruptor.

Results: Histopathological analysis did not reveal significant differences in the relative colon length among mice of the different experimental groups ($p>0.05$). The fecal water content was lower in the EAE group (13% decrease, $p< 0.001$) than in the control group. Full caecum and cecal content were significantly increased in EAE mice in comparison with those of the control one. Low motilin levels were detected in serum from EAE mice, compared to healthy mice (161±18 and 538±45pg/ml, respectively; $p< 0.001$); and a similar pattern was observed in colon samples. An inverse correlation was found between motilin and the clinical signs score ($r=-0.6294$, $p< 0.001$). We found that OA treatment to EAE mice had a protective effect attenuating all these alterations. In addition, colon from OA-treated EAE mice showed 4.3 times more non-enzymatic antioxidants and 1.9 times more of the ROS disruptor sestrin-3, than untreated-EAE mice. Interestingly, in healthy mice, high levels of FRAP and sestrin-3 were observed in the OA-treated group, compared with untreated animals ($p< 0.001$). These markers correlated with the lipid peroxidation levels ($r=-0.694$, $p=0.0007$; $r=-0.696$, $p=0.0007$; respectively) as well as with the clinical signs score.

Conclusion: Our data contribute to the idea that GI dysfunction influences MS pathogenesis, and provides new findings regarding the beneficial activity of OA in EAE.

Disclosure

nothing to disclose

EP1458

Impact of A20 deficiency in myeloid cells: study in a murine model

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Introduction: A20, codified by *TNFAIP3* gene, is an ubiquitin-ending enzyme involved in the inhibition of NF-kB and is a central gatekeeper in inflammation. Genetic variants in the *TNFAIP3* locus are associated with several autoimmune disorders, including multiple sclerosis (MS). A significant A20 down-regulation is frequently observed in blood cells from MS patients, particularly in monocytes.

Aims: based to the crucial role of myeloid cells in the pathogenesis of MS, we aim to investigate the effects of A20 deficiency in these cells *in vivo*.

Methods: we generated the conditional knock-out (KO) murine model (A20lox::CX3CR1) crossing A20lox/lox mice with transgenic mice carrying the Cre recombinase under the control of a specific promoter for myeloid/microglial cells (CX3CR1). We performed cytofluorimetric and histologic analysis to characterize the phenotype of conditional homozygous KO mice (A20lox/lox::CX3CR1) compared to their wild type (WT) littermates (A20wt/wt::CX3CR1).

Results: KO mice show a mortality rate of 40% during post-natal development. Moreover, starting from 1 month of age they are smaller compared to the WT littermates, regardless of gender. At a cytofluorimetric analysis, spleens from 3-months old KO mice display a reduction in the percentage of CD11c+CD86+ dendritic cells, CD11b+Ly-6C+Ly-6G+ monocytes and CD11b+F4/80+ macrophages compared to WT. These findings are corroborated by the histological analysis, which highlights a massive hypertrophy of the spleen in KO mice. This is mainly due to the expansion of the red pulp, which is characterized by an increased extramedullary haematopoiesis with various degrees of normal differentiation. Spleen architecture is also altered by a partial substitution of the white pulp sheaths of lymphoid cells by myeloid cells.

Conclusions: the phenotypical analysis of the A20lox::CX3CR1 murine model clearly suggests a crucial role for A20 in the development of myeloid cells.

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EP1459

Expression of the Nerve Growth Factor and its receptors, TrkA and p75NTR, in the spinal cord in Experimental Autoimmune Encephalomyelitis

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Background: Nerve Growth Factor (NGF) and its receptors, TrkA and p75NTR, are involved in the interplay of the nervous and immune system, especially in inflammatory conditions such as Multiple Sclerosis (MS) and its experimental model Experimental Autoimmune Encephalomyelitis.
Goals: The expression of TrkA, p75NTR and NGF in the spinal cord in EAE was investigated.
Methods: MOG-EAE mice were examined at three time-points (preclinical (D10), acute (D20) and chronic (D50)) compared to controls. The expression of TrkA, p75NTR and NGF were studied by RT-PCR, Western blotting and immunohistochemistry.
Results: Increased expression was observed of TrkA-mRNA at D20 (4.82-fold, p=0.0002) and D50 (4.25-fold, p= 0.0016), whereas p75NTR-mRNA and NGF-mRNA were up-regulated at D50 compared to D0 ((2.1-fold, $p < 0.0001$), (5.2-fold, $p < 0.0001$) respectively). At protein level, Western blotting of the spinal cord samples revealed an increase of TrkA, p75NTR and NGF at D20 and D50 ($p < 0.0001$). Increased expression of TrkA at D10 (p=0.048), D20 and D50 ($p < 0.0001$) was observed immunohistochemically in the white matter of spinal cord. p75NTR was increased at D20 and D50 ($p< 0.0001$). NGF in the white matter showed high expression at D20 and D50 compared to D0 ($p< 0.0001$). In the grey matter, TrkA and p75NTR were increased at D20 ($p < 0.0001$, p= 0.0011 respectively). NGF was highly expressed at D20 and D50 compared to D0 ($p< 0.0001$, p=0.001, respectively).
Conclusions: The expression profile of NGF and its receptors, TrkA and p75NTR, in areas of inflammatory demyelination indicates their possible involvement in the underlying pathology and reorganization of degenerated spinal cord during the course of EAE.

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Genetics/Epigenetics

EP1460
Difference of tissue-specific networks where the associated genes are densely interconnected between Japanese and European descent patients with MS

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Background: Many associated variants were detected in multiple sclerosis (MS) from genome-wide association studies (GWAS). However, not much is known about the biological effect of each variant and difference of associated tissues among races.
Objective: To reveal specific tissues where the associated genes with Japanese MS are more densely interconnected than expected and clarify difference of associated tissues between Japanese and European descent MS.
Methods: GWAS was conducted in 533 Japanese patients with MS and 1,789 controls. After converting variant p values into gene p values, the values except for the MHC region were applied to tissue-specific regulatory networks which were composed by merging transcription factor sequence motifs with promoter/enhancer activity data from the FANTOM5 project (Marbach D, et al. Nat Methods, 2016). Interconnectivities were compared with index calculated in the same way for 10,000 permutations of the ranked gene list. Those enrichment scores were compared with ones calculated by using GWAS results in European descent MS.
Results: In 32 high level regulatory networks, genes associated with Japanese MS were densely interconnected in networks of neurons and fetal brain, connective tissue, lymphocytes, connective tissue and integumental cells, and lymphoma (FDR corrected $p value < 0.05$). On the other hand, any specific networks were detected by using genes associated with European-descent MS. Among networks of lymphocytes, the associated genes were most interconnected in the network of natural killer cells (FDR corrected $p = 0.00070$).
Conclusions: The associated genes were functionally different between Japanese and European descent MS from the view point of tissue specific regulatory network.

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EP1461

Cross-sectional and longitudinal analysis of clinical parameters in a large-scale, national, multicentric multiple sclerosis cohort and the influence of MC1R SNPs

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The Melanocortin 1 Receptor (MC1R) determines skin type and hair color. As the *MC1R* gene is highly polymorphic, there are several variants known, some of which result in diminished receptor function associated with reddish hair, but also risk for melanoma. The MC1R has also been implicated in diseases like Alzheimer's and Parkinson's. Notably, a relationship between the MC1R single nucleotide polymorphism (SNP) Arg160Trp and MS incidence has been found in a previous study.

In our study we investigated the impact of MC1R SNPs on clinical parameters of MS patients. We used data from a multicentric German registry with knowledge of the patients' MC1R status for 21 different SNPs including the most common variants Asp84Glu, Arg151Cys, Arg160Trp, Val92Met, Arg163gln. Variants with low allele frequency were excluded from analysis but information for all 21 SNPs was used to define a WT group. Baseline characteristics were distributed as follows: 986 patients, mean age of 34.31 years, 69.9% women, 45.4% CIS patients, 54.5% RRMS, 32.4% ever-smokers, 40.1% WT, 8.1% with the SNP Arg151Cys, 18.4% with Arg160Trp, 22.7% with Val92Met, 10.1% with Arg163Glu. The mean clinical scores were 1.50 (EDSS), 24.01 (MUSIC), and 39.11 (FSMC).

For baseline analysis of clinical scores, we specified a generalized linear mixed model, which allows for binary responses (e.g. dichotomized EDSS), adjustment for confounders (sex, age, smoking) and a random intercept to account for center variability. All patients were untreated at baseline (inclusion criterium). Upon testing we found a significant influence of Arg160Trp on EDSS (p=0.016) and MUSIC (p=0.027) with a trend in the FSMC score (p=0.064). There was no such relationship for the other variants tested.

To further test our hypothesis over time we chose a nested panel data model with three time points and adjustment for treatment (yes/no). We found an effect of the Arg160Trp variant on EDSS (p=0.008), MUSIC (p=0.011) and FSMC (p=0.042). Furthermore, carriers of this variant show an overall trend towards a higher annualized relapse rate (p=0.064). This is intriguing, as Arg160Trp has already been associated with MS incidence and Parkinson's severity, but also melanoma, where it is associated with high risk and bad prognosis.

Finally, we aim at validating these findings in other national cohorts. Taken together, this study suggests that MS patients with the MC1R SNP Arg160Trp, suffer from worse MS symptoms compared to WT patients.

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Conflicts of interest:NS has received travel support from Genyzme and Novartis. PO, JB, TA, GA, TD, NM, KL have no conflicts to report. HW has received honoraria for acting as a member of Scientific Advisory Boards for Biogen, Sanofi-Genzyme, Merck Serono, Novartis, Evgen, MedDay Pharmaceuticals, Roche Pharma AG); speaker honoraria and travel support (Biogen, Sanofi-Genzyme, Merck Serono, Novartis, Roche Pharma AG, Alexion, Cognomed, F.Hoffmann-LA Roche Ltd, TEVA, WebMD Global, Gemeinnützige Hertie-Stiftung, Peervoice, Swiss Multiple Sclerosis Society); compensation as consultant (Biogen, Novartis, Sanofi-Genzyme, Abbvie, Actelion, IGES, GlaxoSmithKline GmbH, Roche Pharma AG, Swiss Multiple Sclerosis Society) an received research support by the German Ministry for Education and Research (BMBF), Deutsche Forschungsgesellschaft (DFG), Else Kröner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies (IZKF) Muenster and RE Children's Foundation, Biogen, GlaxoSmithKline GmbH, Roche Pharma AG, Sanofi-Genzyme and Novartis.

EP1462

Involvement of NINJ2 in inflammatory activity in MS

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Introduction: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by demyelination and axonal degeneration. Several risk factors are involved in the disease; immune cells, that are known to migrate from peripheral blood to CNS, play a key role in MS pathogenesis. In a recent genome-wide association study we identified rs7298096, located 3.5Kb upstream to *NINJ2* gene, which encodes for an adhesion molecule, as associated with response to Interferon β (IFNβ) treatment in MS patients.
Aims: To study the functional role of rs7298096 and NINJ2 in MS inflammatory activity.
Methods: We performed survival analyses on 3 cohorts of IFNβ-treated MS patients (n=928) from Italy, Spain and Australia to study the association between rs7298096 and time to first relapse (TTFR) after drug start (4-year follow-up). eQTL analysis was performed using GTEx Portal and an *in vitro* luciferase assay was also conducted. To better characterize the role of NINJ2 in inflammation, co-expression analysis was performed using COXPRESSdb, followed by pathway analysis. Expression of NINJ2 in immune cell types from 24 untreated MS patients was measured through RNAseq. NINJ2 mRNA and protein expression will be evaluated in monocytes of MS patients under several conditions through qPCR and immunocytochemistry assays.
Results: $Rs7298096_G$ patients showed a longer TTFR after IFN-β therapy start compared to $rs7298096_{AA}$ patients (HR=1.51,P=$2x10^{-4}$). The SNP had a strong eQTL association with *NINJ2* gene expression in whole blood (P=$7.0x10^{-6}$;β=0.13); the effect of rs7298096 on gene expression was confirmed *in vitro* (P=0.01). Co-expression analysis suggests an involvement of NINJ2 in pathways related to immune system and, among them, in the leukocyte transendothelial migration pathway (P=$5.0x10^{-4}$). Monocytes showed a higher NINJ2 expression compared to the other immune cell types (P< 0.0001, fold increase: monocytes-B cells=1.8; monocytes-T cells=1.7). qPCR and immunocytochemistry experiments are ongoing.
Conclusions: Starting from genetic data, we focused our attention to a specific membrane adhesion molecule, the ninjurin2, encoded by the *NINJ2* gene, that is already known to play a role in the adhesion between monocytes and endothelial cells and that could be involved in the migration of immune cells inside the CNS and in the onset of relapses. Additional analyses and experiments are required to better assess the role of the protein in inflammation.

Disclosure

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EP1463

A whole-exome sequencing approach in multiplex Italian multiple sclerosis families to identify new genes involved in the disease

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Introduction: Multiple Sclerosis (MS) is a multifactorial inflammatory and neurodegenerative disease in which both genetic and environmental factors contribute to the pathogenesis. More than 200 common variants have been already identified to be associated to MS susceptibility, however it is still unclear the role of rare/private variants in raising disease risk.
Aim: to explore the role of rare functional variants in MS by studying multiplex families.
Methods: We recruited a total of 29 families with ≥ 3 affected relatives (2 of them with first-degree relationship). Whole exome sequencing (WES) was performed on Illumina Hiseq2500 platform.

An internal pipeline based on BWA aligner and GATK UnifiedGenotyper was used for alignment and calling steps, while variant annotation was performed using SnpEff suite.
For each family with at least two sequenced cases (24 families) we selected variants with: (a) High or moderate impact, (b) allele frequency (AF) ≤ 5% according to public databases and (c) AF≤10% in Italian population according to our internal database of healthy controls (HC).
For each family we generated lists of genes according to two different strategies:
(i) "sharing model" including genes with at least one variant shared by all affected members in at least one family followed by comparison across families; (ii) "segregation model" including genes with at least one variant that segregates according to family's pedigree. Pathway analysis was then performed within each model using WebGestalt tool.

Results: A preliminary analysis on 12 families (37 MS and 30 HC) allowed to identify:
(i) 2130 genes containing variants in at least one family, 119 of which were present in at least 3 families;
(ii) 359 genes harbouring variants present in at least one family, of which 11 in common between at least two families.

In either model pathway analysis showed an enrichment of genes involved in immunity (i.e. Th1 and Th2 cell differentiation (FDR=0.018 and 0.065 respectively in sharing and segregation model), Cell adhesion molecules (CAMs) (FDR=0.095 and 0.065 respectively in sharing and segregation model)).
Analyses on the overall cohort are ongoing.

Conclusions: The application of WES in familial cases can be useful in identifying rare variants potentially contributing to the disease and in unravelling novel genes, pathways and mechanisms involved in MS pathophysiology.

Disclosure

E. Mascia, A. Zauli, C. Guaschino, L. Ferrè, M. Sorosina, A.M. Osiceanu, S. Santoro, S. Peroni, D. Biancolini, S. Bonfiglio, D. Lazarevic, N. Barizzone, C. Basagni, M. Zuccalà, D. Vecchio, M. Liguori, F.M. Guerini, D. Caputo, G. Tonon, S. D'Alfonso : nothing to disclose.
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EP1465

Functional relevance for *CXCR5* variants associated with multiple sclerosis

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Background: A number of multiple sclerosis (MS) risk common variants have been successfully identified through genome-wide association studies (GWAS), and they explain about 40% of the genetic predisposition to MS. Here, we aimed to identify new common variants associated with MS and investigate their potential functional implications in the disease.

Methods: Coding and regulatory regions of 14 MS-risk genes were resequenced using the Illumina Hiseq technology in 524 DNA samples from MS patients and 546 from healthy controls (HC). Raw data were mapped to the human reference genome (hg19) using the BWA aligner and variant discovery were performed with the HaplotypeCaller tool. Top associated variants were selected for validation in 3450 DNA samples from MS patients and 1688 from HC using the MassARRAY System (Agena Bioscience), and the top validated variant in the *CXCR5* gene was chosen for further functional studies. Linkage disequilibrium (LD) analyses were performed to select variants in high LD (r^2>0.5) with the top one and encountered variants were included in the successive studies. HEK cells were transfected with the pGL4.23-GW plasmid containing the insert under study and the *CXCR5* gene promoter transcriptional activity was then assessed by luciferase reporter assays.

Results: Targeted resequencing revealed a total of 32 variants differentially distributed between MS patients and HC ($p< 0.05$), of which 9 polymorphisms within 7 genes were selected for further genotyping in an independent cohort of cases and controls. The following three polymorphisms were validated: rs10892307 (*CXCR5*, $p=1.37\times10^{-6}$, OR=0.76), rs2762943 (*CYP24A1*, p=0.047, OR=1.16) and rs1599932 (*TSFM*, p=0.001, OR=0.85). Variants rs3176905, rs11602393 and rs55756957 were in high LD with the most strongly associated variant, rs10892307, and hence were included in the luciferase assays. Statistical analysis demonstrated a modest but significant increased transcriptional activity of the minor alleles of rs11602393 and rs55756957 when compared with their respective major alleles in the forward orientation, showing a 2.16-fold (p=0.005) and a 1.75-fold (p=0.01) higher ratio of luciferase activity, respectively.

Conclusions: We report a novel association with MS susceptibility in the *CXCR5* gene. Functional studies suggest that the rs11602393 and rs55756957 variants impair CXCR5 transcriptional activity and may explain the association of the rs10892307 variant with MS.

Disclosure

E. Gil-Varea, F. Matesanz, M. Fedetz, N. Spataro, S. Malhotra, A. Navarro, E. Bosch and A. Alcina report no disclosures.

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.

M. Comabella has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma, Merk Serono, Biogen-Idec, Teva Pharmaceuticals, Sanofi-Aventis, Genzyme and Novartis.

O. Fernández has received honoraria as consultant in advisory boards, and as chairmen or lecturer in meetings, and has also participated in clinical trials and other research projects promoted by Biogen-Idec, Bayer-Schering, Merck-Serono, Teva, Novartis, Roche, Allergan and Almirall.

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Ll. Ramió-Torrentà has received speaking honoraria and travel expenses for scientific meetings and has participated in advisory boards in the past years with Bayer Schering Pharma, Biogen, EMD Merck Serono, Sanofi Genzyme, Novartis, Sanofi-Aventis, Teva Phramaceuticals, Almirall and Roche.

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EP1466

The MS risk variant rs2762943 of the *CYP24A1* gene is associated with decreased serum levels of the active form of vitamin D

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Background: Genetic and environmental factors are known to influence the complex pathogenesis of multiple sclerosis (MS). In recent years, numerous studies have suggested that vitamin D deficiency contributes to MS risk. By means of targeted resequencing (524 MS patients and 546 healthy controls) and subsequent genotyping in an independent cohort (3450 MS patients and 1688 healthy controls), we identified a variant located in the *CYP24A1* gene, rs2762943, that was associated with increased MS risk. The *CYP24A1* gene encodes a protein that initiates the degradation of the physiologically active form of vitamin D [1,25-dihydroxyvitamin D - $1,25(OH)_2$-D]. Here, we aimed to assess the functional role of the rs2762943 polymorphism in the pathogenesis of MS.

Methods: By means of chemiluminescent immunoassay technologies, serum levels of 25-hydroxyvitamin D [25(OH)-D] and $1,25(OH)_2$-D were measured in two independent cohorts of 101 MS patients (30 minor allele - MA carriers, 71 MA non-carriers for rs2762943) and 100 MS patients (26 MA carriers, 74 MA non-carriers for rs2762943) respectively. In addition, peripheral blood mononuclear cells (PBMC) from 16 MS patients (8 MA carriers, 8 MA non-carriers for rs2762943) were cultured with 25(OH)-D (500nM), $1,25(OH)_2$-D (1nM) or vehicle for 24 h. Total RNA was extracted and *CYP24A1* mRNA expression levels were analyzed by RT-PCR.

Results: Serum levels of $1,25(OH)_2$-D were significantly lower in MA carriers for rs2762943 compared to MA non-carriers ($p=0.004$), whereas serum 25(OH)-D levels were comparable between MA carriers and non-carriers. After 24 h of 25(OH)-D stimulation, no differences in the *CYP24A1* gene expression levels were found in PBMC from MA carriers and non-carriers. Interestingly, a 4-fold higher *CYP24A1* mRNA expression was observed in MS patients carrying the MA for rs2762943 compared to MA non-carriers after 24 h of $1,25(OH)_2$-D treatment.

Conclusions: The decreased $1,25(OH)_2$-D serum levels observed in MA carriers may be associated with a *CYP24A1* gain of function conferred by the rs2762943 variant. Additional functional studies are needed to confirm these initial findings and further explore the implication of the rs2762943 variant in MS pathogenesis.

Disclosure

E. Gil-Varea, R. Ferrer, F. Matesanz, N. Spataro, S. Malhotra, A. Navarro, E. Bosch and A. Alcina report no disclosures.

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.

M. Comabella has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma, Merk Serono, Biogen-Idec, Teva Pharmaceuticals, Sanofi-Aventis, Genzyme and Novartis.

O. Fernández has received honoraria as consultant in advisory boards, and as chairmen or lecturer in meetings, and has also participated in clinical trials and other research projects promoted by Biogen-Idec, Bayer-Schering, Merck-Serono, Teva, Novartis, Roche, Allergan and Almirall.

A. Saiz has received compensation for consulting services and speaker honoraria from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd and Novartis.

Ll. Ramió-Torrentà has received speaking honoraria and travel expenses for scientific meetings and has participated in advisory boards in the past years with Bayer Schering Pharma, Biogen, EMD Merck Serono, Sanofi Genzyme, Novartis, Sanofi-Aventis, Teva Phramaceuticals, Almirall and Roche.

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EP1467

Long noncoding RNA-Ccr2-5As and THRIL as novel prognostic epigenetic biomarkers in patients with multiple sclerosis

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Background: Long non-coding RNAs (lncRNAs) have been reported to be involved in the pathogenesis of various human diseases, however, few studies had investigated the potential link between lncRNAs and MS pathology. The aim of the study was to study the expression of long noncoding RNA-Ccr2-5As and THRIL (TNF alpha and heterogenous nuclear ribonucleoprotein hnRNPL) in MS patients and to correlate them with the disease progression and level of disability.

Subject and methods: Seventy two MS patients (relapsing remitting and secondary progressive types) and 30 healthy controls were recruited for the study. They were tested for Long noncoding RNA-Ccr2-5As and THRIL quantitation in serum by real time PCR.

Results: LincR-Ccr2-5'AS was found to be significantly down-regulated in MS patients as compared to controls; the decrease was ≥2 compared to controls (the fold change = 0.34, p = 0.03). On the other hand, LincRNA THRIL was significantly up-regulated in MS patients compared to controls with increase ≥ 6 fold from controls (the fold change = 6.18 , p = 0.02). THRIL fold change was found to be higher in RRMS compared to SPMS patients (p-=0.04).
Conclusion: lincRNA-Ccr2-5As and THRIL are novel and potentially useful prognostic epigenetic biomarkers for development and progression of multiple sclerosis.
Key words: multiple sclerosis; Long noncoding RNA, biomarker, epigenetics

Disclosure

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EP1468

Multiple sclerosis genetic risk variants correlate with protein expression in monocytes of relapsing remitting patients: a protein quantitative trait loci study

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Background and aim: The genetic contribution to Multiple Sclerosis(MS) susceptibility is well established, with more than 30 HLA and 200 non-MHC variants linked to disease susceptibility; though, the mechanisms of increased risk due to these SNPs are unclear and studies exploring their association with gene(eQTL) and protein(pQTL) expression can help to shed light on their role in pathogenesis. We found that 3 MS risk variants, rs3809627, rs35218683 and rs6032662 correlated with mRNA levels of MAPK3, IFITM3 and CD40 in peripheral blood mononuclear cells. Here, we investigated the association of these SNPs with protein expression in monocytes from MS patients to better clarify their biological effect.
Methods: CD14+ cells were isolated from 118 RRMS patients treated with glatiramer acetate(n=54) or dymethylfumarate(n=64) and expression of MAPK3, IFITM3 and CD40 was measured with flow cytometry(CFM) as median fluorescence intensity(MFI). Array genotyping was performed, followed by imputation, and genotypes in rs3809627 and rs6032662 were obtained; rs34481144 was used as a tagging SNP(r2:0.48) for rs35218683. Association of MS-related and surrounding variants with protein expression was tested under a linear regression model, covarying for clinico-demographic characteristics (age, gender, therapy) and technical parameters (batches, CFM quality); significance was assessed with permutation testing. A colocalization analysis was performed to test overlap with MS signals.
Results: MS risk alleles rs3809627^{C}, rs6032662^{C} and rs34481144^{T}, were associated to a lower expression of MAPK3, CD40 and IFITM3 compared to the alternative alleles($p< 0.01$). When analyzing the nearby genomic regions, we found stronger pQTL signals in MAPK3 and IFITM3 region but we failed to identify any pQTL in the CD40 region after multiple testing correction. The posterior probability of colocalization with the MS signal was high for IFITM3(71.6%) while results for the MAPK3 region were inconclusive.
Conclusions: Our results suggest that the MS-risk region on chr11 likely modulate both gene and protein expression of IFITM3, an interferon induced protein with antiviral and anti-inflammatory properties. It is not clear whether the MAPK3 variant affects protein expression: the overlap in association may be coincidental. This effort prioritizes IFITM3 as a locus with a clear functional effect on downstream biology that we can pursue further as we develop strategies to reverse effects of risk variants

Disclosure

Dr Laura Ferrè, Dr Tina Roostaei, Dr Charles White, Dr Laura Martinez-Calvo, Dr Daniel Felsky, Dr Belinda Kaskow have noting to disclose. Dr Philip De Jager served as a member of advisory board for Celgene, Roche, Sanofi/Genzyme, received grant funding from Eisai, Roche, Biogen, Lundbeck and speaker honorarium from GlaxoSmithKline.

EP1469

Genome-wide DNA methylation in secondary progressive multiple sclerosis patients reveals unique epigenetic signature

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Our understanding of relapsing-remitting MS (RRMS) has improved markedly, leading to several new therapies for RRMS patients; however, the pathology of progressive disease remains poorly understood. Epigenetics, such as DNA methylation, provide a logical interface for environmental factors to influence the genome. Our previous work identified two major differentially methylated regions (DMRs) at the *HLA-DRB1* and *RNF39* loci in $CD4^+$T cells of RRMS patients. The aim of this study was to better understand the processes involved in secondary progressive MS (SPMS) by investigating the DNA methylation profiles of SPMS patients.

We performed an epigenome-wide association analysis of DNA methylation in $CD4^+$ T cells from 24 SPMS patients and 24 healthy controls and a replication cohort of 12 SPMS patients and 12 healthy controls. DNA was bisulfite converted and hybridised to Illumina EPIC arrays. Data was analysed using a combination of R/Bioconductor and custom scripts.

Genome-wide methylation analysis revealed that the majority of differentially methylated sites (75%) in SPMS patients were hypermethylated. We did not identify the DMR at the *HLA-DRB1* locus that we previously identified in the $CD4^+$ T cells of RRMS patients. We did identify a DMR at the *RNF39* locus as previously identified in RRMS patients. This DMR contains 7 of the sites contained in the RRMS cohort, which ranged from 10-13% differential methylation. In contrast to the hypermethylation seen in the RRMS cohort, the SPMS DMR is hypomethylated.

This data suggests that progression to SPMS results in increased DNA methylation. In addition, the differential methylation identified at *HLA-DRB1* is only present in RRMS patients and not SPMS, suggesting this DMR may be unique to the earlier stage of disease. Finally, our data suggest *RNF39* may switch from hypermethylated to hypomethylated in response to change in disease course. The biological relevance of this DMR can only be speculated on at this stage. *RNF39* remains poorly characterized but is located in the major histocompatibility complex (MHC) class I region, suggestive of a role in immune system function. Consistent with this, *RNF39* has been previously associated with other autoimmune conditions such as systemic lupus erythematosus and Becet's disease. Taken together, these results highlight the importance of epigenetic factors at the MHC region in MS.

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EP1470

Circulating miR-320b and miR-421 are deregulated in primary progressive MS patients

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Background: Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) which causes inflammation, demyelination and neurodegeneration. Different clinical subtypes as relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS) have been described.

Circulating microRNAs (miRNAs), as an epigenetic mechanism of susceptibility to MS, might provide us useful biomarkers to identify disease subtypes, and also increasing knowledge about the biological processes involved in each one. The aim of this study was to identify a differential miRNA signature in PPMS patients.

Methods: Serum samples of 36 patients were collected (10 controls, 10 RRMS and 16 PPMS patients). Total RNA was extracted from serum using the mirVana™ PARIS™ RNA miRNA kit. TaqMan Advanced miRNA cDNA Synthesis Kit was used to retrotranscribe and preamplify circulating miRNAs and TaqMan OpenArray Human Advanced MicroRNA Panels were run to study the presence of 754 well-characterized human miRNAs.

OpenArray profiling data was filtered guaranteeing good quality of the detection and cut-off thresholds were set at 28 Cts. Data was normalised using geometric mean and differential expression analysis was performed by Kruskal-Wallis test.

Results: A total of 217 miRNAs were detected in at least 75% of serum samples, 175 of which presented Ct values equal or below 28. 13 significantly deregulated miRNAs between different groups were detected. Two miRNAs (miR-320b and miR-421) presented a singular signature in PPMS patients compared to controls and RRMS in the post hoc analysis.

While miR-320b levels were significantly down-regulated in PPMS patients compared to both controls and RRMS ($p=0.035$ and $p=0.017$ respectively), miR-421 expression was up-regulated ($p=0.008$ and $p=0.015$ respectively).

Pathway analyses showed that those miRNAs regulates the Hippo signalling pathway, a non-classical inflammatory pathway that seems to be involved in several chronic diseases such as neurodegeneration.

Conclusions: The results presented herein pointed out a deregulation of miR-320b and miR-421 as a key factor for PPMS development. However, further research must be addressed in order to determine the underlying mechanisms that are involved in the different subtypes of MS.

Disclosure

Muñoz-San Martín M reports no disclosures.

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Tomàs-Roig J reports no disclosures.
Celarain N reports no disclosures.
Gómez I reports no disclosures.
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Quintana E reports no disclosures.
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EP1471

Total absence of the dominant HLA-DRB1*15 allele among patients with positive and most frequent HLA-DPB1*03, in a Hellenic cohort with multiple sclerosis

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Buckground: Multiple Sclerosis(MS) is the most studied demyelinating disease of the Central Nervous System, affecting mainly young adults. The role of HLA-DRB1*15:01 allele is well established in MS and confirmed in many Caucasian populations, the Hellenic included. Recently, carriage of DPB1*03 allele has been identified as another genetic predisposing factor for developing MS, in Hellenic and other Caucasian populations.
Objectives: In this study we aimed towards showing the DRB1* allele distribution in the cohort of Hellenic MS patients, who are positive for the DPB1*03 allele, in an attempt to clarify the putative interaction of these HLA-class-II groups.
Methods: A total of 70 MS outpatients were genotyped for DPB1* polymorphisms(140 alleles), and 20 of them for DRB1* polymorphisms(40 alleles), after obtaining formal consent. All patients were of Hellenic origin and diagnosed with clinically definite MS according to the McDonald criteria. HLA-genotyping was performed by Sequence Specific Oligonucleotide(SSO) technique. Statistical processing(SPSS V.21 software) included univariate analyses with chi-square tests (level of significance set at p=0.018 after Benjamini- Yekutieli correction).
Results: Our patients were predominantly women (64.3%), with mean age 38.1(+/- 11.4) years, and mean age of MS onset 29.6(+/- 11.4) years. DPB1*03:01 allele frequency was significantly increased in MS patients compared to controls(p=0.001). There were also trends towards increase of the DPB1*10(p=0.04) and DPB1*14 (p=0.05) alleles and towards reduction of DPB1*02(p=0.08), DPB1*13(p=0.09) and DPB1*17(p=0.08) alleles. Interestingly, no coexistence of DRB1*15:01 and DPB1*03:01 was found in any patient of our sample.
Conclusions: Although DRB1*15:01 allele has an established role in MS (risk, vit D, EBV, clinical phenotype, therapy response) there is inadequate information concerning the impact of DPB1* region in MS genetic burden and impact on clinical phenotype. Our observations are in accordance with recent studies, regarding increased DPB1*03:01 frequency in Caucasian and non-Caucasian MS patients. The total absence of the dominant HLADRB11*15 allele among patients with positive and most frequent HLADPB1*03allele enhances the possibility that it maybe has an independent role that has to be further studied in larger cohorts of MS patients, of various origins, aiming potentially at more individualized therapeutic decision-making in the future.

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EP1472

Family distribution in multiple sclerosis: a study of the prevalence of familial recurrence in Puerto Rico

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Background: Multiple sclerosis (MS) is a disease in which family distribution, genetic/environmental factors, and geographical location has been well documented worldwide to have effect on prevalence and incidence. With the increased incidence of MS in Puerto Rico (PR), family distribution correlation is a factor that requires further investigation in order to describe the risk it represents in the Puerto Rican population. From 2013 to 2016, a total of 583 new cases of MS were diagnosed in PR. The genetic makeup of the Puerto Rican population is comprised of African American, Native American, and European ancestry. It is well-documented that descendants of European ancestry have increased likelihood of developing MS. Research on familial aggregation seems to be a good source to address the relationship between genetic susceptibility and environmental factors that trigger the onset of MS in a specific population.
Objective: Analyze the presence of MS patients who have family member with MS in hopes of further elucidating the possible genetic factors associated with MS
Methods: As part of this study, we investigate a population of patients with MS who attend to San Juan MS Center to identify if they have a first, second or third-degree relative that is also affected with MS. This effort was performed in an attempt to describe the risk of developing MS within a family with relatives with previous history of the condition and to describe the prevalence of MS between relatives in Puerto Rico. For this, 405 patients were analyzed using descriptive statistics.
Results: 10.1% of MS patients had one or more family members with MS. The most common family member with MS among the studied population was male cousins from mother's side (16.1%). This was followed by fathers and sisters (both 12.5%), and female cousins on mother's side (10.7%).
Conclusion: Here we show that 10.1% of MS patients have a family member with MS and that the most common family

relation was male cousins from mother's side. As previously stated, Puerto Ricans have a European, African, and Native American genetic composition. However, it has been shown that most of the PR population has higher percentages of European ancestry. This together with the family data presented here suggest that further genetic analysis should be performed on this population in order to establish a possible genetic marker for MS in this Hispanic population.

Disclosure
Nothing to disclose

Immunology

EP1473
A possible association between circulating vitamin D and haptoglobin concentrations in multiple sclerosis patients

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Background: Evidence continues to accumulate supporting a protective role for vitamin D in multiple sclerosis (MS) risk and progression. However, whether vitamin D immunomodulatory effects can be translated into clinical benefits in patients with MS is still a matter of debate. Finding modulator factors in relation to vitamin D an MS could be helpful for clinicians to optimize individual therapies. We aimed to investigate association between circulating levels of vitamin D and haptoglobin as mediators in inflammatory and autoimmune pathways in different types of MS.
Methods: This crass-sectional study enrolled 72 MS patients. The diagnosis of MS was made by a neurologist according to the McDonald criteria. The inclusion criteria were set as: clinically definite MS with an expanded disability status scale (EDSS) score ≤5.5 and without history of other chronic disorders. The MS patients was comprised of three clinical subtypes: relapsing remitting-MS (RR-MS, n=45, 62.5%), secondary progressive-MS (SP-MS, n=12, 16.5%) and primary progressive - MS (PP-MS, n=15, 21%). The serum vitamin D, haptoglobin, Interleukin 1-beta (IL-1β) and Tumor necrosis factor-alpha (TNF-α) levels were measured by immunoassay.
Results: The MS patients consisted of 76.2% (n=54) female with a mean age of 34.78±8.89 years and the mean disease of 7.02±5.41 years (mean±SD). In subgroups, there was no significant difference between RR-MS, SP-MS and PP-MS, regarding age (P=075), sex (p=0.23), body mass index (p=.63), and duration of disease (p=0.40).
There were not any significant correlations between haptoglobin levels and age and duration of diseases and IL-1β and TNF-α levels in each sub-group (p>0.05).
Notably, in RR-MS patients, there was negative correlation between circulating vitamin D and haptoglobin (p=0.005, r=-0.43). The result remained significant even after adjustment for age, and sex (p=0.03).
Conclusion: Our data suggest the negative correlation between circulating vitamin D and haptoglobin concentration in RR-MS patients may be explained by anti-inflammatory effect of vitamin D. The results will be helpful to explore the new therapeutic targets in MS patients.

Disclosure
Zhila Maghbooli: I have *no conflict of interest* to declare.
Yasaman Aghababaei: I have *no conflict of interest* to declare.
Arash Hossein-nezhad: I have *no conflict of interest* to declare.
Mohammad Ali Sahraian : I have *no conflict of interest* to declare.

EP1474
360° immune-profiling reveals new pathogenic immune cell subsets in multiple sclerosis: effects of glatiramer acetate

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Introduction: Multiple sclerosis (MS) is thought to be caused by a complex interaction between genetic and environmental factors. With the advent of new technologies, it has become increasingly clear that the cellular populations involved in immune responses are heterogeneous, and that multiple mechanisms may be involved in the pathogenesis of MS. The general picture which emerges from the studies on MS pathogenesis underlies the notion that all immune cell subpopulations are involved in disease induction and/or progression. Moreover, it is also clear that immune responses, both physiological and aberrant, are triggered by a very small number of cells within distinct cell subtypes. Thus, in order to identify unequivocally the subpopulations which are predominantly involved in the damage to myelin, a multivalent approach is required: each cell type must be classified and the pattern of expressed markers must be followed during the course of the disease, and monitored during therapy.
Methods: Serum cytokines, chemokines and growth factors and peripheral blood leukocyte (PBL) phenotypes were analyzed in patients undergoing treatment with glatiramer acetate 40 mg/gml (GA40) as part of the PhIV CONFIDENCE trial. Serum and PBLs were collected at baseline (BL) prior to GA40 treatment and at 3,6 and 12 months after initiating GA40.
Results: Compared to BL, GA40 treatment resulted in reduced pro-inflammatory cytokine production by all the analysed subsets of stimulated innate immune cells, and reduced activation by CD4 and CD8 T cells. For instance, monocytes produced less GM-CSF, a cytokine whose prominent role in neuroinflammation has recently been unveiled, and non classical monocytes reduced their release of IL6 and TNF-a.

Conclusions: In the present work we have used a strategy which has provided a comprehensive picture of markers in MS that change significantly in patients treated with DMT. The main findings indicate that over the course of 12 months after initiating GA40, there is a significant reduction in the production of proinflammatory cytokines by all the myeloid cell subsets that have been analysed. To this reduced cytokine production by innate immune cells corresponds a decrease in the activation and consequent functional response of cells of the adaptive arm of the immune response: indeed a lower frequency of activation was detected in all T cell compartments.

Disclosure

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The other authors have no disclosure to declare.

EP1475

The difference of intercellular cytokine profiles among MOG$^+$CNS disorders, AQP4$^+$NMOSD, and MS patients

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Background: Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are both autoimmune central nervous system (CNS) disorders. And anti-aquaporin-4 (AQP4) positive patients represents overwhelming majority in NMOSD. Anti-myelin oligodendrocyte glycoprotein (MOG) positive CNS disorder (MOG$^+$CD) involves a case who had both anti-MOG antibody and CNS involvement. These disorders share similar but diverse pathological and clinical characteristics. It is worth noting that T cell and related inflammatory cytokines have been proved to make considerable contributions for these diseases.
Objective: Investigate T cell subsets in peripheral blood monocytes (PBMCs) among MOG$^+$CNS disorders, AQP4$^+$NMOSD and MS, on basis of which, their contribution to the pathogenesis and clinical features of those disorders.
Methods: We enrolled 10 healthy controls (HCs)、20 relapse-remitting MS patients, 20 patients with MOG$^+$CD, 20 patients with AQP4$^+$NMOSD, who were all in remitting phase. Flow cytometry (FCM) was employed to detect T cell subsets (CD3, CD4, CD8, Th1, Th2, Th17, Treg, Th1/Th2, Th17/Treg). Meanwhile, evaluate the otherness of these cell subsets of and their correlation with clinical information.
Results and conclusions: MOG$^+$ CD has equivalent sex and age constituent but less EDSS score (P=0.014) compared with AQP4$^+$NMOSD. Compared with HCs, there is lower level of lymphocyte in AQP4$^+$NMOSD group (P=0.02), similar level of CD3$^+$ T cell, CD4$^+$ T cell, CD8$^+$ T cell,Th1 and Th1/Th2 among MOG$^+$CD group、AQP4$^+$NMOSD group and MS group, relatively lower level of Th2 in AQP4$^+$NMOSD group (P=0.073) and MS group (P=0.053) but the difference is not significant and higher level of Th17 and Th17/Treg in both AQP4$^+$NMOSD (P^{Th17}= 0.003, $P^{Th17/Treg}$< 0.001) and MS group (P^{Th17}< 0.001,$P^{Th17/Treg}$< 0.001) but milder these index in MOG$^+$CD group. And in MS group, Th17 could be viewed as disease predictive factor of prognosis. Additionally, the potential contribution of Th2 to relapse in both AQP4$^+$NMOSD and MOG$^+$CD group are also identified and in lower range of Th2, appropriately increasing it could be helpful for prolonging the average attack interval in AQP4$^+$NMOSD group. For Treg, its compensatory increasing effect when relapse is more sufficient in MOG$^+$CD group compared to AQP4$^+$NMOSD group, which resulted in severe neurological function damage (higher EDSS score) even though unfrequently attack recently resulting from steroid application.

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EP1476

Neuromyelitis optica and the role of Foxp3+ regulatory T cells

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Background: Alterations in the frequency or function of regulatory T cells (Tregs), which play a critical role in the maintenance of peripheral immune tolerance, are known to be involved in the pathogenesis of several autoimmune diseases. Neuromyelitis optica (NMO) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS), of which the etiology and mechanisms underlying its development are not completely understood. Although there is increasing evidence for the involvement of effector T cells in NMO, no data are available regarding the role of Tregs in its pathogenesis.
Aim: The aim of this study was to investigate the expression of regulatory T cell genes in NMO.
Results: A distinctive Treg gene signature in the peripheral blood of NMO patients is described, as well as significantly decreased Foxp3 mRNA expression in the peripheral blood mononuclear cells (PBMCs) of the patients vs that in the healthy controls (HCs) (NMO,1.8RQ vs HC, 6.8RQ, p=0.01).

Conclusions: The present study shows downregulation of key transcription factor Foxp3, one of the Treg genes that are abnormally expressed in NMO. Exploration of their function and interconnections in the peripheral immune system should advance our understanding of NMO pathogenesis.

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EP1477

Characterization of the immunophenotye of clinically isolated syndrome patients and conversion to multiple sclerosis

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Introduction: Clinically isolated syndrome (CIS) is the prodromal phase of multiple sclerosis (MS) course, with patients having suffered only one neurological episode. Up to 70% of CIS patients are subsequently diagnosed with MS, and therefore it is important to distinguish between those who will and will not convert to relapsing remitting multiple sclerosis (RRMS) at a later time point. This will not only allow for an earlier start of treatment but also help improve our understanding of the MS disease course.
Objectives: This study aimed to: (1) immunophenotype PBMC subsets in CIS and RRMS patients who are not receiving any disease modifying therapy; (2) identify markers that predict later progression from CIS to RRMS; and (3) analyze any changes in the PBMC subpopulations between early and late phases of RRMS.
Methods: Multi-colour flow cytometry panels were designed to identify up to 50 peripheral blood lymphocyte subpopulations. CIS patients were divided into those who do (CIS-C) or do not (CIS-N) covert to RRMS at a later point. The RRMS patients were further divided into early (RRMS-E) and late RRMS (RRMS-L).
Results: In B cells, naïve/transitional cells are significantly higher in RRMS-L than RRMS-E, which is similar to CIS-C. In female patients, RRMS-L have a higher amount than both RRMS-E and CIS-C. Pre-switch memory (CD27+IgD+) cells are significantly higher in RRMS-E than CIS-N. In the T cell compartment, the CD4-to-CD8 ratio is higher in the overall RRMS group than CIS-N. Both TfH and Th22 T helper amounts are lower in RRMS than both of the two CIS groups. CD8+CD127+CD45RA-, a memory subpopulation, is higher in RRMS than CIS-N, while CD8+CD62L-, an effector subpopulation, is lower in RRMS than CIS-N.
Conclusions: These results show that CIS patients who do or do not later convert to RRMS can be differentiated in some immune subpopulations. Those who later convert are similar to diagnosed RRMS patients in some lymphocyte subsets. They also show that the levels of immune cells in converter CIS patients are more similar to early than late RRMS patients in many subpopulations. These results partially support the view that CIS patients who convert are functionally the same as RRMS patients and suggests that the immunophenotyping of peripheral blood markers may be used to predict future conversion of CIS patients to RRMS and allow for earlier treatment of the disease.

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EP1478

The contribution of monocytes and the purinergic receptor, P2X7, in MS relapse

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Multiple sclerosis (MS) is a chronic neuroinflammatory condition with associated demyelination and neurodegeneration. The most common type of MS is relapsing-remitting (RRMS) where new symptoms occur in isolated attacks (relapses). The relapses can consist of new physical disability, cognitive deficits, or optic neuritis. Between the attacks, the symptoms may dissipate completely; however permanent neurological deficits can often remain leading to accumulation of disability. MS generally affects those in their early 30s and 40s and therefore the lifelong burden of disease and the effects of MS on quality of life can be very devastating. In this study we will look at the peripheral immune system and in particular the contribution of innate immune cells, monocytes, to MS relapse. Monocytes are immunoresponsive cells in the blood stream and they respond to various injurious agents by becoming activated and releasing various biologically active factors. The plaques of MS in the brain, spinal cord and along the optic nerve consist of large numbers of monocytes and their counterpart cells microglia (immunocompetent cells of the CNS). There is a large cohort of data indicating that monocyte and microglial activation can contribute to worsening disease and can play an important role in acute attacks. Microglia and monocytes express a purinergic (ATP sensing) receptor on their cell membrane, called, P2X7 receptor (P2X7R). We have previously shown that P2X7R expression can cause microglial activation. In this study we will be examining the role of monocytes and P2X7R in the setting of MS relapse. Patients who are having an acute MS relapse are recruited into this study, and 50mL of blood is collected from them. The blood is used to isolate and culture their

monocytes, as well as processing of serum for proteomic analysis and enzyme linked assays for various cytokines and chemokines. We have been able to show that monocytes from patients with RRMS at the time of MS relapse express P2X7R with increased P2X7R channel activity. The proinflammatory cytokine, interleukin 1β was also elevated from monocytes derived from patients with MS relapse and when exposed to GMCSF (granulocyte colony stimulating factor). Our data thus far highlights a critical role for P2X7R in MS relapse indicating that antagonism of this receptor could serve a key therapeutic strategy to combat the peripheral and central inflammation that is seen during MS flare.

Disclosure

I do not have any conflicts of interest.
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EP1479
T cell receptor repertoire in multiple sclerosis patients

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Objectives: To identify the T cell receptor (TCR) characteristics associated with multiple sclerosis (MS) pathogenesis by comparing the TCR repertoire of MS patients and healthy controls (HC).
Methods: Peripheral blood mononuclear cells from 39 MS patients and 19 HC were obtained. There was no significant difference in age at examination, sex, and positivity rate of the susceptibility alleles (*HLA-DRB1*04:05* and *HLA-DRB1*15:01*) in Japanese between the two groups. Next-generation sequencing with an adaptor ligation PCR was conducted for TCR genes (*TRA/B/D/G*). Diversity index was compared, and the effect of age was examined. Additionally, complementarity determining region 3 (CDR3) sequences of TCR β-chain were extracted and compared between 16 MS patients and 9 HC subjects with *HLA-DRB1*04:05*.
Results: TCR diversity declined with age in all four TCR genes, especially in the small-expanded clones. In *TRA/TRB*, diversity index was higher in MS than HC, which was still significant even after correcting for age at examination (p = 0.0043 and 0.024, respectively in Shannon's Index). In *HLA-DRB1*04:05*-positive individuals, when we focused on the hyper-expanded *TRB* clones by excluding small-expanded clones to eliminate the effect of age, unique clonotypes exclusively shared by 20% or more of each group was 36 in MS and 106 in HC. By comparing relatedness in all clonotypes, difference was found in amino acids located at the center of the CDR3, which is important for antigen binding, between MS and HC.
Conclusions: In TCR repertoire, small-expanded clones decreased with age and resulted in loss of diversity by aging. There was a difference at the center of the CDR3 between MS and HC with *HLA-DRB1*04:05*, suggesting a pathogenic role of TCR in MS.

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EP1480
CSF kappa light chain ratios potential prognostic impact in clinically isolated syndrome conversion to multiple sclerosis

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Background: Previous studies suggested that the detection of elevated kappa free light chain (KFLC) levels in the CSF might have diagnostic value in Multiple Sclerosis (MS). We hypothesize that CSF KFLC concentration might also have prognostic impact. We aimed to study whether CSF KFLC concentration in Clinically Isolated Syndrome (CIS) predicts conversion to clinically definite MS (CDMS) and disability progression.
Methods: We retrospectively selected adult patients with a typical CIS submitted to diagnostic lumbar puncture during the first 3 months after clinical presentation at a University Hospital, between January 2008 and December 2017. Additional selection factors were baseline MRI and oligoclonal band status availability and minimum 1 year of follow-up.
Consecutive patients paired CSF/serum samples, stored according to international consensus guidelines, were evaluated for KFLC concentration, using immunonephelometry (BN ProSpec, Siemens) and immunoturbidimetry (Optilite, Binding Site). KFLC values were expressed as KFLC quotient (CSF/serum KFLC) and KFLC index (CSF KFLC/serum KFLC)/(CSF albumin/serum albumin). A value of KFLC index >100 was considered significant for high KFLC intrathecal concentration.
We estimated risk of conversion CIS-CDMS and risk of disability progression after conversion, as measured by Expanded Disability Status Scale (EDSS) confirmed progression at 3 months, using a Cox univariate and multivariate regression (accounting for other established prognostic factors).
Results: Of the 31 patients analysed, 27 were women (87.1%), with a mean age of 30.5 years (± 8.4). Medular CIS was the most

common type, accounting for 12 patients (38.7%). 12 patients (38.7%) had 0-3 T2 lesions on baseline MRI, with 67.7% showing absent baseline Gad+ lesions. A majority of patients (87.1%) had positive oligoclonal bands in the CSF. Median KFLC quotients were 0.47 (IQR 0.72) (BN ProSpec) and 0.41 (IQR 0.64) (Optilite), with 48.1% of patients showing KFLC index>100.
26 patients (83.9%) converted to CDMS in a median follow-up time of 64 months (IQR 69.0). Higher KFLC index (>100) was not associated with CIS to CDMS conversion (HR 0,931, 95% CI 0.400-2.167; p=0.868), or EDSS progression (HR 1.191, 95% CI 0.397-3.574; p=0.775)
Conclusion: In our cohort, KFLC index does not seem to independently influence risk to conversion or risk of disability progression. Further studies with larger samples are necessary to accurately define prognostic value.

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EP1481

In vitro verification of *in silico* predicted antigenic properties of intrathecal B cell receptor repertoires - a pilot study

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Introduction: The pathogenic role of B cells in multiple sclerosis (MS) is not known. We have previously demonstrated that B cells from cerebrospinal fluid (CSF) of MS patients can activate T cells through specific recognition of antigenic determinants (idiotopes) from their own B cells receptors (BCR). The aim of the present study was to test whether antigenic properties of immunoglobulin variable heavy chain (IGVH) repertoires can be predicted *in silico*.
Methods*:* Transcribed IGVH repertoires from MS patients were sequenced and translated. *In silico* predicted human leukocyte antigen (HLA) class II affinity and endosomal processing, as well as T cell exposed motif rarity and transcript frequency, guided selection of ten potential stimulatory (rare) and five potential regulatory (frequent) idiotope-peptides from two MS patients. To validate the predictions, peripheral blood mononuclear cells from these patients were stimulated with 15-mer idiotope-peptides in presence of anti-CD40 for 16 hours. T cells were then labeled for activation status with anti-CD154 antibodies and phenotyped with anti-CD3, -CD4, -CD45RO, -CXCR5, -GARP and -PD-1, as well as anti-CD14 and -CD8 for dump channel. Unstimulated cells and/or insulin peptides were used as negative controls, and HLA class II restricted virus peptides including EBNA-1 were used as positive controls.
Results: In two MS patients, four of eight and seven of 14 idiotope-peptides predicted to be T cell antigens induced similar $CD4^+$ T cell activation as the positive control peptides. The responding $CD4^+$ T cells were mainly $CD45RO^+$ memory T cells, and included more $CXCR5^+$ follicular-like helper cells than those activated by negative control peptides. Activation of Tregs ($GARP^+CD154^-CD4^+$ T cells) was equally low for idiotope- and control peptides.
Conclusion: This *in vitro* pilot study suggests that MS patients have a memory T cell repertoire capable of recognizing frequent BCRs from endogenous CSF. It further indicates that antigenic properties of BCR-idiotopes from CSF of MS patients can be predicted in *silico* using HLA affinity and endosomal processing predictions. The rarity of one particular idiotope does not seem to predict whether T cells are tolerant to that idiotope.

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EP1482

Could basal levels of B cells and memory B cells identify responders to disease modifying treatments for MS?

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Background: Recent experience with new available immunomodulatory treatments depleting B cells has revealed the crucial role of this immune cell type in multiple sclerosis (MS) pathogenesis. Specifically, there is increasing evidence that lower frequency of B cells and particularly, memory B cells are associated with optimal response to immunomodulatory drugs. Thus,

monitoring memory B cell population would be useful to assess the effectiveness of immunotherapies in MS patients.
However, there is little evidence related to the predictive role of their levels at MS diagnosis. For this reason, we aimed to study the basal levels of both B and memory B cells in MS patients and their relation to MS treatment approach.
Methods: A total of 28 individuals were included (11 controls and 17 MS patients). We defined controls as patients with non-MS neurological disease. Blood samples were collected from both controls and recently diagnosed MS patients and then peripheral blood mononuclear cells (PBMC) were isolated and frozen in liquid nitrogen. B(CD45+CD19+)andmemoryBcells(CD45+CD19+CD27+CD38-) were quantified from thawed PBMC by flow cytometry in an ACURI-C6 apparatus (BD Bioscience). Cells were stained with specific previously titrated anti-human antibodies: CD45-APC, CD19-PE-Cy7, CD27-PE and CD38-FITC.
Data were shown as percentage of B and memory B cells from total PBMC count. Mann-Whitney U test was used for comparisons between groups and Fisher's exact test to compare percentages.
Results: At the disease diagnosis, MS patients showed no differences in the percentage of neither B (p=0.404) nor memory B cells levels (p=0.860) when compared to controls.
Then, MS patients were classified as responders to moderate-efficacy treatments (MET) or patients who received high-efficacy treatments (HET) as the first treatment after MS diagnosis. We measured lower levels of B cells [MET: median 7.6 (IQR: 4.0) versus HET: median 4.3 (IQR: 3.5); p=0.056] and memory B cells [MET: median 3.1 (IQR: 2.1) versus HET: median 1.8 (IQR: 0.9); p=0.046] in patients with clinical and radiological data to consider HET strategies from disease onset.
Conclusions: These exploratory findings suggest that levels of memory B cells have to be taken into account during the selection of the optimal therapeutic strategy. Because of the small sample size and the slightly significant values, further research must be addressed to confirm these preliminary results.

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Environmental factors

EP1483
Vitamin D levels and epidemiology of multiple sclerosis in Spain: Madrid vs Lanzarote

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Background: Low levels of 25-hydroxyvitamin D (25-(OH)D) have been described as one of the possible environmental factors involved in multiple sclerosis (MS) etiopathogenesis.
Objectives: To analyse 25-(OH)D serum levels of MS patients from Madrid and Lanzarote, two regions of Spain with completely different UV radiation rates, and to correlate them with epidemiological data.
Methods: 60 RR-MS patients from Lanzarote and 538 RR-MS patients from Madrid were included in a prospective study of one year of follow-up. Serum samples were collected in such a way that we got 25-(OH)D serum levels data from every month of the year. Incidence in Lanzarote was assessed in MS patients according to McDonald criteria between 2008 and 2015, while prevalence date was 12/31/15. Epidemiological data from Madrid was identified by bibliographic searches.
Results: 25-(OH)D serum levels were significantly higher in Lanzarote than in Madrid (median: 30.94 vs 20.50 ng/ml, respectively; p=1.60e-76). This difference appears throughout the year, but it is more pronounced in the first semester of the year (p=1.69e-58) than in the second one (p=7.25e-28). Moreover, percentage of patients with 25-(OH)D< 20 ng/ml was significantly lower in Lanzarote than in Madrid, especially in the first semester of the year (p=7.75e-44). Age of disease onset was significantly higher in Lanzarote than in Madrid (p=0.04). In terms of epidemiology, prevalence in Lanzarote was 50/100000, and incidence was 2.5/100000 inhabitants. Meanwhile, for Madrid, prevalence and incidence, according to bibliography, would be approximately 100/100000 and 3.8/100000, respectively.
Conclusions: MS patients from Lanzarote showed significantly higher 25-(OH)D serum levels and later median age of disease onset than the ones from Madrid. Moreover, incidence and prevalence rates were lower for Lanzarote. However, further studies are required in order to elucidate whether UV radiation rates, 25-(OH) D serum levels or lifestyle could be responsible of the latitudinal gradient observed for MS.

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EP1484

Serum levels of leptin and adiponectin are not associated with disease activity or treatment response in multiple sclerosis

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Background: Obesity increases the risk of multiple sclerosis (MS), but mechanisms behind this are unknown. The adipokines leptin and adiponectin are secreted by fatty tissue and have inflammatory properties. They could therefore be possible biomarkers of disease course and treatment response in MS.
Objective: To explore if adiponectin and leptin were associated with MS disease activity and could have a potential as biomarkers of MS disease activity and interferon beta (IFNB)-treatment response.
Methods: Cohort study of 88 patients with relapsing-remitting MS followed for two years with clinical scoring, repeated MRI scans and serum measurements, 6 months before and 18 months during IFNB-treatment. Association between serum level of adipokines and MRI activity were assessed by a generalized linear mixed model.
Results: The levels of leptin were lower (p=0.008) and the levels of adiponectin higher (p=0.037) during IFNB-treatment as compared to the treatment-naïve period reflecting the anti-inflammatory effect of the drug, but the changes in serum levels were not associated with disease activity. There was no association between serum-levels of leptin (OR= 0.99 (0.99-1.00; p=0.66)) or adiponectin (OR=1.02 (0.96-1.08; p=0.52)) and MRI disease activity. This was consistent before and during IFNB-treatment and after adjustment for age, gender and BMI. 18% of the patients obtained NEDA-3 status during IFNB-treatment, but there was no difference in serum adipokine levels between these patients and the patients that had disease activity. There was no association between serum-leptin level and EDSS score at baseline (p=0.89).
Conclusion: Our findings indicate that serum-leptin and adiponectin do not have a profound role in the immune mechanisms of MS-disease activity, and are therefore not suitable as potential biomarkers of disease activity or IFNB-treatment response in RRMS.

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EP1485

Ditary animal protein sources in relation to risk of neuromyelitis optica spectrum disorder

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Background: Neuromyelitis optica spectrum disorder (NMOSD) is an uncommon autoimmune disorder. Until now dietary risk factors of NMOSD remained unknown. The present study aimed to determine the effects of protein consumption on NMOSD risk.
Method: we performed a case-control study in sina hospital which has the only NMOSD specialist clinic in Tehran, Iran. We enrolled 70 cases with definite diagnosis based on NMOSD international consensus criteria published in 2015 and 214 controls. Cases were included in the study if they didn't change their diet after NMOSD onset and had disease duration less than 3 years. Demographic and anthropometric information were collected. Data on nutritional intake during the past year of study obtained by a validated 168-items food frequency questionnaire (FFQ) in control group. For completing the same FFQ, cases were asked to report dietary consumption of the year prior of NMOSD diagnosis. Dietary analysis was performed using nutritionist 4 (N4) software.
Result: The mean age of individuals were 35.34 years among cases and 43.31 years in control group. Eighty-five percent of patients in case group and 61% of control groups were women. After adjustment for age, gender, body mass index (BMI), total energy intake, smoking and alcohol consumption, total protein intake has been associated with 61% decrease in NMOSD risk (OR=0.39;95%CI: 0.18-0.83; p-for-trend:0.01) in third tertile, compared with first tertile. Also higher poultry intake in third tertile diminished NMOSD risk by 64% (OR=0.36; 95%CI: 0.16-0.83; p-for-trend:0.01:0.01). Conversely, a higher consumption of red and processed-meat was positively associated with a 2.31 folds increase risk of NMOSD (95%CI:1.10-4.84; p-for-trend:0.01) in third tertile of red and processed-meat intake.
Conclusion: Our finding proposed probable protective effects of a diet containing high protein with white meat source against NMOSD. Conversely, high red and processed- meat consumption might be a risk factor for NMOSD.

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EP1486

Environmental risk factors for NMO-IgG sero-positivity in neuromyelitis optica spectrum disorder

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Background: Neuromyelitis optica spectrum disorder (NMOSD) is referred to inflammatory demyelinating disease of the central nervous system. Data suggest that the presence of a highly specific serum autoantibody (NMO-IgG) that reacts against the water channel aquaporin-4 (AQP4), causes the inflammation and demyelination in NMOSD .Here, we studied the association between NMO-IgG and as cigarette smoking and alcohol use.
Methods: A case-control study was conducted in a referral hospital center in Tehran from 2015 to 2016 among patients with a definite diagnosis of NMOSD based on the international 2015 consensus criteria to assess the possible relation between positivity of NMO-IgG and environmental factors such as cigarette smoking and alcohol use. The enzyme-linked immunosorbent assay (ELISA) was used for checking the presence of aquaporin-4 immunoglobulin G (AQP4-IgG) status. Most of the tests have been completedduring the relapse before receiving corticosteroid. We designed a questionnaire to cover important epidemiological data of NMOSD and conducted structured face to face interviews patients by trained interviewers to collect the data.Finally the logistic regression was appliedin analysis via SPSS software package.
Results: The presence of NMO-IgG was positive for 71 (54.2%) and negative for 60 (45.8%) of patients.
The increased NMO-IgG positivity odds among life time smokers (OR = 3.24; 95% CI= 1.16, 9.08), Current smokers (OR = 6.08; 95% CI= 1.26, 29.39), passive smokers (OR = 2.22; 95% CI= 1.10, 4.50),and Whisky/vodka consumption (OR = 3.65; 95 CI= 1.21, 10.93) was observed.
An association between water-pipe smoking, bear and wine intake and NMO-IgG positivity was not observed (P value > 0.05).
Conclusion: life time and current smoking, passive smoking and Whisky/vodka consumption are risk factors for NMO-IgG positivity. Studies have been revealed the role of smoking in development of autoantibodies.
Therefore NMO-IgG as an important autoantibodies is not an exception.

Disclosure

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EP1487

Vitamin D and body mass index in Egyptian multiple sclerosis patients

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Background: Vitamin D and obesity may be related to the pathogenesis and disease activity of multiple sclerosis (MS).
Objectives: To study the role of vitamin D and obesity in the pathogenesis and disease activity of MS in Egypt.
Aims: To assess the correlation between the serum level of vitamin D, body mass index (BMI) and the Expanded Disability Status Scale (EDSS) in a sample of Egyptian MS patients.
Methods: This was a retrospective study that included 130 MS patients who were recruited consecutively among the patients

attending the MS unit of Ain Shams University Hospital, Cairo, in the period between December 2017 - March 2018. The serum level of 25(OH) D, BMI and EDSS were recorded.
Results: Females represented 77.7% of the study sample. The mean age was 32.4±8.2 years. MS types were: RRMS 83.1%, SPMS 14.6% and PPMS in 2.3%. Serum level of vitamin D was deficient (less than 10ng/ml) in 69.2% and insufficient (10-30ng/ml) in 19.2% of the study population. The mean BMI was 25.5±4.7 kg/sqm (classified as obese). The mean EDSS was 3.5±1.9. The relationship between the EDSS score and vitamin D level was inversely correlated; all patients with EDSS ≤ 2 had sufficient levels while all patients with EDSS ≥ 4.5 had deficient levels. High EDSS scores were statistically correlated ($p < 0.001$) to high BMI and low Log vitamin D levels. An inverse correlation was found between the BMI and log vitamin D. **Conclusions:** Vitamin D deficiency and obesity are predominant among Egyptian MS patients and may possibly play a role in the pathogenesis and progression of MS in Egypt. Higher EDSS scores were statistically significantly correlated to lower vitamin D levels and higher BMI.

Disclosure
nothing to disclose

EP1488
Coffee intake and multiple sclerosis disability

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Introduction: Previous studies on caffeine and risk of MS yielded different results; one study suggests a positive effect on disease progression.
Aims: We aimed to investigate if coffee consumption is associated with MS disability.
Methods: Questionnaires were applied to 126 MS patients that attended Neuroimmunology consultation between January-November/2017. MS severity was evaluated by EDSS, 9-HPT, T25-FW and SDMT. High coffee intake was considered ≥4 cups/day; lifetime consumption was calculated multiplying espressos per day by years of consumption. Fisher exact test (categorical variables), Mann-Whitney test (categorical and continuous variables) and Pearson correlations (continuous variables) were used.
Results: Our cohort had an average age of 45.3 years and 76 (60.3%) were women. Mean age of MS onset was 29.7 years and mean duration of disease 15.6 years. Seventy-nine percent had relapsing-remitting MS; 50% had EDSS 0-3.5, 35.7% EDSS=3.5-6.0, and 14.3% EDSS≥6.0. Regular coffee intake was observed for 78.6%. High coffee intake was present in 17.2%.
Men had more high coffee intake (29% vs 10.3%, p=0.03) but total coffee consumption was not different between genders (p=0.48). High coffee intake and total coffee consumption was associated with higher smoking habits (3.85 vs 0 pack-years,p=0.01;r=0.29,p< 0.001).
No significant association was found between EDSS and high coffee intake or total coffee consumption (3 vs 3.5, p=0.79; r=0.06, p=0.48). Also, we did not find any differences regarding coffee intake and performance in 9-HPT, T25-FW and SDMT.
Conclusions: In our cohort, coffee consumption does not seem to have a role in progression of disability. Further studies, namely prospective, are required to access this association.

Disclosure
All authors have nothing to disclose.

EP1489
High dietary carbohydrate to protein ratio as a risk factor for neuromyelitis optica spectrum disorder: a case-control study

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Background: The pathogenesis of neuromyelitis optica spectrum disorder (NMOSD) is characterized by neuro-inflammation of the central nervous system (CNS). Based on inflammatory effects of high carbohydrate intake, we investigated the role of carbohydrate to protein ratio (cho:pro ratio) in NMOSD incidence.
Method: this case-control study included 70 NMOSD patients diagnosed by international 2015 consensus criteria with disease duration< 3-years who didn't change their diet after NMOSD diagnosis and 214 healthy controls. Demographic and anthropometric data were collected. Also dietary intakes of subjects during the year prior to study in control group and the year before NMOSD diagnosis in the case group were assessed using a validated 168-item food frequency questionnaire (FFQ). Nutritionist-4 (N4) software was used to calculate cho:pro ratio.
Result: Eighty-five percent of patients in case group and 61% of controls were women. The mean age of participants was 35.34 and 43.31 years in case and control groups, respectively. The Mean carbohydrate intake increased from 363.55 to 403.86 g/d across cho:pro quintiles. Inversely, the mean protein intake decreased from 133.29 to 74.26 g/d across quintiles.
Individuals with higher cho:pro ratio met increasing risk of NMOSD. After adjustment for age, gender, Body mass index (BMI) and total energy intake the odds ratios(OR) of suffering from NMOSD were as follows: OR=3.122(95%CI: 1.04-9.30) for the second and OR=4.50(95%CI: 1.50-13.46) for the fifth quintile of cho:pro ratio compared to the first quintile (p-trend< 0.02). The other model which additionally adjusted for smoking and alcohol

consumption showed OR=3.13(95%CI: 1.04-9.44) and OR=4.46(95%CI: 1.48-13.40) in the second and the fifth quintiles, respectively compared to the first quintile (p-trend< 0.02).
Conclusion: Our results suggest high dietary cho:pro ratio as a risk factor for NMOSD. Given that this study is the first investigation in this field, further researches are needed to confirm our results.

Disclosure

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EP1490

Incidence of multiple sclerosis following bariatric surgery: a case series

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Multiple sclerosis (MS) is a central nervous system demyelinating disease. Known devastating and disabling, with lot of socioeconomic consequences. It affects more than 2 million people annually worldwide. The pathophysiology of multiple sclerosis is not well known although various predisposing factors are determined. Number of Bariatric surgeries is increasing nowadays especially between young adults. Multiple neurological complications commonly peripheral neuropathy have been reported following such operations. A clear association between multiple sclerosis and bariatric procedures has not yet been established. Herein, we describe five patients diagnosed with MS following bariatric surgeries.
After getting the approval from the Institutional review board (IRB), This prospective study was conducted between January 2016 and January 2017 at King Fahd Hospital of the University, a tertiary medical center. All patients suffered neurological deficits following Bariatric surgeries were referred to our well established demyelinating diseases clinic. All patients underwent careful neurological examination, complete cerebrospinal fluid (CSF) study, enhanced cranial as well as spinal cord magnetic resonance (MR) images. McDonalds criteria (2010) was used for diagnosing Multiple Sclerosis in these patients.
Inclusion criteria:
Age: ≥ 18 years
Gender: both genders
Patients recovering from Bariatric operations
Exclusion criteria:
Previous diagnosis of Multiple Sclerosis
Conclusion: Neurological complications following bariatric surgeries are not restrictedly dietary deficiencies related. Early recognizition of such complications as well as early referral to neurologists would help establishing needed investigations and diagnosis of Multiple Sclerosis. Prospective multi center studies are warranted.

Disclosure

nothing to disclose

EP1491

Diet during adolescence and its association with multiple sclerosis in Bogota, Colombia

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Introduction: It is known that environmental and genetic factors are implicated in the pathogenesis of multiple sclerosis (MS). Currently there are no studies evaluating the correlation between dietary habits during adolescence and MS in areas near the equator.
Objective: To determine whether there is an association between MS and dietary habits during adolescence.
Aims: Uncrease knowledge about risk factors for multiple sclerosis in our region.
Methods: With a cross-sectional study, we applied a questionnaire including dietary habits during adolescence to 87 patients with MS and 87 healthy subjects. Information regarding sunlight exposure, physical activity, personal and family medical history, and hormonal factors was also collected. A blood sample was gathered to measure vitamin D and Epstein-Barr virus antibodies. Bivariate and multivariate analysis were performed with MS status as the outcome.
Results: 174 participants were analysed, patients (n=87) had a mean age at enrolment of 40.9 years and 65.52% of them were women. 83.9% had relapsing-remitting MS, 6.89% secondary-progressive MS and 4.59% primary-progressive MS. Multivariate analysis showed significant association between fast food and sugary drinks consumption during adolescence and MS (OR 6.14, CI95% 1.68-22.34, p=0.006; OR 3.72, CI95% 1.25-11.09, p=0.018). Dairy products, gluten, meat, alcohol, coffee, seafood, fruits, vegetables, eggs and grains consumption did not have a significant association. As sugary drinks and fast food could be confounding factors for each other, an additional analysis controlling for both was done which showed that only fast food consumption during adolescence was significantly associated with MS (OR 4.94, CI95% 1.29-18.93, p=0.02).
Conclusions: Fast food consumption during adolescence significantly increases the risk of later MS development. Additional studies should be done to evaluate this association in other regions in Latin America and near the equator.

Disclosure

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Neurobiology

EP1492
Interoception as a neurocognitive mechanism underlying fatigue in multiple sclerosis

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Background: Fatigue is one of the most common and disabling symptoms undermining the life quality of patients with multiple sclerosis (MS). Although the pathophysiology of MS-related fatigue is poorly understood, abundant evidence points to a key role of altered interoceptive mechanisms -those implicated in monitoring of autonomic bodily information. Yet, no previous study has empirically evaluated the neurocognitive relationship between interoception and fatigue symptoms in MS.
Goal: To conduct a systematic and multidimensional assessment of the relationship between interoception and fatigue in MS, integrating behavioral and neuroimaging evidence.
Methods: The study comprised 29 patients with relapsing-remitting MS. Sixteen of them surpassed the cut-off of the Fatigue Severity Scale (FSS > 37) and were classified as fatigued MS (F-MS) patients, while 13 presented normal FSS values (< 37) and were classified as non-Fatigued MS (nF-MS) patients. A control group was formed with 28 sociodemographically matched healthy subjects presenting no fatigue symptoms (FSS < 37). Interoceptive accuracy (i.e., precision in tracking cardiac body-signals) was evaluated through a heartbeat detection task. Participants underwent a neuroimaging protocol (MRI and resting-state fMRI) to evaluate the link between fatigue levels and anatomical and functional connectivity (FC) properties of key interoceptive regions.
Results: F-MS patients presented significant decreased interoceptive accuracy compared to controls (Tukey's HSD test $p < .05$) and nF-MS (Tukey's HSD test $p < .05$), while no differences were found between the latter two groups (Tukey's HSD test $p > .05$). Only F-MS patients showed decreased gray matter volume and FC alterations in key interoceptive areas (cingulate cortex and the insula, uncorrected p-value < .001, extent threshold = 50 voxels). Fatigue scores in F-MS patients were negatively correlated with grey matter volume and FC in those areas (uncorrected p-value < .001, extent threshold = 50 voxels).
Conclusion: This study offers unprecedented evidence that fatigue symptoms in MS are linked to behavioral, structural, and FC dysfunctions in the interoceptive domain. Our findings indicate that disruptions in neural regions and networks subserving interoception, alongside their outward manifestations, may constitute a neurocognitive signature of fatigue in MS patients.

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EP1493
The phosphatase CPI-17 as a regulator of oligodendrocyte degeneration

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CPI-17, encoded by the gene *ppp1r14a*, is a 17 kDa cytosolic protein that functions as a potent inhibitor of certain type 1 protein serine/threonine phosphatases (e.g. smooth muscle myosin light-chain phosphatase (MLCP)). In the central nervous system, CPI-17 is, besides by smooth muscle cells, specifically expressed by mature oligodendrocytes. The role of CPI-17 for oligodendrocyte physiology and pathology is not known.
The aim of this study was to examine the role of CPI-17 during experimental demyelination. CPI-17 $^{-/-}$ and wildtype C57/BL6J mice were fed cuprizone for 1, 3, and 5 weeks and densities of myelin (anti-PLP, LFB/PAS stain), microglia (anti-IBA1), and oligodendrocytes (anti-OLIG2) were compared. Furthermore, extent of acute axonal injury was quantified in anti-APP stained sections.
Immunohistochemical studies showed that CPI-17 is exclusively expressed in mature oligodendrocytes. CPI-17 expressing cells are lost under various demyelinating conditions including the cuprizone model. At week 1 and 3, loss of mature oligodendrocytes was more severe in CPI-17 $^{-/-}$ compared to wildtype mice. This was paralleled by more severe microgliosis in CPI-17 $^{-/-}$ mice. Surprisingly, at week 5, the peak of cuprizone induced demyelination, anti-PLP and LFB/PAS stained sections showed severe demyelination in wildtype but not CPI-17$^{-/-}$ mice.
In this study, we identified a novel regulator of oligodendrocyte pathology. Future studies are now needed to understand how CPI-17 regulates remyelionation.

Disclosure
nothing to disclose

EP1494
Different blood-brain barrier disruption profile in multiple sclerosis, neuromyelitis optica spectrum disorders and neuropsychiatric systemic lupus erythematosus

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Blood-brain barrier (BBB) disruption is one of the key pathological processes involved in the Central Nervous System (CNS) autoimmunity. However, the exact role of BBB disruption in the immunopathomechanism of different CNS diseases with disseminated white matter lesions remains unknown. BBB damage may be defined by the increase of concentrations of cell adhesion molecules, which shed into the serum compartment upon BBB destruction. The aim of the present study was to assess the differences in the profile of BBB damage in relapsing-remitting multiple sclerosis (RRMS), neuromyelitis optica spectrum disorders (NMOsd) and neuropsychiatric systemic lupus erythematosus (NPSLE) patients.

We recruited 46 RRMS (median age 38), 19 NMOsd (median age 45) and 35 NPSLE patients (median age 32). All RRMS subjects were treatment-naïve, while NPSLE and NMOsd were on low doses of oral steroids plus azathioprine (NMOsd, NPSLE) or cyclophosphamide (NPSLE). Serum samples were obtained from study subjects and kept frozen at -80°C until further analysis. Serum sVCAM1, sPECAM1, sICAM1 , and VE-Cadherin levels were determined using ELISA, according to manufacturer´s instructions [BioVendor Laboratory Medicine, Inc. Czech Republik and R&D Systems Inc. Minneapolis]. We found that ICAM-1, PECAM-1 and VE-Cadherin serum levels were significantly lower in MS (median ICAM-1 386 ng/ml, PECAM-1 85 ng/ml, VE-Cadherin 4002 pg/ml) and NMOsd (median ICAM-1 319 ng/ml, PECAM-184 ng/ml, VE-Cadherin 4490 pg/ml) than in NPSLE (ICAM-1 median 483 ng/ml, PECAM-1 119 ng/ml, VE-Cadherin 6258 pg/ml). On the contrary, VCAM-1 was significantly higher in NMOsd (median 1024 ng/ml) than in MS (median 839 ng/ml), but comparable for MS and NPSLE (median 830 ng/ml).

To conclude, there is a different profile of cell adhesion molecules shedding in the spectrum of autoimmune CNS disorders with disseminated white matter lesions. Interestingly, all adhesion molecules levels, except for VCAM-1, are increased in NPSLE, as compared to NMOsd and MS. Although NMOsd is attributed to astrocyte pathology, and MS is primarily demyelinating, the pathomechanism of BBB disruption seems similar, especially when compared with lupus. Should these findings be repeated on larger populations, the BBB disruption profile could serve as another differentiation tool between MS, NMOsd and NPSLE.

Disclosure

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EP1495

NR4A impairment in multiple sclerosis patients: defects in blood and in central nervous system

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Introduction: Multiple sclerosis (MS) is a chronic autoimmune disease in which inflammation exerts a key pathophysiological role. Recently, we reported a down-regulation of the anti-inflammatory NUclear receptor related protein 1 (Nurr1, also called NR4A2) gene expression level in blood of treatment-naïve relapsing-remitting MS (RRMS) patients as compared to healthy controls (HC). Notably, we observed the abnormal expression levels of NR4A2 being reverted in MS patients during pregnancy, which represents a transitory state of immune tolerance associated with reduced disease activity. The transcription factor NR4A2 belongs to the steroid nuclear hormone receptor subfamily 4, group A (NR4A), which includes NR4A1 and NR4A3 as well. The three members of the NR4A family share a high degree of homology and a common structure, particularly in their DNA-binding-domain, which may give rise to functional compensation mechanisms. Several evidences report a neuro-protective function of the NR4A exerted through the inhibition of the pro-inflammatory transcription factor NF-kB in microglia and astrocytes.

Objective and aims: Based on the evidence that systemic inflammation induces cell infiltration into the brain parenchyma enhancing the central nervous system (CNS) damage, we characterized NR4A expression in human HC and MS blood samples and brain cryo-sections.

Methods: Gene expression levels of NR4A were evaluated by RT Real time PCR analysis. Demographical and clinical parameters were correlated to the expression level.

Results: First, gene expression levels of NR4A are down-regulated in whole blood obtained from treatment-naïve RRMS patient compared to HC. Second, moving into the CNS, we observed that NR4A1, NR4A2 and NR4A3 are expressed in WM and in GM of HC as well as in normal appearing WM (NAGM) and normal appearing GM (NAGM) of MS patients. Furthermore, we reported a reduction of the NR4A1 and NR4A2 transcripts in GM lesions

in comparison to their relative NAGM. On the contrary, the NR4A resulted not modulated in WM lesions in comparison to their relative NAWM.
Conclusions: The present results refer to a defect of the NR4A in blood and damaged brain samples obtained from MS subjects.

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Neurodegeneration

EP1496
Intrathecal syntheis of free light chains of immunoglobulins is associated with brain atrophy in multiple sclerosis

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Introduction: Multiple sclerosis (MS) is autoimmune demyelinating disorder of central nervous system. Brain atrophy is more prominent on the later stage of disease and correlates with MS progression. Increased intrathecal synthesis of free light chains (FLC) was shown to be highly sensitive marker of MS and also predicts early prognosis of disorder, but its probable association with brain atrophy remains to be elucidated.
Objectives: To find correlations of brain matter volumes with kappa and lambda FLC and their quotients. To identify difference in brain volume in patients with high FLC (more than 75 percentile) and low FLC (less than 25 percentile).
Aim: The aim of the study was to find association between FLC and brain volumes of MS patients.
Methods: 100 patients with MS were participated in the study. FLC-concentration in cerebrospinal fluid (CSF) and serum were measured by ELISA assay (Polignost Ltd., Russia). Quotients of kappa and lambda FLC were calculated. Normalized grey matter (GMV) , white matter (WMV) and brain volume (NBV) were measured using automatical brain morphometric technique called SIENAX.
Results: The concentration of kappa FLC and kappa quotient showed significant inverse correlation with NBV (kappa FLC: p=0.0045, r=-0.2845; kappa quotient: p=0.013, r=-0.3042). Intrathecal concentration of kappa FLC also had a trend to inverse correlation with GMV (p=0.0579, r=-0.1913). Additionally, lambda quotient inversely correlated with WMV (p=0.0032, r=-0.3571). We also showed that patients with higher level of kappa FLC and quotient kappa have decreased volume of NBV (kappa FLC: p=0.0047; quotient kappa: p=0.038) and GMV (kappa FLC: p=0.0297). Additionally, patients with higher level of lambda FLC had decreased WMV (p=0.0446) and NBV (p=0.0026).
Conclusions: In accordance with results of the study FLC can be a prognostic marker of brain atrophy and neurodegeneration.

Disclosure
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EP1497
Brain atrophy in multiple sclerosis: how patients understand the role of brain atrophy in the management of their MS

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Introduction: Brain atrophy is increasingly being used as an outcome measure in MS clinical trials and is strongly correlated with the development of disability and neuropsychological impairment in patients. Unfortunately, many MS patients generally do not have a clear understanding of all of the factors that can affect the path or progression of their disease, and this is particularly true as it relates to brain atrophy.
Objectives and Methods: The Multiple Sclerosis Association of America disseminated a survey to assess MS patients' understanding of the concept of brain atrophy and determine how this issue was being discussed between patients and their healthcare professionals. 1,337 MS patients completed the survey, with a majority of respondents reporting that they were currently using a FDA approved MS disease-modifying therapy and primarily receiving their care at a MS comprehensive center with a team of MS specialists.
Results: Respondents most associated brain atrophy with the loss of cognitive function (43%) and as a sign of disease progression (38%). While respondents ranked preventing physical disability progression as most important in the management of their MS (45%), maintaining cognitive function came in as the second most important consideration in the management of their MS (27%).
MS-related cognitive loss was shown to be an area of high concern for MS patients and to have a great impact on patients' quality of life. 78% of respondents reported being either very or extremely concerned about MS-related cognitive loss, and 29% of respondents reported that MS-related cognitive issues had made a significant impact on their quality of life (32%: some impact on QoL; 22.9%: minor impact on QoL). While these issues were clearly of high concern to MS patients, only 20% reported being either moderately or very satisfied with the amount of information available to them on how to prevent brain atrophy.

The findings also suggest that the issue of brain atrophy is not often discussed between patients and their healthcare professionals, with 62.7% of respondents reporting that they have never talked with any member of their medical team about brain atrophy.
Conclusions: Overall, the data suggests that there is a real need and an opportunity to better educate MS patients on the role that brain atrophy plays in disease progression. Implications of the findings and recommendations for future research on this topic will be presented.

Disclosure

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EP1498

Corneal confocal microscopy detects progressive axonal degeneration in patients with multiple sclerosis which is progressive

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Introduction: A major challenge in multiple sclerosis (MS) is in accurately quantifying axonal degeneration and regeneration to assess disease progression and the benefits of new therapies in clinical trials, respectively.
objectives: to evaluate CCM performance in MS over time.
Aims: to evaluate if corneal confocal microscopy (CCM), a non-invasive ophthalmic imaging modality can assess axonal degeneration and progression in MS.
methods: MS patients (n=78) were assessed at baseline and 1-year follow-up (n=15) and compared to 25 age-matched controls. The MS group was comprised of clinically isolated syndrome (CIS, n=9), relapsing-remitting MS (RRMS, n=47) and secondary progressive MS (SPMS, n=22). Participants underwent assessment of the expanded disability status scale (EDSS), quantification of retinal nerve fibre layer (RNFL) thickness and CCM to quantify corneal nerve fiber density (CNFD), branch density (CNBD) and length (CNFL).
Results: At baseline, EDSS was significantly increased in SPMS compared to CIS and RRMS (0.7±0.7v0.9±1.2v1.8±1.6v4.1±2.3,P< 0.0001). There was a significant reduction in CNFD (27.4±6.9v38.1±4.9,P< 0.0001), CNFL (15±4.1v27.9±5.5, P< 0.0001) and CNBD (39.3±21.5v92.8±34,P< 0.0001) in MS compared to controls, with no relationship to optic neuritis history or MS stage. The reduction in CCM parameters remained significant in CIS [CNFD (P< 0.01), CNBD (P< 0.0001), CNFL (P< 0.0001)], RRMS [CNFD (P< 0.0001), CNBD (P< 0.0001), CNFL (P< 0.0001)] and SPMS [CNFD (P< 0.0001), CNBD (P< 0.0001), CNFL (P< 0.0001)] compared to controls. There was a significant reduction in temporal (55.7±12.6v73.3±12.9,P< 0.0001) and temporal-inferior (120.4±22.9v139.9±9.8,P=0.0002) RNFL independent of optic neuritis history. Compared to RRMS, temporal (P=0.007) and temporal-inferior (P=0.01) RNFL was significantly lower in SPMS. EDSS was inversely correlated with CNFD (P=0.05), temporal (P=0.01) and temporal-inferior (P=0.03) RNFL. At follow-up, MS patients showed a further significant reduction in CNBD (P=0.007) and CNFL (P=0.0005) with no change in RNFL thickness, CNFD and EDSS. Controls showed no change over 12 months.
Conclusions: We show for the first time that CCM detects significant axonal degeneration in MS subtypes which appears to be progressive. A prospective study is underway to determine the diagnostic and prognostic ability of CCM in relation to retinal and quantitative brain imaging.

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Repairing mechanisms

EP1499

Investigation of astrocytic functions and involvement in remyelination in an animal model of multiple sclerosis

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Astrocytes are impressive versatile cells and seem to have functions in driving inflammation as well as in facilitating remyelination dependent on their immediate plaque milieu by expressing a variety of mediators. How astrocytes intervene and what forces them to act in the one or other way is still poorly understood, making astrocytes an interesting research aim. In our previous work we investigated the astrocytic reaction in experimental autoimmune encephalomyelitis in Dark Agouti rats by correlating glial scar reaction with the presence of oligodendrocyte precursor cell over the full course of lesion evolution up to a successfully completed remyelination. We furthermore investigated remyelination facilitating factors adumbrating a beneficial role of astrocytes during the remyelinating process. We assume that at least in our investigated animal model an abundant glial scar reaction does not prohibit remyelination.
To further characterise the astrocytic involvement during destruction and repair we investigated the following remyelination

inhibiting factors expressed by astrocytes: Hyaluronan, Tenascin C and Fibronectin 1. All of them are suggested in literature to substantially contribute to remyelination failure. We performed immunohistochemical double staining of those factors and GFAP to find co-localisations in our sample set. Quantitative evaluation and statistical analysis were performed for all lesion stages in a total of 300 lesions so far.

In comparison to the remyelination facilitating factors, where most of them reached their peak during early remyelination process, the maximum of remyelination inhibiting factors were found during active demyelination. Preliminary data show that over 80 % of all GFAP positive cells in actively demyelinating lesions were carrying Hyaluronan binding protein 2 on their surface. In comparison approximately 50 % of GFAP positive cells in active lesions were carrying Fibronectin 1 and Tenascin C respectively.

There is evidence that there are different phenotypes of astrocytes correlated to their facilitating or prohibiting function on remyelination. In our further research we want to correlate A1 and A2 astrocytic phenotypes to the investigated remyelination facilitating and prohibiting factors expressed by astrocytes in all lesion stages of our animal model. Our work aims to describe astrocytic involvement from active demyelinating lesions up to successful repair in this animal model of Multiple Sclerosis.

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EP1500

Reduced levels of Coco in the sera of patients with RRMS may be related to the insufficient oligodendrogenesis and neurogenesis

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Background: Neurogenesis and oligodendrogenesis in MS lesions are negligible, and it is assumed that anti- neurogenic factors suppress them. Bone morphogenetic proteins (BMPs) are known to promote astrogenesis, at the expense of NSCs acquisition of neuronal/ oligodendroglial phenotype. Coco is a secreted 25 kDa protein, a member of the Cerberus/Dan/Gremlin superfamily of BMP inhibitors. It is known to inhibit BMP2 and BMP4. We have previously reported that BMP2 levels are elevated in sera of RRMS patients.

Objective: To study Coco levels in the sera of RRMS patients and their biological significance in a bioassay.

Methods: Sera samples were collected from 41 untreated RRMS patients, 37 IFNβ treated RRMS patients, and 36 matched HC. Sera Coco levels were examined by ELISA. Dose response experiments of Coco on P19 cells differentiation into $MAP2^+$ neurons was done in the presence of retinoic acid (RA) and BMP-2.

Results: Coco serum levels were significantly reduced in untreated RRMS patients, vs. matched HC (1219.7 ± 195.1 pg/ml vs. 1883.3 ± 243.2 pg/ml, respectively, p=0.03). Treatment with IFNβ did not affect Coco serum levels (1256.9 ± 256.2 pg/ml). Stimulation of P19 cells with $5x10^{-7}$M RA for 4 days triggered the emergence of $MAP2^+$ cells on day 8 (66.6 ± 6.1% in response to RA vs. 3.2 ± 1.6% in response to no stimulation, p=0.001). Addition of 5 ng/ml rhBMP-2 significantly reduced the number of $MAP\text{-}2^+$ cells (6.4% ± 2.6, p=0.01 vs. RA alone), whereas the addition of 500 ng/ml anti-BMP2/4 mAb reversed the effect of BMP2 on neurogenesis by inducing acquisition of the neuronal phenotype (49.4 ± 4.0%, p=0.004 vs. RA+BMP-2). Replacement of the anti- BMP2/4 Ab with 500 pg/ml Coco, or with 1200 pg/ml Coco, did not significantly induce neurogenesis (9.1 ± 1.8% and 21.4 ± 4.3%, respectively, p=0.43 and p=0.08 vs. RA+BMP2 alone). However, addition of 1800 pg/ml Coco significantly enhanced $MAP2^+$ cells (51.9 ± 4.4%, p=0.004 vs. RA+BMP2 alone, and p=0.008 vs. RA+BMP2+1200 pg/ml Coco). Stimulation with 5000 pg/ml Coco did not further augment $MAP2^+$ cells (55.3 ± 1.1%, p=0.49 vs. 1800pg/ml Coco).

Conclusions: Reduced Coco levels in the serum of RRMS patients, concomitant with elevated levels of BMP2, may contribute to the anti- neurogenic niche in MS lesions. The difference between Coco levels in the serum of RRMS patients and HC may have a biologic significance as was demonstrated in P19 model, suggesting an additional mechanism for neurogenesis failure in MS.

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EP1501

AZD4547, a potent FGFR inhibitor, regulates myelin gene expression in OLN-93 oligodendrocytes

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Background: Multiple sclerosis, a chronic inflammatory and degenerative disease of the CNS, is associated with damage of oligodendrocytes and myelin sheaths. Proliferation and differentiation of oligodendrocytes are influenced by fibroblast growth factors (FGFs) and mediated through FGF receptors (FGF1-3). To study the role of FGFR inhibition in myelin gene expression, we treated OLN-93 oligodendrocytes with AZD4547, a potent FGFR inhibitor, which is currently used in Phase II cancer trials and analyzed gene expressions of myelin markers and myelin inhibitors.

Methods: OLN-93 oligodendrocytes were incubated with AZD4547 (1 μM) and basic bFGF (25 ng). After 24 and 48 hours of incubation, proliferation of OLN-93 was measured using WST-1 proliferation assay and DAPI staining. Cytotoxicity was

measured by LDH assay. Dead cell population was analyzed by 7AAD staining by FACS. Myelin inhibitors gene expression, FGF receptor (FGFR1) and the myelin marker CNPase was measured by RT-PCR. Phosphorylation of ERK1/2, AKT and p38 were analyzed by western blot.

Results: OLN93 cells treated with AZD4547 showed less proliferation ($P < 0.01$). Cytotoxicity was increased by AZD4547 ($P < 0.05$). There was no regulation of dead cell population by AZD4547. Phosphorylation of downstream molecules ERK, AKT and p38 was reduced by AZD4547. Gene expression of myelin inhibitors FGF2 ($P < 0.05$), SEMA3A ($P < 0.05$) and TGF-β ($P < 0.01$) was reduced, whereas the myelin marker CNPase was increased ($P < 0.05$).

Conclusions: Myelin inhibitors are known to play a key role in remyelination. FGFR inhibition by AZD4547 showed decreased proliferation and myelin inhibitors gene expression, whereas cytotoxicity was increased. Our data show that FGFR inhibition by AZD4547 mediates the myelin repair process through regulating myelin gene expression. The underlying downstream signaling mechanisms are downregulation of ERK and AKT phosphorylation by AZD4547.

Disclosure

Bischand Sharifi has nothing to disclose.
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Martin Berghoff has nothing to disclose.

EP1502

Myelin related gene expression in oligodendrocytes is regulated by FGFR inhibition with BGJ398 *in vitro*

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Background: Fibroblast growth factors (FGFs) regulate the differentiation of immature oligodendrocytes into myelin-producing mature oligodendrocytes in the CNS. FGFR signalling is associated by activation of multiple cellular responses such as growth, proliferation, differentiation, and survival. *In vitro* and *in vivo* studies identified LINGO-1, TGF-β, SEMA3A and FGF2 as inhibitors of remyelination. BGJ398 is an orally bioavailable pan inhibitor of FGFRs with potential antiangiogenic and antineoplastic activities. In this study, we analysed the effect of BGJ398 on FGFR inhibition in oligodendrocytes and myelin related gene expression.

Methods: OLN93 oligodendrocytes were treated with BGJ398 (1 μM) and stimulated with basic FGF (20 ng) for 24 hours. Cell proliferation was analyzed by WST1 proliferation assay and DAPI staining. After treatments total mRNA was isolated from the cells and cDNA was synthesized. Myelin proteins (MBP, PLP, CNPase), myelin inhibitors (SEMA3A, FGF2, TGFβ) and NFG expression were analyzed by real time PCR. Quantitative expression of the genes was calculated by ΔΔCT method. MBP, TrkB and BDNF protein expression was analyzed by western blot and immunocytochemistry.

Results: Proliferation of OLN93 oligodendrocytes was reduced by BGJ398 ($P < 0.05$). FGFR1 ($P < 0.05$) and SEMA3A ($P < 0.05$) gene expression was downregulated by BGJ398. There was no regulation of FGF2 or TGFβ gene expression after BGJ398 treatment. CNPase ($P < 0.05$) and neural growth factor NGF gene expression ($P < 0.05$) were upregulated by BGJ398. There were no regulations in gene expression of MBP or PLP following BGJ398 treatment. MBP and BDNF protein expression was not regulated by BGJ398 or FGF. TrkB receptor expression was increased in BGJ398 treatment in western blot and immunocytochemistry ($P < 0.05$).

Conclusions: Our findings suggest that FGFR inhibition by BGJ398 in OLN93 oligodendrocytes enhances myelin gene expression and downregulates myelin inhibitor gene expression. The number of proliferating cells was less after BGJ398 treatment suggesting that FGFR inhibition supports the recovery of cells by enhancing myelin gene and growth factor expression. Application of BGJ398 is functional in the study of basic mechanisms involved in FGFR signaling in cells such as oligodendrocytes.

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MRI and PET

EP1503

Brain and deep grey-matter atrophy in relapsing-remitting multiple sclerosis with cortical lesions based on double inversion recovery MRI

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Background: Recent studies have found grey-matter (GM) lesions play an important role in multiple sclerosis (MS). GM lesions are present at disease onset and correlate better with cognitive and physical disabilities. The 2017 revisions of the McDonald criteria added identification of cortical lesions as an MRI criterion for MS diagnosis. However, the relationship amongst GM lesion count and volume, with brain atrophy remains to be explored. The aim of this study is to investigate the correlation of GM lesion counts and volume with total brain (TB), white-matter (WM), GM, and deep grey-matter (DGM) volumes. Comparison also made with clinical scores.

Methods: T1WI and double inversion recovery (DIR) at 3T were acquired on relapsing remitting multiple sclerosis (RRMS) patients (N=35) and 14 matched healthy controls. Lesions were segmented based on DIR. Brain volume segmentation done with FSL SIENAX and DGM volumes with FSL FIRST, normalized to age and brain size. Clinical data included 25-foot walk test.

Results: A total of 271 GM cortical lesions (CL) carefully contoured. In our cohort the average disease duration was 7 years. White matter atrophy was significant in RRMS when compared to controls (p=0.04), but not TB or GM atrophy. We also found a

difference in DGM in thalamus, caudate, putamen, amygdala and accumbens between groups ($p < 0.05$).
GM cortical lesion count significantly correlated with GM ($p=0.004$) and TB ($p=0.005$) volume, but not with WM volume. GM CL volume correlated with GM, WM, TB and putamen volume ($p < 0.05$).
RRMS divided into less severe (< 5s) and more severe (≥5s) disability based on 25-foot walk test**.** Significant differences were found in thalamus, caudate, putamen hippocampus, amygdala, accumbens and brainstem volume atrophy between less and more severe disability group.
Conclusion: Increased GM lesions counts and volume negatively correlated with TB, GM, and DGM volume atrophy, emphasizing the importance of identifying GM CL lesions. More physical disability, as measured with 25-foot walk test, negatively correlated with DGM atrophy. Improved understanding of GM lesion count and volume with respective to various regional brain atrophy could improve understanding MS pathophysiology and its effects in cognitive and physical disability. Future studies will need to focus on longitudinal data to assess volume changes as well as include cognitive tests.

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Gray and white matter brain pathology in highly active multiple sclerosis patients

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The objective of the study was to analyze white matter (WM) and gray matter (GM) pathology in highly active MS (HAMS) vs. no-HAMS patients.
Methods: we included patients with MS older than 18 years and with at least 2 years of follow up. HAMS was defined as patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other DMDs, or patients with 2 or more relapses in the previous year, whether on DMD treatment or not. Only patients naïve to previous treatment were included. High-resolution T1-3D weighted MRI scans were acquired at baseline and every 12 months for 2 years. Brain volume measures were determined on 3D T1-WI. At baseline, whole brain, GM and WM tissue volumes, were calculated using the SIENAX method, whereas for longitudinal changes, the SIENA method was used to calculate the percentage brain volume change (PBVC), and the SIENAX multi-time point method was used to obtain GM volume and WM volume changes. Between-group differences of volume analysis were assessed by logistic regression analysis ($p < 0.05$ significant).
Results: 64 patients, mean age 38.4 years, 35 (57%) women were included. A total of 14 (21%) were classified as HAMS. At baseline, HAMS patients showed lower GM and WM volume compared with no-HAMS ($p=0.001$ and $p=0.01$ respectively). All patients received fingolimod to treat their disease. During the follow up, HAMS showed a higher decrease in the percent of gray matter volume change compared with no-HAMS (-0.61 vs. - 0.77 $p < 0.001$) but a similar percent of white matter change between groups were found (-0.43 vs. -0.50 $p=0.04$).
Conclusion: HAMS patients developed similar rates of WM but different rates of GM atrophy over 24 months, compared to non-HAMS patients.

Disclosure

The study was done without external support

EP1505
Multi-modal MRI intensity distributions reveal differences in normal-appearing white matter between MS subtypes

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Background: A great deal of imaging research in MS focuses on the segmentation and analysis of lesions. Yet it is known that MS is additionally characterized by diffuse damage in normal-appearing white matter (NAWM) that may precede overt lesion formation. Though these processes can sometimes be observed using summary statistics of voxel intensities, incorporating multiple modalities into these analyses can be difficult, and the appropriate summary statistic for a given situation is often unknown. As such, in this study we introduce a method for the naïve discovery of covariate effects in diffuse processes.
Methods: Brain magnetic resonance imaging (MRI) was performed on patients with relapsing-remitting (RR, n = 32) or secondary-progressive (SP, n = 23) MS. 3D T_1-weighted (T1) and T_2-weighted fluid-attenuated inversion-recovery (FLAIR) sequences were acquired. We then tested for differences in the joint distribution of T1 and FLAIR intensities in the NAWM across disease subtypes using the novel naïve method, and compared the results to the use of a conventional summary statistic approach.
Results: Using the novel screening method, significant differences were found between the two MS groups in the joint distributions of T1 and FLAIR intensities within NAWM ($p = 0.038$). Post-hoc analysis revealed that both subtypes showed negative associations between T1 and FLAIR intensities, but voxels more commonly deviated from the linear trend (i.e., were high/low on both T1 and FLAIR) in secondary-progressive patients. Using the correlation between T1 and FLAIR as an outcome measure did not yield a significant difference between subtypes, regardless of correlation method ($p_{Pearson} = 0.062$; $p_{\text{Spearman}} = 0.107$).
Conclusion: This study introduces a novel method for naïvely detecting covariate effects on joint distributions of MRI intensities in NAWM of people with MS. This method detected differences between RR and SP subtypes and indicated that SP patients show less

coherence between T1 and FLAIR intensities in NAWM, potentially indicating more damage. Importantly, the most relevant conventional summary statistic - the T1-FLAIR correlation - was unable to capture this difference, suggesting potential benefit of this novel approach when testing for unknown or complex changes in the brain.

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EP1506
Radiological characteristics of patients with multiple sclerosis in Egypt

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Background: Radiological characteristics of multiple sclerosis (MS) in Egypt are lacking.
Objective: This study describes the radiological characteristics of Egyptian patients with multiple sclerosis in a major tertiary referral center in Egypt.
Aim: To study the different MRI characteristics and their relation to disability progression.
Methods: This was a retrospective study including 693 Patients with MS (McDonald 2010 criteria). Their data was extracted from the database of the MS unit of Ain Shams university hospital in the period between 2015-2017. The MRI's were evaluated by an MS radiology team.
Results: A total of 693 Egyptian patients were included in this study. Females represented 72.4%. The mean age of disease onset was 26.1 ± 7.7 years. Relapsing-remitting MS (RRMS) was the most common type (76.5%). Visual and motor symptoms were the most common initial presentation. The mean Expanded Disability Status Scale (EDSS) score was 3.5 ± 2.1. Our patients showed the following MRI findings : The total T2 lesions were > 10 in 73.9%. Periventricular lesions were found in 98.7% (41.6% of them had 4-10 lesions, while 38.2% had > 10 lesions). Juxtacortical lesions were found in 84% (34.2% of them had 1-3 lesions, 31% had 4-10 lesions, and 18.8% had > 10 lesions). Infratentorial lesions were found in 69.3% (45.2% of them had 1-3 lesions and 20.8% had 4-10 lesions). Confluent lesions were found in 48.5%, T1 black holes in 52.1%, enhancing lesions in 29% and Cord lesions in 47.9%. T1 black holes, confluent lesions and infratentorial lesions showed the strongest correlation with high EDSS ($p=0.003$, $p< 0.001$, $p< 0.001$ respectively).
Conclusions: Egyptian MS patients showed a radiological pattern that was similar to western countries in brain lesions but with probably more infratentorial lesions. Spinal lesions were not as frequent as Asian countries. Black holes, confluent lesions and infratentorial lesions were statistically correlated with high EDSS.

Disclosure

nothing to disclose

EP1507
Cognitive phenotypes in MS: underlying changes in structural connectivity

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Background: Patients with multiple sclerosis (MS) frequently show difficulties in episodic memory, attention, information processing speed and executive functions. Some of them have selective deficits of a given cognitive domain, and different cognitive phenotypes involving memory or processing speed disturbances have been described.
Aim: To analyse the underlying patterns of damage in structural networks according to the cognitive phenotypes observed in a large sample of MS patients.
Methods: A cohort of 183 patients (age: 43.1±10 years; disease duration: 12.1±9.3 years; Expanded Disability Status Scale, EDSS: 2 (0-6.5)) was assessed by the Rao Battery. Whole brain structural connectivity was obtained from diffusion magnetic resonance imaging and mean fractional anisotropy (FA) in each connection was compared among patients' groups.
Results: Thirty-two patients (18%) showed memory impairment (z-score of Selective reminding test-delayed or Spatial recall tests-delayed below -1.5), 29 (16%) patients had attention deficits (below -1.5 z-score in Symbol Digit Modalities Test or Paced Auditory Serial Addition Task) and 21 (11%) had global impairment. The remaining 101 (55%) patients were cognitively preserved (CP). Patients with global impairment were older, more frequently secondary-progressive MS, and had higher EDSS score. While connectivity was similar in patients with memory and attention phenotypes compared with CP patients (decreased FA in 6% of connections), those with global impairment displayed more widespread reduction in connectivity (decreased FA in 63% of connections). Patients with global impairment showed larger number of connections with reduced FA (adjusted $p< 0.05$) in frontal and parietal areas, and insula, compared with the other cognitive groups.
Conclusions: In contrast to patients with global impairment, those with predominant memory or attention deficits have similar brain connectivity to that seen in CP patients, suggesting that they are at an early stage of cognitive disability and do not have specific patterns of network modifications. Furthermore, the results reinforce the importance of the frontoparietal network damage in the development of cognitive deficits in MS.

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EP1508

High reproducibility and robustness to lesions, but large software and scanner effects for mean upper cervical cord area (MUCCA) measurement in MS

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Background: Cervical cord atrophy occurs in MS and is associated with disease severity (1-3).
Aim: To assess within-scanner reproducibility, between-scanner agreement, and sensitivity to MS lesions, for four software methods to measure mean upper cervical cord area (MUCCA): SCT-PropSeg, SCT-DeepSeg, NeuroQLab and ITK-Snap.
Methods: MUCCA was always assessed in the same manually selected 30-mm slice range starting at C1, to ensure comparability between results. Two archive datasets were used. Same-day scan-rescan 3DT1-weighted head imaging (head coil, including cervical spine as much as possible) performed on three 3-Tesla MR scanners (GE MR750, Philips Ingenuity, Toshiba Vantage Titan) in 21 MS patients and 6 healthy volunteers was used to assess within-scanner reproducibility and between-scanner agreement by intra-class correlation coefficient (ICC) and repeated measures ANOVA. To investigate lesion effects, we selected from a larger cohort (3T GE HDxT, head-neck-spine coil) archive cervical 3D T1-weighted images of 7 MS patients without cervical MS lesions and 14 MS patients with at least 12 cervical MS lesions, balanced on sex, disease types, and previously measured MUCCA. ICC and Dice overlap coefficient (DOC) compared to manual reference segmentations were assessed.
Results: MUCCA had high within-scanner reproducibility on all scanners for PropSeg, DeepSeg and NeuroQLab (ICC for absolute agreement all >0.98) and ITK-Snap (0.90-0.95). Systematic differences were observed between scanners and especially between software methods (interaction method*scanner p=0.002); PropSeg and DeepSeg produced lowest MUCCA values. ICC for consistency with manual MUCCA were largely similar for patients with and without lesions (PropSeg: 0.57 vs. 0.71; DeepSeg: 0.89 vs. 0.95; ITK: 0.88 vs. 0.69; NeuroQLab: 0.93 vs. 0.95). Somewhat unexpectedly, DOC were slightly higher for patients with many lesions compared to patients without lesions for PropSeg (0.81 vs. 0.79), DeepSeg (0.83 vs. 0.81) and ITK (0.96 vs. 0.94); DOC could not be assessed for NeuroQLab because it does not produce a binary segmentation.
Conclusion: MUCCA was highly reproducible within-scanner, was not systematically affected by lesions, but varied between scanners and software. Results should be confirmed in multi-center cervical scans and at different vertebral levels.

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EP1509

A magnetoencephalographic investigation of working memory function in MS

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Introduction: Working memory problems are one of the main symptoms of cognitive impairment in multiple sclerosis (MS), with which about 30-70% of persons with MS (PwMS) are confronted (Amato et al., 2001). Previous event-related potential (ERP) studies have shown that P300 amplitudes decrease with increasing working memory load (Covey et al., 2017; Dong et al., 2015; Scharinger et al., 2017), and PwMS display lower P100 and P300 amplitudes than healthy controls (Covey et al., 2017). However, these studies have all been limited to sensor space and did not explore the role of functional reorganisation. This has been a well-documented phenomenon in MS (Pantano et al., 2006) and could cause variability in the locations of the neural generators of ERPs, which would lead to decreased ERP amplitudes.
Aims: In this study, we want to investigate the neurophysiology of working memory function in PwMS.
Objectives: We investigated the neural generators of working memory activity and related them to cognitive impairment in MS. In addition, we tried to confirm previous ERP findings and explored the role of functional reorganisation.
Methods: We performed an event-related field (ERF) analysis on magnetoencephalographic (MEG) data of a visual n-back task. In the n-back task, subjects are asked to press a button when they see an 'X' (0-back), the same letter as the previous one (1-back) or the same letter as two letters before (2-back) in a sequence of letters. The dataset consists of 79 MS patients and 38 healthy controls, who were matched on age, gender and education level. Data were source-reconstructed using a using a linearly constrained minimum variance beamformer.
Results: The MS group displayed increased reaction times for all three conditions ($p < 1e\text{-}9$) and lower accuracy rates on the 1- and 2-back trials ($p < 0.01$) compared to the healthy control group. Preliminary ERF results suggest decreases in M300 amplitudes in different regions for the three types of trials that seem to be a consequence of functional reorganisation in the MS group.
Conclusions: PwMS performed worse on the working memory task, and preliminary ERF results confirm previous findings on reduced M/P300 amplitudes in PwMS but suggest that this could be due to functional reorganisation as a consequence of MS-related structural damage.

Disclosure

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EP1510

Identifying pathological brain volume loss in individual early MS patients

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Background: Measurements of brain volume loss (BVL) in individual multiple sclerosis (MS) patients is a current controversial issue. Recently, age-dependent cutoffs for BVL per year (BVL/year) have been suggested to help distinguish between physiological and pathological BVL in MS patients with an error rate of 20% (elevated BVL) or 5% (pathological BVL). Recent evidence suggests that the intra-patient fluctuation range accounting for the intrinsic measurement error of the volumetry method applied and potential short-term biological confounders is ± 0.54/(length of scan interval)%.
Methods: A cohort of 78 early relapsing MS patients (median age at baseline: 34.3 years, interquartile range (IQR) [29.2, 40.6], median disease duration at baseline: 0.7 years, IQR [0.3, 3.2]) from the Neuroimmunology and MS Research Section at the University Hospital Zurich received two standardized MRI examinations with an average interval of 2.4 years (IQR [1.7, 3.3], min 1.1, max 5.1 years). SIENA from the FMRIB Software Library (FSL) with optimized pre-processing parameters was used to determine BVL. The number of patients featuring an annualized BVL (BVL/year) higher than the 20% (elevated BVL) and 5%

(pathological BVL) age-dependent cut-offs for BVL after subtracting the fluctuation range of 0.54% as an safety margin (to account for potential intra-patient brain volume fluctuation) were assessed.
Results: The median BVL/year in the cohort was 0.35% (IQR [0.15, 0.54%]). Taking into consideration both intra-patient fluctuation and age of the patients, 19 (24%) patients showed elevated BVL rates, while 13 (16%) patients showed pathological BVL rates. From 10 patients with a scan interval of less than 1.5 years, 2 patients (20%) featured elevated BVL/year and 1 patient (10%) showed pathological BVL/year. Out of the 68 patients with scan intervals longer than 1.5 years, 17 patients (25%) showed elevated BVL/year and 12 patients (17%) showed pathological BVL/year.
Conclusions: Even in an early MS patient cohort with relatively short disease duration we were able to show that pathological BVL can be detected in a reasonable subgroup on an individual patient level. With increasing length of the scanning interval, pathological BVL/year can be detected in a higher proportion of patients. In individual patients, intra-patient fluctuation in addition to age-effects needs to be considered to interpret BVL values.

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EP1511

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

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Introduction: It is well known that the administration of interferon (IFN) beta-1a in patients with relapsing-remitting (RR) MS reduces brain lesion accumulation over time, as assessed by magnetic resonance imaging (MRI). It is less clear, however, whether such reduction may have treatment-specific spatio-temporal characteristics.
Objective: To assess spatio-temporal characteristics of active MRI lesions in patients treated with IFN beta-1a or placebo, by using a lesion mapping approach on monthly-acquired MRI data.
Methods: We performed a post-hoc analysis of MRI data in RRMS patients from the IMPROVE study, a randomized (2:1) clinical study (ClinicalTrials.gov identifier NCT00441103) comparing patients treated with IFN beta-1a 44 mcg given subcutaneously three times per week (n=120) versus placebo (n=60). We used MRI examinations acquired at weeks 4, 8, 12 and 16 to create lesion probability maps (LPMs) of the cumulative combined unique active (CUA) lesions in each patient group. At each time-point, differences in lesion location between treated and placebo groups were assessed along several white matter (WM) tracts by using predefined anatomic WM atlases. Differences in lesion frequency were assessed with a voxelwise comparison between treated and placebo groups within the general linear model framework and using nonparametric permutation test ($p< 0.05$, cluster-corrected).
Results: The progressive involvement of the WM area occupied by CUA lesions was half in the treated (41 cm^3 at week 4, 95 cm^3 at week 16, mean: 24 cm^3/month) than in the placebo group (62 cm^3 at week 4, 196 cm^3 at week 16, mean: 48 cm^3/month). Similar results were obtained with the WM tract analysis, with a reduction of lesion accumulation in the treated group in the order of 50% in the corticospinal tract (CST), 52% in the anterior thalamic radiation (ATR) and 65% in the superior longitudinal fascicle (SLF). At voxelwise analysis, LPM of the treated group showed lower frequency of CUA lesions than that of the placebo group since week 4. This became particularly pronounced at week 16 in the left CST ($p< 0.005$), left ATR ($p< 0.005$) and right SLF ($p< 0.02$).
Conclusions: Treatment with IFN beta-1a, in comparison to placebo, rapidly reduces lesion accumulation in RRMS patients along specific WM tracts, reaching the highest local differences in clinically eloquent WM tracts such as CST, SLF and ATR.

Disclosure

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EP1512

Quantification of lesion evolution in primary progressive and relapsing remitting MS

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Purpose: Explore differences in lesion formation and growth in primary progressive and relapsing remitting MS patients using MRI segmentation with ico**brain ms**.
Materials and methods: Longitudinal MRI follow-up of 30 relapsing remitting (RR) and 20 primary progressive (PP) MS patients was conducted using a 1.5T MR system (Sonata Siemens). For each patient, MRI sessions from 2-10 time points were available, 0.5-1 year apart. Automated image analysis was conducted with **icobrain ms**. This software employs T1w and FLAIR images from two time points simultaneously to segment lesions and indicate their changes over time. Distinction is made between FLAIR lesions and T1 hypointesities (blackholes).Longitudinal changes

in FLAIR lesions and T1 blackholes were first assessed in terms of total volume change by linearly regressing each patient's volumes in function of time. The slopes of all linear models were compared between RRMS and PPMS using Wilcoxon rank-sum test at 5% significance level. Secondly, a distinction was made between volumes of new lesions and volumes of enlarging regions around existing lesions. Potential differences in these volumes between the two groups were evaluated with a bivariate rank sum test.

Results: FLAIR and T1 lesion volume evolution was well fitted by a linear model in most patients, with less than 15% of patients showing a nonlinear volume evolution in time (R2< 0.25). Both groups had a broad intra-class variability, including relatively stable patients (< 0.01ml lesion volume change per year) to highly lesion-active patients (>1ml per year). There was no significant difference between PPMS and RRMS slope coefficients, with median [interquartile range] values of 0.1 [-0.07; 0.75] ml/year in RRMS and 0.2 [-0.08; 0.34] ml/year in PPMS for FLAIR lesions, and 0.2 [0.06; 0.51] ml/year in RRMS and 0.2 [-0.01; 0.42] ml/year in PPMS for T1 blackholes.

Bivariate distributions of new and enlarging lesion volumes were significantly different (rank sum test, p< 0.001) between PPMS and RRMS groups. For T1 blackholes, there was a clear pattern of more new lesions in RRMS patients and more lesion enlargement in PPMS patients.

Conclusion: Inter-individual variability is too large in RRMS and PPMS to reveal significant differences in total lesion volume change. Nevertheless, lesion segmentation with ico**brain ms** confirms that lesion activity in PPMS manifests more as enlargement of existing lesions rather than formation of new lesions, as opposed to RRMS.

Disclosure

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EP1513

Comparison of 24 month changes in brain volume among long term users of fingolimod versus glatiramer acetate in patients with multiple sclerosis

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Objective: To compare brain atrophy rates for multiple sclerosis (MS) patients treated for ≥2 years with fingolimod (FTY) vs. age and gender matched MS patients on glatiramer acetate (GA) in a prospective two-year study examining brain volume, cognition and patient reported outcomes (PROs).

Background: Clinically stable MS patients on long-term FTY therapy often have little if any overt inflammation on MRI. Brain atrophy rates may provide insight into subclinical disease progression in these populations and may determine whether long-term FTY patients have brain volume loss that is different to patients on GA.

Methods: Relapsing MS patients, age 18-60, on FTY and GA for ≥2 years were followed prospectively for two years. MRI outcomes, cognitive measures, and PROs were collected yearly. Baseline normalized brain volume (NBV), yearly T2 lesion volume (T2LV), and percent brain volume change (PBVC) were measured using SIENA, JIM 6.0, and SIENAX respectively and correlated with cognitive measures (including Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT)) and PROs (including Neuro-QOL scales). Statistical analyses were conducted in SAS 9.4.

Results: Forty-three FTY and 43 GA patients completed baseline, 12, and 24 month visits. Mean age is 49.2_{FTY} (+/- 7.7) and 49.7_{GA} years (+/- 7.7, p=0.73); $79.1\%_{FTY}$ vs.$79.1\%_{GA}$ were female (p=1.00). Median EDSS score was 2.50_{FTY} (IQR 2.00, 3.00) and 2.00_{GA} (IQR 1.50, 3.00) (p=0.22) while mean disease duration was 13.1_{FTY} (+/-4.3) and 11.0_{GA} years (+/-6.6, p=0.09). Unadjusted NBV was similar at baseline for this subset (FTY=1491.67cm3 vs. GA=1507.97cm3; p=0.30); as was baseline T2LV (FTY=3211.51mm3 vs. GA=1443.08mm3; p=< 0.0075). The mean unadjusted 24 month PBVC for FTY was -0.60% (p< 0.0001) and -0.57% (p< 0.0001) for GA. The mean PBVC, adjusted for gender (averaged), baseline age (47 years old), and baseline brain volume (1520cm3) for FTY was -0.74% (p< 0.0001) and -0.65% (p< 0.0001) for GA. The PBVC between these groups were not statistically significant -0.088% (p=0.64). Relationships to cognitive testing and PROs will be presented.

Conclusion: There is no evidence patients on FTY and GA for ≥2 years have different brain volume loss. We report brain volume loss rates comparable to rates previously reported for healthy nonMS patients, which suggests normalization of brain volume loss compared to MS patients who have been stable ≥2 years.

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Disclosure

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EP1514

Microstructural changes in the mesocorticolimbic fiber pathway may play a role in the comorbid development of fatigue and depression in multiple sclerosis

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Background: Alterations in reward mechanisms have been associated with fatigue in patients with multiple sclerosis (MS). However structural integrity of the mesocorticolimbic reward pathway has not been investigated.

Objectives: To investigate the association of fatigue with diffusion abnormalities of the superolateral medial forebrain bundle (slMFB) in MS patients.

Methods: Patient stratification: 1. Sustained Fatigue (SF): latest two Modified Fatigue Impact Scale (MFIS)≥38; 2. Reversible Fatigue (RF): latest MFIS< 38, and at least one previous MFIS≥38; 3. Never Fatigued (NF): MFIS always< 38 (5 assessments minimum). We selected from the CLIMB Study cohort 93 MS patients with relapsing-remitting (82) or secondary-progressive (9) disease type (26SF/25RF/42NF). Disability and depression were assessed using the Expanded Disability Status Scale (EDSS) and Center for Epidemiologic Studies Depression Scale (CES-D), respectively. Cross-sectional 3T diffusion tensor (DT) brain MRI was used to compare fractional anisotropy (FA), axial (AD), mean (MD) and radial diffusivity (RD) of the slMFB between the groups controlling for age+sex+disease duration+EDSS±CES-D. In post-hoc analyses, we (1) investigated the association of DT metrics with CES-D in each group and (2) compared DT metrics between SF patients with high (SFhd, ≥16) versus low (SFld, < 16) depression scores.

Results: CES-D was significantly higher in SF versus RF (p< 0.001) or NF (p< 0.001) patients. No difference was found in slMFB DT metrics between the SF, RF and NF patients. Left slMFB FA (p=0.039), MD (p=0.012) and RD (p=0.013) showed positive correlation with CES-D in SF, but not in RF or NF patients. SFhd (N=14) versus SFld (N=12) patients showed significantly higher MD (p=0.027) and RD (p=0.044) in the left slMFB.

Conclusion: Our results suggest that microstructural changes to the mesocorticolimbic reward pathway may play a role in the comorbid development of fatigue and depression in MS.

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EP1515

Structural MRI correlates of PASAT performance in multiple sclerosis

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Background: PASAT is a useful cognitive test in Multiple Sclerosis (MS) assessing sustained attention and information processing speed. However, neural underpinnings of its performance are controversial. We aimed to study the neural basis of PASAT in a large series of 242 patients with MS using structural magnetic resonance imaging (MRI).

Methods: PASAT-3 seconds was administered together with a comprehensive neuropsychological protocol. Global brain volumes and total T2-weighted lesion volume were estimated. Voxel-based morphometry and lesion symptom mapping analyses were performed.

Results: Mean PASAT score was 42.98±10.44, and it was impaired in 75 (31.0%) of cases. PASAT correlated with several clusters involving the following regions: bilateral precuneus and bilateral posterior cingulate, bilateral caudate and putamen, and bilateral anterior cerebellum. Voxel-based lesion symptom mapping did not show any significant clusters. ROI-based analysis restricted to white matter regions revealed a correlation with left

cingulum, corpus callosum, left and right corticospinal tract, and right arcuate fasciculus. Correlations between PASAT and global volumes were low.

Disclosure

PASAT was associated to regional atrophy in posterior cingulate/precuneus and several subcortical structures, specifically caudate, putamen, and cerebellum. This emphasizes the role of both cortical and subcortical structures in cognitive functioning and information processing speed in MS.

EP1516

Longitudinal changes in advanced diffusion MRI of normal-appearing white matter and chronic lesions in ocrelizumab treated relapsing MS

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Introduction: A recently developed MRI technique, diffusion basis spectrum imaging (DBSI) provides markers related to oedema, inflammation, demyelination and axonal loss. Ocrelizumab has been shown to be an effective treatment in relapsing multiple sclerosis (RMS) in preventing new relapses, disability progression and new MRI lesions. We hypothesise that this potent anti-inflammatory therapy will be associated with improvement in DBSI imaging biomarkers in normal-appearing white matter (NAWM) and chronic lesions.
Objective: To investigate the effect of ocrelizumab treatment on tissue microstructure as found by DBSI for RMS patients beginning treatment with ocrelizumab over 1 year.
Methods: 16 RMS patients (9M/7F, ages 21-44 (mean 31)) participating in a substudy of VELOCE (NCT02545868) had advanced 3T MRI including DBSI prior to and 1 year after first ocrelizumab treatment. 10 healthy controls (HC) were scanned once. DBSI was analysed to calculate maps of hindered and restricted fractions (related to oedema and microglia content), fibre fraction (fibre density), fractional anisotropy (FA, affected by axon/myelin loss) and axial and radial diffusivities (axon and myelin integrity, respectively). Mean values in NAWM and chronic lesions (without Gd enhancement) were calculated.
Results: Mean ± standard deviation values in RMS NAWM improved over 1 year ($p \leq 0.0001$):

- Hindered fraction decreased from 0.27±0.02 to 0.24±0.03 (HC 0.19±0.02)
- Restricted fraction decreased from 0.08±0.01 to 0.06±0.01 (HC 0.07±0.01)
- Fibre fraction increased from 0.54±0.02 to 0.6±0.03 (HC 0.63±0.03))
- FA increased from 0.66±0.02 to 0.72±0.02 (HC 0.76±0.01)
- Axial diffusivity increased from 1.41±0.03 to 1.58±0.06 (HC 1.57±0.07)
- Radial diffusivity decreased from 0.4±0.02 to 0.37±0.02 (HC 0.32±0.01)

In RMS chronic lesions over 1 year, fibre fraction increased from 0.43±0.04 to 0.52±0.08 and FA from 0.58±0.03 to 0.63±0.04.
Conclusions: The decreases in hindered and restricted fractions may reflect receding oedema and decreased microglia content across MS brain. Changes in FA and radial diffusivity could correspond to myelin recovery. DBSI is sensitive to detecting microstructural changes in a relatively small group within 1 year of follow-up. Longitudinal results showed improvement towards HC values in patients treated with ocrelizumab over 1 year. DBSI could improve the understanding of the mechanism of action of MS therapies beyond the effect of preventing new lesion formation.

Disclosure

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EP1517

Surface-based cortical gray matter correlates of personality traits in multiple sclerosis

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Background: People with multiple sclerosis **(**PwMS) can exhibit perturbations in personality, including elevation in Neuroticism and diminution of Conscientiousness and Extraversion. Lower Conscientiousness and Extroversion in particular have been shown to correlate with globally decreased cortical gray matter (GM) volume in PwMS. These trait alterations influence disease trajectory and functional outcomes such as work capacity.
Objective: To identify localized patterns of cortical gray matter (GM) atrophy associated with each personality trait as measured by the NEO Five Factor Inventory (NEOFFI).
Methods: Psychological assessment and brain MRI was carried out for 131 PwMS. Surface-based cortical parcellation and measurement of cortical thickness was completed using FreeSurfer. Then, surface-based group analysis was completed to evaluate the association between localized cortical thickness and sex-corrected t-scores of Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness. In order to control for global disease progression, age and normalized whole brain volume were included as covariates in the models. Results were controlled for multiple comparisons using Monte Carlo Null-Z Simulation at a cluster-wise level of $p< 0.05$.
Results: Lower Conscientiousness correlated with decreased cortical thickness in two separate clusters within the left precuneus ($T_{max}=3.19$, $p< 0.001$; $T_{max}=2.93$, $p=0.001$), left postcentral gyrus ($T_{max}=3.83$, $p=0.001$), right paracentral gyrus ($T_{max}=4.40$, $p< 0.001$), and right inferior-parietal gyrus ($T_{max}=4.26$, $p< 0.001$). Lower Extraversion correlated with decreased thickness in the right inferior-parietal cortex ($T_{max}=2.99$, $p=0.001$). No significant correlations were observed for the remaining NEOFFI traits.
Conclusions: Findings suggest that personality trait alterations in PwMS may be driven at least in part by localized cortical GM atrophy, although longitudinal research is needed to confirm this hypothesis. These results are consistent with previous studies which indicate a correlation between cortical morphometry and personality traits Conscientiousness and Extroversion.

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EP1518
The impact of field strength on structural network organization: a comparative study between 3T and 7T in multiple sclerosis patients

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Background: Recent work showed a vast structural grey matter networks reorganization in patients with multiple sclerosis (MS) and depicted quantifiable longitudinal patterns of increased local clustering, increased modularity and long-range disconnection. These are detectable even beyond clinical markers of disease progression as measured with established MRI pipelines. The use of higher magnetic fields (i.e. at 7 Tesla, 7T) opens up important possibilities to detect more sensitively structural dynamics in the grey and white matter and ongoing subtle neuroinflammatory processes in early MS. However it is not yet clear which advantages for the quantification of network behavior adds up the 7T imaging in comparison to the state-of-the-art scanning procedures at 3 Tesla.
Methods: Seven relapsing remitting MS patients (disease duration < 3 years) were scanned at 3 Tesla and 7 Tesla, no more than 48 h apart. Signal-to-Noise Ratio (SNR) and Contrast-to-Noise-Ration (CNR) values were calculated. All images were processed using the standard pipeline in FreeSurfer to compute regional measures of cortical thickness (CT). Structural network covariance was determined from the regional CT values based on the Desikan-Killiany atlas. Thereafter we applied the graph theoretical framework for the quantification of the grey matter structural topology at the local, modular and global network level (modularity, clustering coefficient, transitivity and global and local efficiencies).
Results: While 3 and 7 Tesla MRI revealed comparable values for assessing cortical thickness, only one single region (left posterior cingulate) showed significant cortical thinning at 7T in comparison to 3T images after the correction for multiple comparisons ($p = 0.01$, $T = 5.76$). The network analysis, however, showed increases in modularity ($p < 0.001$, $T = 8.8$), clustering ($p < 0.001$, $T = 9.1$), transitivity ($p < 0.001$, $T = 25.4$) and local efficiency ($p < 0.001$, $T = 6.9$) at 7T but no changes in global efficiency ($p > 0.02$, $T = 1.6$). At 7 T the MR images presented lower SNR and CNR than the 3T data ($p = 0.01$, $T = 3.5$).
Conclusion: Although there are only subtle differences for the quantification of cortical thickness between 3- and 7T imaging, the derived network measures differ considerably. Further studies are needed to determine the interrelationship of structural integrity and network parameters as derived from 7T imaging for the characterization of the disease processes and neuroinflammation.

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Nothing to Disclose

EP1519

Resting-state functional correlates of social cognition in multiple sclerosis

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Introduction: Impairment in Social Cognition has been showed in multiple sclerosis (MS). Theory of mind (ToM), a proxy of Social Cognition, is the ability to understand and interpret another person´s beliefs, intentions (cognitive ToM) and emotions (affective ToM). In particular, ToM impairment in MS has been related to focal gray matter atrophy and microstructural white matter damage. To date no studies have explored functional connectivity (FC) changes related to social cognition in MS.
Objectives: To assess the contribution of resting-state FC (RS-FC) changes of the default mode network (DMN) to social cognition impairment.
Methods: Forty-one relapsing remitting (RR) MS patients and 25 sex, age and education-matched healthy controls (HC) were evaluated by a neurological examination and tasks assessing cognitive (the ToM Pictures Sequencing Task) and affective (the Reading the Mind in the Eyes Task) ToM. All subjects underwent a 3T magnetic resonance imaging (MRI) protocol including structural and RS-fMRI (RS-fMRI) sequences. FC of the DMN was evaluated by independent component analysis (ICA).
Results: MS patients performed worse on ToM, compared to HC. Compared to HC, RRMS patient showed a reduction of FC in posterior cingulate cortex (PCC). In MS patients, performance on "cognitive" ToM tasks was negatively correlated to PCC FC. All detected RS-FC changes did not co-localize with regional gray matter atrophy.
Conclusions: ToM performance in MS is associated to significant DMN-FC changes in MS. Further research is warranted to clarify the adaptive or maladaptive role of this FC changes in MS.

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EP1520

Training a pattern classifier to distinguish cognitive phenotypes in multiple sclerosis

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Introduction: Deriving biomarkers for cognitive impairment based on single neuroimaging modality analysis is limiting due to the complexity and heterogeneity of multiple sclerosis (MS) disease. Hence, a method which simultaneously analyzes many variables complementing each other is needed to better understand cognitive decline in MS.
Objectives: In this study we applied machine learning method to cognition in MS to determine relationships among different variables of disease beyond their individual values and find inherent patterns in data. We aimed to test if our algorithm classifies memory-impaired and cognitively preserved patients into different groups accurately.
Methods: 36 relapsing remitting relapsing remitting MS (RRMS) patients (16 with isolated memory impairment, 20 cognitively preserved) from MEM CONNECT cohort were included in this study. We trained a linear discriminant analysis based pattern classifier using MRI based neuroimaging data (cortical thickness/volume, global brain and subcortical gray matter structure volumes, T2 lesion loads, diffusion tensor imaging based white matter integrity measures and resting state fMRI) and other patient characteristics (disease duration, IQ, years of education, age, sex, depression and fatigue levels) as the features.
Results: Our results revealed that, when all above mentioned features were combined, our algorithm produced a classification with 70 % accuracy, 67% sensitivity and 65 % specificity for isolated memory impaired-cognitively preserved MS patients comparison.
Conclusions: These results show that isolated memory impairment in MS can be predicted using MRI based neuroimaging data and other patient characteristics with machine learning method. This pattern can be used as a biomarker and would help to develop personalized therapies specific to memory impairment in MS. Future studies with larger sample sizes should address impairments in the

other domains (e.g., processing speed, attention, executive functions, language). In addition to supervised method, application of unsupervised pattern classification methods should be used to find new cognitive phenotypes which have not yet been detected.

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EP1521

Signal mass change as a marker of brain tissue loss in multiple sclerosis patients following immunoablative therapy and autologous hematopoietic stem cell transplantation

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Background: 23 rapidly-progressing MS patients were treated with immunoablation and autologous stem cell transplantation (aHSCT). Despite stoppage of all inflammatory activity indicated by MRI and relapses, high rates of short-term brain volume loss (atrophy) were observed following aHSCT. The EDSS score worsened in 30% of the patients.

Signal mass (SM) is an MRI metric that combines both the tissue volume change and MRI signal intensity change (representative of change in tissue density) to address some of the limitations of brain volume change related to tissue injury and volume loss that is partially replaced by water and reactive processes.

Objectives: To compare SM loss 1) within normal-appearing brain tissue (NABT) versus T2-weighted lesions, and 2) between EDSS worsening versus non-worsening subgroups.

Methods: The patients were followed from 1.5 to 10.5 years (mean 5.5y) on 1.5T scanners. Percent SM changes (PSMC) between baseline and follow-up magnetization transfer ratio (MTR) images were calculated as follows: images were linearly registered to a standard template; brain parenchymal masks were obtained using SPM, and T2-weighted lesions were segmented using locally-developed software and manually corrected; follow-up images were non-linearly registered to the baseline image and Jacobian determinant maps (J), quantifying local volume change at the voxel level, were calculated; maps of MTR SM at baseline and follow-up were computed as $SM_{BL} = I_{BL} \times vol$ and $SM_{FU} = I_{FU} \times vol \times J$ where I is the MTR image intensity and vol is the voxel volume. PSMC for a given tissue type (NABT or T2 lesions) was the % difference between SM_{BL} and SM_{FU} in the corresponding tissue mask.

Data was modelled using non-linear mixed-effects models including an exponential decay term estimating the amount and rate of short-term SM loss. The models tested 1) whether tissue in in lesions exhibited disproportionate SM loss, and 2) whether patients with post-treatment EDSS progression had greater SM loss.

Results: The amount of short-term SM loss was greater in lesions compared to NABT (p=0.0001). Progressing patients showed greater amount of SM loss in NABT (p=0.04), but not in lesions (p=0.7).

Conclusion: A disproportionate amount of rapid brain tissue loss after aHSCT may be due to loss of already damaged tissue in lesions. However, greater tissue injury / loss in NABT (rather than in lesions) is associated with disability progression following treatment.

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EP1522

A deep learning based semantic segmentation framework for multiple sclerosis in MRI

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Introduction: Automated segmentation of multiple sclerosis (MS) in magnetic resonance imaging (MRI) can be particularly challenging since MS lesions exhibit large variation in intensity, size, shape, and location. While many MS segmentation methods have been reported in the literature, segmentation performance remains relatively poor and emerging deep learning models may provide an effective solution.

Objectives: To design a new deep learning-based semantic segmentation model for MS lesions on MRI.

Methods: A total of 69 patients with relapsing-remitting MS were included in this study. Both baseline and follow-up images were acquired, producing a total of 126 scans with T1 and FLAIR data. The first 9 patients were selected to form the test group, resulting in 20 test volumes. Images from the remaining 60 patients were used as the training data.
We adopted the LinkNet encoder-decoder network as our base deep learning model. In this network, a whole 2D image serves as the input, and produces a corresponding MS lesion segmentation mask. To integrate both T1 and FLAIR data, we modified the LinkNet structure to contain two encoding paths, which were combined before linking to the decoders. Two such encoder-decoder networks were generated from the training data,: one for the MS lesion objects and the other for the lesion boundary areas. The boundary areas were created by dilating the lesion ground truth by 3 pixels. Given a test image, each network generated a probability map, and the two probability maps were combined with intersection operations to produce the final segmentation mask.
Results: We evaluated the segmentation results using the Dice coefficient and object-level F-score. We compared our results with several other well-known deep learning models, including U-Net, Global Convolutional Network (GCN), and DeepMedic. Our method produced the best segmentation results with a Dice of 0.658 and F-score of 0.705, compared to U-Net (Dice 0.405 and F-score 0.359), GCN (Dice 0.490 and F-score 0.467), and DeepMedic (Dice 0.623 and F-score 0.556).
Conclusions: Our semantic segmentation model consists of two encoder-decoder networks with multimodal encoding paths, and the fusion of boundary network with object network helps to refine the segmentation and filter false positives. The evaluation results on 126 MRI scans show that our method is more effective than the other popular deep learning models.

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EP1523

Brain atrophy correction in longitudinal neuroimaging analysis of chronic white matter lesions

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Introduction: Monitoring the evolution of white matter lesions in Multiple Sclerosis (MS) is essential for assessment of disease progression and the effect of therapeutic interventions; and for investigation of underlying pathophysiological mechanisms. Brain atrophy can lead to marked ventricular expansion and lesion displacement, and is a significant confounding factor in the longitudinal assessment of white matter lesions. It is therefore imperative that propagated lesion masks are adjusted for brain atrophy to avoid contamination by adjacent tissue structures.
Objective: In this study, we propose a novel method to minimize the partial volume effect induced by brain atrophy in longitudinal modeling of chronic white matter lesions.
Methods: Longitudinal MRI sequences, including 3D T1, FLAIR and diffusion MRI, were acquired from each patient on a 3T GE MRI scanner. White matter lesions were identified on the co-registered FLAIR and T1 images and semi-automatically segmented using JIM 7 software. Chronic inactive lesions that showed a stable lesion appearance with no evidence of acute inflammation between baseline and follow-up were selected for analysis. A localized linear mapping (LLM) algorithm was developed to map individual lesions onto the follow-up scans using a 6 degree of freedom transform with cross correlation as the similarity measure. The combined nonlinear registration (ANTs) and lesion inpainting (NiftySeg) method was used as the baseline method for comparison.
Results: MRI examinations were performed on 20 patients with relapsing-remitting MS (male / female: 8/12, age: 43.3±11.2, disease duration: 4.8±2.9 years, EDSS: 1.42±1.05) at baseline and follow-up (44.4±5.6 months). Sixty-one chronic inactive lesions were identified in these patients. The LLM-corrected lesion masks achieved a higher Dice score with the JIM segmentation at follow-up as the ground truth compared to the baseline method (0.88 vs 0.80) and also significantly reduced contamination with cerebrospinal fluid (overlap ratio: 2.1% vs 0.8%) and grey matter (overlap ratio: 1.4% vs 0.7%).
Conclusion: Elimination of impact of brain atrophy has a critical effect on the quality and sensitivity of the longitudinal lesion analysis. This study represents the first attempt to automatically correct brain atrophy induced tissue displacement in longitudinal modelling of chronic white matter lesions.

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EP1524

Relationship between cortical grey matter volume and cognitive impairment perception in multiple sclerosis

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Aim: Cognitive impairment is a frequent clinical manifestation of multiple sclerosis. Several correlations with MRI structural biomarkers have been highlighted. Perception of cognitive concerns appears to be related to several factors other than formal assessment results. Generally, caregiver perception of cognitive function in MS shows a stronger correlation with assessment results than patient's perception. The aim of our study was to evaluate the relationship between brain volume and cognitive impairment perception by MS patients and their caregivers.
Methods: a group of MS patients and their caregiver was recruited. All MS patients underwent to brain MRI to estimate brain volumes using SIENAX and to neuropsychological assessment using BICAMS battery results. Perception of cognitive impairment was evaluated using the patients and caregivers versions of the MSNQ (Multiple Sclerosis Neuropsychological Questionnaire). Clinical and demographical variable of included patients were also recorded. Depression and anxiety were evaluated using, respectively, Beck Depression Inventory and Zung Anxiety Scale.
Results: 75 MS patients and their Caregivers were recruited. Demographic and clinical features: Mean Age (42.3, SD: 11.2), mean EDSS 2.5 (S.D:1.3) ; Female/Male: 53/22.
BICAMS results showed a stronger correlation with the caregivers (r:-0.46, p< 0.001) than patients perception (r:-0.25; p:0.021) Cortical grey matter volume showed a significant correlation with mean BICAMS results (r: 0.53, P:< 0.001), with caregivers perception (r: 0.64, p< 0.001) but not with patients perception. The difference between patients and caregiver MSNQ scores showed a relationship with cortical grey matter volume (linear regression, p: 0.001) also controlling for age, EDSS and BICAMS results.
Conclusion: In our study caregiver perception is more related to cognitive assessment results than patient perception. Furthermore, our results support the hypothesis that brain volume loss could play a role in alteration of self- judgment in MS patients and confirm the importance of the caregiver point of view in cognitive function evaluatio
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EP1525

Decreased interhemispheric connectivity in multiple sclerosis

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Introduction: MS related cognitive impairment can be measured by neuropsychological testing, but a surrogate marker is lacking. Several biomarker candidates were examined, but neurochemical markers (Sharief and Hentges 1991), structural neuroimaging (Barkhof 1999), PET imaging (Sun et al. 1998) and neurophysiology (Tewarie et al. 2013) only show moderate correlations with neuropsychological measures in group analyses, and do not allow us to reach conclusions at the individual patient level.
Objectives: Our group reported a reduced interhemispheric connectivity for an EEG dataset, indicating a shift from global to local connectivity in cognitively impaired people with MS (PwMS) (Van Schependom et al. 2014). Limitations of this study were the confounding effects of volume conduction, and the low number of electrodes which restricted us to a sensor space analysis. For these reasons we wanted to examine a potential shift from global to local connectivity in fMRI data.
Aims: Our hypothesis was that interhemispheric connectivity would be on average lower in PwMS compared to normal controls, and lower in cognitively impaired in as compared to cognitively preserved PwMS.
Methods: 61 PwMS and 28 Healthy were scanned on a 3T MRI scanner to obtain a 3D T1 weighted image and a 7min rs-functional MRI image. After re-alignment, slice timing correction, co-registration to T1, normalisation to MNI space and global signal regression from non-grey matter , signals were parcellated according to the AAL atlas (Rolls, Joliot, and Tzourio-Mazoyer 2015). Timeseries were extracted for 94 parcels and filtered between 0.009 and 0.08Hz. Pearson correlation coefficients between those timeseries were used as a measure of connectivity.

Results: Interhemispheric connectivity was significantly lower in PwMS compared to matched controls (0.28±0.06 vs 0.31±0.06, p=0.023). Intrahemispheric connectivity did not show a significant difference between groups (p=0.089). Neither measure was significantly different between cognitive preserved and impaired groups.
Conclusions: PwMS show a decreased global organisation on rs fMRI network analysis compared to controls. We were not able to confirm the shift from global to local organisation when comparing cognitively deteriorated patients to cognitively preserved patients. We discuss potential explanations for these findings such as the level of cognitive deterioration in our subjects, dimensionality of the data, and statistical power aspects.

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EP1526

A distributed platform for making large scale manual reference datasets for MS lesion segmentation

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Introduction: Manual delineation is the gold standard for measuring MS WM lesion (WML); however, it suffers from inter and intra-rater disagreement and is too resource demanding to be feasible for large studies. Automated methods can be an alternative, but their training and validation requires manually labelled reference datasets, which poses the same challenges above.
Aims: Here we present a platform for making the manual segmentation of WML feasible at a large scale by distributing the segmentation to many raters as small, quick tasks so that many raters perform a single segmentation to generate a consensus segmentation. This should make the consensus segmentation more robust and faster to generate.
Methods: Since the platform is intended for crowd-sourcing we need to ensure full anonymity to safeguard patients' identity. Images are anonymised, skull-stripped, and divided into rectangular sub-slices, hence patch, not covering more than a quarter of the brain visible in the slice. Raters are presented with a patch to rate, as well as the corresponding patches from slices immediately above and below. Raters select parts of the image they think contain WML, and parts they deem WML free. This is done simply by clicking on the relevant sub-regions into which the image has already been divided. These so-called super-pixels are irregularly shaped regions automatically generated from the image (1). At the time of abstract writing, the platform is undergoing evaluation in a pilot study comparing the consensus segmentations from multiple raters to fully manual segmentations. Raters are drawn from different groups: radiologists, medical students and general public. Using Dice overlap, the effect of number and experience of raters is evaluated.
Conclusions: If confirmed, distributed segmentation provides key benefits over manual segmentation which enables usage in large studies: (a) since patches are segmented by many raters, the results are less prone to bias (b) Each rater can contribute many or few tasks, making rater recruitment feasible (c) Raters' expertise can be traded by number of raters and thus a variety of raters can contribute to a study. With these benefits, distributed segmentation can generate large scale segmentation for research as well as training and validation of automatic WML segmentation tools.
1 Radhakrishna A., et al. SLIC superpixels compared to state-of-the-art superpixel methods. IEEE Trans. Pattern Anal. Mach. Intell 34.11 (2012)

Disclosure

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EP1527

Identification of cortical and subcortical correlates of cognitive performance in multiple sclerosis using voxel-based morphometry

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Objective: To identify correlations between specific brain regions andperformance in neuropsychological tests evaluating different cognitive functions in a large series of patients with multiple sclerosis (MS).
Methods: A total of 375 patients were evaluated with a comprehensive neuropsychological battery and with magnetic resonance imaging. Voxel-based morphometry with Statistical Parametric Mapping was conducted to analyse the correlation between cognitive performance and grey matter damage.
Results: The following correlations were found: Corsi block-tapping test with right insula; Trail Making Test with caudate nucleus, thalamus, and several cortical regions including the posterior cingulate and inferior frontal gyrus; Symbol Digit Modalities Test with caudate nucleus, thalamus, posterior cingulate, several frontal regions, insula, and cerebellum; Stroop Color and Word Test with caudate nucleus and putamen; Free and Cued Selective Reminding Test and Rey-Osterrieth Complex Figure with thalamus, precuneus, and parahippocampal gyrus; Boston Naming Test with thalamus, caudate nucleus, and hippocampus; semantic verbal fluency with thalamus and phonological verbal fluency with caudate nucleus; and Tower of Londontest with frontal lobe, caudate nucleus, and posterior cingulate.

Disclosure

Our study provides valuable data on the cortical and subcortical basis of cognitive function in MS. Neuropsychological tests mainly assessing attention and executive function showed a stronger association with caudate volume, while tests primarily evaluating memory were more strongly correlated with the thalamus. Other relevant regions were the posterior cingulate/precuneus, which were associated with attentional tasks, and several frontal regions, which were found to be correlated with planning and higher order executive functioning.

OCT

EP1528
Correlation between retinal Optical Coherence Tomography Measures and cognitive/physical disability in patients with early multiple sclerosis: a prospective study

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Introduction: Multiple Sclerosis (MS) is a chronic inflammatory disease associated with cognitive impairment. Optical Coherence Tomography (OCT), a non-invasive modality that enables the measurement of different retinal layers. Changes in the retinal nerve fiber layer (RNFL) correlate with brain atrophy. We explored the retinal Ganglion Cell-Inner Plexiform Layer (GCIPL) and RNFL changes in Relapsing-Remitting MS (RRMS) patients treated with Fingolimod or Interferon. Correlations between GCIPL and RNFL changes, and cognitive/physical disability in early RRMS were explored.
Methods: RRMS patients (with disease duration < 6 years) were recruited from the MS center between 2014 and 2017. Patients with at least one eye without clinical optic neuritis; and stable on treatment for at least 3 months were eligible to participate in the study. Clinical-demographic variables, physical disability, cognitive function, and OCT were collected at baseline (V1) and during the second year (V2). The Expanded Disability Status Score (EDSS), 25 Foot Walk Test (25-FWT), and 9-Hole Peg Test (9-HPT) were measured. Processing speed was measured using the Symbol-Digit Modality Test (SDMT).
Results: 48 patients with RRMS (25 on Interferons, 23 on Fingolimod) with mean (SD) disease duration of 38±26 months, were followed for 22.2 ± 7.7 months. No differences between treatment groups in clinical-demographic characteristics were found. Patients on Fingolimod had longer mean disease duration (45.5 ±27.8 months) than those on Interferon (30.6 ±25.4) (p=0.045). The pRNFL thickness decreased by 3.27 ± 4.3% between V1 and V2 while GCIPL decreased by 1 ± 2% (p< 0.0001). After controlling for age, gender, disease duration, educational level and depression, pRNFL at V1 correlated with SDMT (r= 0.5, p=0.001) and 9-HPT (r= -0.35, p=0.02) at V2; similarly GCIPL at V1 correlated with SDMT (r= 0.35, p=0.024) and 9-HPT (r= -0.32, p=0.034) at V2.
Conclusion: RNFL atrophy was more pronounced than GCIPL atrophy during the study period. Baseline OCT measures correlated with SDMT and 9-HPT after 2 years, supporting a role for retinal OCT as a disease progression marker in MS.

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EP1529
The role of optical coherence tomography as a predictor of cognitive impairment in multiple sclerosis

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Background: Retinal layer (RL) atrophy has previously been shown to correlate with brain atrophy in multiple sclerosis (MS), leading to increasing interest in the role of optical coherence tomography (OCT) as a possible indirect marker of neurodegeneration in MS. MS-related cognitive impairment can occur in all stages of the disease, including earlier and more 'benign' forms.

However, current data about the relationship of RL atrophy and cognition in MS patients is scarce.
Aim: To investigate the relationship between retinal layer atrophy and cognitive impairment in MS.
Methods: Sixty consecutive MS patients and 60 healthy controls (HC) were enrolled, matched by sex, age and education level. The patients were further divided according to the presence (MSON, n=21) or absence (MSNON, n=36) of previous optic neuritis. All participants were assessed with a standard neuropsychological battery for MS (MACFIMS), with cognitive impairment being defined as a defect in two or more domains; and underwent OCT scanning. Thickness measures were obtained for each individual RL.
Results: Overall, patients with MS showed a significant thinning of internal RL, including retinal nerve fibre layer (RNFL), ganglionar cell layer (GCL) and internal plexiform layer (IPL), compared to HC ($p< 0.001$ for all variables). These RL were also significantly reduced in both groups of MSNON ($p=0.001$ for RNFL and $p< 0.001$ for all other RL) and MSON ($p< 0.001$ for all variables) patients compared to HC. As expected, HC outperformed patients in all cognitive domains. There were no significant differences in RL thickness between MS patients with cognitive impairment (n=34; 56.7%) and those with normal cognitive performance (n=26; 43.3%). IPL thickness in MS group correlated modestly with scores for Symbol Digit Modalities Test ($r=0.332$ $p=0.012$) and Judgment of Line Orientation Test ($r=0.280$ $p=0.035$). However, no correlation was found when excluding MSON patients. No correlation between RL thickness and cognitive performance was found for all other RL or cognitive domains.
Conclusion: While there was a relationship between RL atrophy and impairment in cognitive tests dependent on visual ability in patients with previous optic neuritis, RL thickness did not globally correlate with cognitive impairment in our sample. We believe that further studies with prospective evaluation are warranted to clarify this relationship.

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EP1530
Cross-sectional OCT study of ON and non-ON MS eyes: non-effect of smoking exposure

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Objective: The objective of this cross-sectional study was to assess the association of smoking history in multiple sclerosis (MS) subjects on retinal nerve fibre layer (RNFL) and combined ganglion cell-inner plexiform (GCIP) thinning measured by optic coherence tomography (OCT).
Background: OCT is a relatively novel technique that has gained increasing support in MS research. Cigarette smoking has been widely acknowledged as a risk factor and a prognostic factor for MS patients.
Methods: 112 MS patients were recruited from the Brigham and Women's Hospital. Spectralis OCT scans acquired macular thickness and peripapillary RNFL measurements with automated segmentation. 9 peripapillary RNFL thickness and 14 macular GCIP layer thickness measurements were acquired using the segmentation software. After scanning, the quality of the scan was reviewed: when multiple valid scans were available, the highest quality scans for each eye were selected. Multivariable linear mixed effects regression model assessed change in RNFL and GCIP measurements with fixed effects for smoking history while adjusting for ON eye status, age, disease duration, and sex.
Results: 102 out of 112 MS patients responded to a smoking history questionnaire, 46 (45.10%) were ever-smokers and 56 (54.90%) were never-smokers. There were no statistically significant differences in retinal thickness measurements between never-smokers and ever-smokers: smokers had lower GCIP total macular volume (1.76 mm^3 vs. 1.79 mm^3, $\beta=-0.0005$, $p=0.9927$), higher mean global RNFL (86.25 μm vs 85.56 μm, $\beta=1.7133$, $p=0.5410$), and lower papillomacular bundle thickness (47 μm vs 49 μm, $\beta=-2.4516$, $p=0.4683$).
Conclusion: Our study shows no significant difference in RNFL and GCIP thickness between ever-smokers and never-smokers. In spite of being a recognised risk factor for MS onset and disease severity, smoking did not impact retinal thickness as measured by OCT measurements.

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Neuropsychology

EP1531
Expanding access to cognitive screening for individuals with multiple sclerosis: preliminary examination of two free web-based processing speed tests compared to the Symbol Digit Modalities Test

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Introduction: Over half of people with multiple sclerosis (MS) experience neurocognitive dysfunction, which contributes to significantly diminished quality of life and loss of employment. Traditional neuropsychological tests that are validated in individuals with MS, like the Brief International Cognitive Assessment for MS (BICAMS), require in-person testing and thereby lead to multiple barriers for research participants and patients. In contrast, the Many Brains Project (MBP) is an alternative, open-source, web-based cognitive battery that can overcome these obstacles. The MBP offers two tests of processing speed: the Digit Symbol Coding (DSC), which is similar to the BICAMS' Symbol Digit Modalities Test (SDMT); and the Forced Choice (FC), a reaction time measure.
Objective: To assess the concurrent validity of the DSC and FC processing speed tests with oral and written versions of the SDMT.
Methods: Data from 19 participants with MS were collected as preliminary data for a larger ongoing study of individuals with MS and health controls. Participants completed a series of neuropsychological tests in-person, including the SDMT (oral and written versions) from the BICAMS, and the computerized DSC and FC processing speed tests from the MBP battery. Pearson product-moment correlations were calculated between each version of SDMT and each of the two MBP processing speed tests (DSC and FC). Significant correlations were followed by paired-sample *t*-tests. Bland-Altman plots were constructed at the 95% confidence interval to assess agreement between the SDMT and MBP measures.
Results. Strong, significant correlations demonstrated concurrent validity between the DSC and both versions of the SDMT (oral: $r = .85$, $p < .001$; written: $r = .82$, $p < .001$). Correlations were not significant between the FC and either version of the SDMT (oral: $r = .23$, $p = .35$; written: $r = .07$, $p = .77$). Paired sample *t* tests demonstrated no significant differences between the DSC and either version of the SDMT (all $ps > .05$). Bland-Altman plots demonstrated excellent agreement between the DSC and each version of the SDMT.
Conclusion. Preliminary findings suggest that the DSC subtest of the MBP online battery is comparable to the SDMT. Future research may consider using the DSC as an alternative to the SDMT, especially for remote, web-based studies.

Disclosure

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EP1532
Functional MRI correlations between fatigue and cognitive performance in patients with relapsing remitting MS

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The correlation between fatigue and cognitive performance in Multiple sclerosis (MS) is well reported, but the intimate mechanisms of the fatigue impact on cognition are not fully defined yet. The combined assessment with neuropsychological testing and functional MRI (fMRI) has revealed an opportunity for investigating complex compensatory mechanisms involved in cognitive functioning.
The aim of this study is to investigate blood oxygen level dependent (BOLD) activations in relapsing-remitting MS (RRMS) patients with and without cognitive dysfunction and the impact of fatigue on cortical activations.
Forty-two patients diagnosed with RRMS according to McDonald's criteria (2010) in remission phase were enrolled in the study. Cognitive functioning was assessed by Symbol Digit Modalities Test (SDMT). Cut -off point of a total score of 55 on the SDMT was used to divide the patients in two groups: cognitively impaired (CI) - SDMT score equal to or below 55 points and cognitively preserved (CP) - SMDT score above 55 points. Fatigue was assessed by Modified Fatigue Impact Scale (MFIS). The fMRI scanning was performed on a 3T MRI using PVSAT paradigm as a cognitive task. Data were analysed with statistical parametric mapping 12(SPM12) software.
Between-group analysis revealed increased activations in left Brodmann area (BA) 40 in CP patients compared to CI ones ($p< 0.001$ uncorrected). Regression analysis yielded increased activations in left BA 40, right BA 40 and left BA6 in patients with higher MFIS score. Stronger BOLD activation in left BA 31 was associated with lower MFIS score (FWE, $p< 0.05$).
The differences in BOLD activations suggest presence of cortical reorganisation in our CP patients. The impact of fatigue on cortical activation during cognitive task is demonstrated by inconformity of activated areas depending on the MFIS score. Activation in BA 40 may represent a mechanism for diminishing fatigue impact on cognitive functioning in CP patients.

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EP1533
The impact of psychological resilience on cognitive and physical measures of disability in multiple sclerosis

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Introduction: Resilience, a dynamic process of positive adaptation to notable adversity, results in psychophysical stability and higher quality of life. The increasing focus on wellness promotion in Multiple Sclerosis (MS) offers opportunity to further study the role of resilience in MS. We have previously shown the independent contribution of resilience in disability in MS. In this project we further analyzed the impact of resilience on more comprehensive assessments of cognitive and motor function.
Objective: To characterize impact of psychological resilience on measures of cognitive and physical disability in MS.
Aims: To assess a role of psychological resilience in MS.
Methods: Patients with early MS (165 RRMS, 20 CIS; < 5 years diagnosed; median EDSS = 1.0) completed the Connor-Davidson Resilience Scale 10 item (CD-RISC-10): a well-established measure of psychological resilience. Composite measures of Cognitive Efficiency (Symbol Digit Modalities Test, Stroop, Pattern Comparison, Decision Speed), Memory (Story Recall Test, Brief Visuospatial Memory Test-R, CANTAB PAL, Verbal Paired Associates), and Motor Function (Nine Hole Peg Test, Grooved Pegboard, Finger Tapping, Grip Strength) were derived. Partial correlations controlled for age, sex, education, and premorbid intelligence were used.
Results: Higher resilience was associated with better performance on composite measures of cognitive efficiency (r=.197, p=.008) and motor function (r=.293, p< .001), but not memory (r=.063, p>.10), controlling for age, sex, education, and premorbid intelligence.
Discussion: Persons with greater psychological resilience demonstrated greater cognitive efficiency and motor function. Although the underlying mechanism of this relationship requires further study, current results emphasize the importance of resilience in MS and as a potential target for intervention. Further studies are needed to understand and build psychological resilience in persons with MS.

Disclosure

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EP1534
Cognitive impairment in multiple sclerosis is reflected by increased susceptibility for sound-induced flash illusion

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Multiple sclerosis (MS) patients are rarely referred to a neuropsychologist and their cognitive deficits remain undetected until they grow to an alarming extent. Relying exclusively on a brief clinical examination is not suitable for identifying patients who should be referred to a more elaborate neuropsychological examination. A more precise, inexpensive as well as easy to apply screening tool is urgently required. We employed the sound-induced flash illusion (SiFi), a multisensory perceptual illusion, where a single visual flash is presented together with an auditory beep. If shortly thereafter (< 150 ms stimulus onset asynchrony, SOA) a second auditory beep is presented, most of the subjects perceive two instead of one visual flash, e.g. the inputs from the two different sensory modalities fuse and the subjects perceive a second, non-existing visual flash. Healthy subjects usually perceive this illusion if the SOA is less than 150 ms. For SOAs > 150 ms the illusion is less frequently or not perceived at all. However, patients with mild cognitive impairment report seeing the second visual flash even at SOAs up to 300 ms (Chan et al., 2015). Therefore, we performed the SiFi task as well as an extensive neuropsychological testing in 95 subjects (39 patients with relapse-remitting MS (RRMS), 16 subjects with progressive multiple sclerosis (PMS) and 40 healthy control subjects (HC)). MS patients reported more frequently the SiFi as compared to HC as well as compared to control, non-illusion conditions (ANOVA interaction, $p < 0.05$). Essentially, patients with progressive type of MS continued to perceive the SiFi even at SOAs up to 300 and 500 ms. Furthermore, MS patients' performance on cognitive measurement was significantly lower as compared to HC in tests measuring working memory, attention, concentration, speed of information processing as well as visuospatial memory and constructional ability. A linear regression demonstrated that the number of failed neuropsychological tests in MS patients was predicted by their performance in the SiFi task for the longest SOA of 500 ms but not by age or years or education. These findings support the notion that similar mechanisms of cognition and multisensory perception are impaired in MS, most prominently in progressive MS. One possible mechanism is the disruption of brain connectivity in MS due to neuroinflammatory processes. SiFi could be used as a surrogate marker for cognitive impairment in MS.

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EP1535
Cognitive-motor interference while walking in people with multiple sclerosis: a potential maker of functional impairment?

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Introduction: Cognitive-motor interference (CMI) produced by simultaneous performance of a cognitive and motor task has been proposed as a valid marker of daily life impairment in people with Multiple Sclerosis (pwMS).
Objectives and Aim: To assess the CMI in pwMS and to explore its association with neuropsychological and other clinical variables.
Method: The dual task (DT) consisted on the performance of both cognitive (i.e. verbal fluency test) and motor (i.e. walking) tasks independently or *baseline (BL)*, both tasks simultaneously at best capacity or *double prioritization (DP),* and performing only the cognitive task at best capacity while comfortably walking or *cognitive prioritization (CP).* Mean contrasts were conducted to compare DT performance between pwMS (N=11; remittent-recurrent course; mean EDSS= 2.364 ± 1.64) and healthy controls (HC) (N=11). Intragroup comparisons and correlations between DT parameters and neuropsychological and clinical variables were performed.
Results: Both groups were statistically similar concerning age, sex and educational level; and different in SDMT scores, 5-Digit Test, BDI-II, D-FIS, and MSQOL-54. In DT, PwMS walked significantly less distance in all conditions and, during CP provided less number of correct words than HC. There were no differences in cognitive performance between conditions in pwMS nor in HC. PwMS walked significantly less distance in DP vs BL, in CP vs BL, but there were no differences in DP vs CP; whereas HC walked less distance in CP vs BL and in CP vs DP, with no differences in DP vs BL. In pwMS, a greater number of correct words in CP was associated with better general cognitive function (SDMT), higher cognitive flexibility (5-Digit Test) and with time since the last relapse. Moreover, the distance walked in BL and DP correlated negatively with EDSS scores. The distance walked in CP correlated with a measure of fatigue (D-FIS) and self-reported quality of life (MSQOL-54), and the distance in DP correlated with those measures as well and with cognitive flexibility (5-Digit Test).
Conclusions: PwMS and HC perform differently the DT. PwMS tend not to prioritize when required, which may potentially be due to an impairment in cognitive control in situations where their limited-capacity resources would be exceeded. Moreover, CMI measures correlate with various clinical and neuropsychological variables, which also supports the idea that CMI might offer an ecologic measure of functional impairment of pwMS.

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EP1536
The relationship between incidental learning and executive functions in relapsing remitting multiple sclerosis patients

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Background: Cognitive impairment is a frequent feature in relapsing remitting multiple sclerosis (RMMS), with prevalence rates ranging from 40 to 65%. Executive functions (EF) are frequently afected in MS. Incidental learning refers to the ability of learning new information without having the intention to do it. EF are neccesary for incidental learning, however, to date, there are no studies about the relationship between them in relapsing remitting MS patients.
Objectives: To evaluate the performance on EF and incidental learning task in RMMS patients in order to get a deeper understanding of their cognitive profile.
Methods: A complete neuropsychological test battery was performed on 30 relapsing remitting MS patients and 30 healthy controls. This battery included the digit symbol substitution test (WAIS III) (incidental learning), Rey complex figure test (incidental learning) and an ecological incidental learning test. The patients group had a mean age of 40.90 years (SD=10.04), 16.70 years of formal schooling (SD=2.69), a mean premorbid estimated IQ of 103,92 (SD=6.10), 3,40 years of progression (SD=4.33) and a mean EDSS score of 1.87 (SD=2.20). Control group had a mean age of 36.77 (SD=7.53), 17.31 years of formal schooling (SD=2.70) and a mean premorbid estimated IQ of 104.94 (SD=6.42).
Results: We found significant differences in the performance on executive screening tests ($p< 0,00$), phonemic verbal fluency ($p< 0,01$), PASAT 3´´ ($p< 0,00$), symbol search test ($p< 0,00$), digit symbol substitution test ($p< 0,00$), processing speed index ($p< 0,00$), Rey complex figure test (incidental learning, $p< 0,00$) and in the ecological incidental learning test ($p< 0,00$) between groups. Positive correlations were observed on the incidental learning test, executive screening test, working memory test and processing speed index.
Conclusions: The incidental learning is impaired in RMMS patients and it is influenced by executive dysfunction. These results are important to understand these patients cognitive proflile in clinical setting, specialiy in rehabilitation context.

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EP1537

Decision making under explicit risk and prefrontal and thalamus volumes in multiple sclerosis patients

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Background: Executive dysfunction in multiple sclerosis (MS) has generally been partially approached, being working memory (WM) and verbal fluency more frequent analyzed. Only a few studies have focused on decision making (DM) process, mainly using tasks without explicit risk, which do not allow differentiation of DM cognitive components (impulsivity, WM, flexibility, emotion). Data are limited about relationship between DM process and regional brain volumes.
Objective: to evaluate DM process under explicit risk in multiple sclerosis patients and its relationship with prefrontal and thalamus volumes.
Methods: Cambridge Gambling Task (CGT) was used to assess DM process by a prospective and controlled study in 102 MS patients (68 female, aged 42,7± 9 and EDSS 1,86±1,3) and 55 matched healthy controls. CGT evaluates DM process under explicit risk. All patients also underwent another prefrontal task (WM, flexibility and planning) of CANTAB battery, SDMT and PASAT, in order to assess their influence in DM process by a multiple lineal regression. Finally, the relationship between MD and volumes of thalamus, lateral orbitofrontal and caudal middlefrontal (measured using Free Surfer) was analyzed using a lineal regression model.
Results: MS patients showed respect to controls a significant longer deliberation time to make a decision (p=0.037), greater impulsivity (delay aversion p =0.012), less rational choices (quality of DM p=0.002) and worse risk adjustment (p=0.040). Flexibility task explained impulsivity (R^2=0.12, p=0.003) and risk taken (R^2=0.07, p=0.025). Lateral-orbitofrontal and thalamus volumes predict impulsivity, quality of DM and deliberation time.
Conclusions: MS patients showed impairment in MD process under explicit risk conditions with and minor effect of flexibility in impulsivity and risk taking. Lateral-orbitofrontal and thalamus volumes seem predict DM process.

Disclosure

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EP1538

Abnormal network connectivity related to social cognition in relapsing remitting multiple sclerosis

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Introduction: Multiple Sclerosis (MS) is a source of disability and cognitive declining in young patients. Social cognition and its subcomponents, Social Perception and Theory of the Mind, have focused an increasing interest. Nevertheless, the definition of a specific pattern of socio-cognitive impairment and the underlying structural and functional correlates remain undefined.
Objective: To better understand the underlying structural and functional correlates of Social Cognition impairment in MS.
Methods: Relapsing-remitting (RR) MS patients and healthy controls underwent a full neuropsychological evaluation including traditional domains and Social Cognition tasks. Structural and functional Magnetic Resonance Images (MRI) were acquired in a 3T scanner. Volumetric analysis included SIENA and Voxel-Based Morphometry, while functional included resting state analysis. Correlations between neuropsychological performance, structural and functional MRI were assessed.
Results: We recruited 118 Subjects (50 Healthy Controls and 68 RR-MS Patients) obtaining a young sample (37,43 + 11,2 years old vs. 37,97 + 10,76 years in control group, p-value=0,765), with a short disease duration (Median 4,5 years), and higher functional, educational and job status. This was also a low disability sample. Even in the absence of significant traditional cognitive impairment, lower performance in social cognition tasks was observed among patients. The structural analysis has shown regional compromise of areas as Insula, Caudate, Cingulate and Medial Frontal Gyrus, also correlated with performance in the considered tasks. On the other hand, the same areas found in structural analysis exhibit functional changes in patients, showing both increase and decrease in functional connectivity, representing facilitated and impaired information flow between relevant cortices.
Conclusion: Social Cognition exhibits a specific pattern of impairment since earliest stages of the disease even when physical or cognitive disability is absent. It appears to be related to the preferential structural compromise of cortical areas strongly involved in the processing of social information. Functional findings support this notion by reflecting the altered flow of information from socially relevant nodes to the entire brain. Also, our results are compatible with the principles of neural compensation as observed in different cases of brain damage.

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EP1539

Baseline cognitive function of patients with relapsing remitting multiple sclerosis is associated with therapeutic response to natalizumab

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Background: Cognitive dysfunction of patients with multiple sclerosis (PwMS) has been correlated with brain atrophy and neurodegeneration. We hypothesized that potentially treatable inflammatory mechanisms are also important for the pathogenesis of cognitive dysfunction of PwMS. If so, cognitive dysfunction may predict therapeutic response to potent, anti-inflammatory disease modifying drugs.
Aim: To explore whether the therapeutic response to natalizumab is modified by baseline cognitive function or level of disability (EDSS).
Methods: 76 relapsing-remitting PwMS completed a standardized validated computerized cognitive assessment battery (NeuroTrax) with analysis of age-and education-adjusted individual cognitive domain scores and a global cognitive (average) summary score (GCS). Cognitive scores and EDSS were evaluated twice: at baseline and after a time interval of 9-27 months of treatment with natalizumab. Repeated measures ANOVA was used to estimate the effects of baseline EDSS and GCS on the changes in EDSS and GCS after treatment, while controlling for the inter-evaluation time.
Results: 76 PwMS were evaluated [female: 54 (71%); EDSS 3.5±2; education: 14.8±2.7 years; time between evaluations:16.8±4.6 months]. A significant interaction was found between baseline global cognitive score and change in EDSS after natalizumab infusions [F(1,71)=4.6, P=0.035]. EDSS and GCS changes after natalizumab were not significantly modified by baseline EDSS. In line with our hypothesis, patients with low baseline cognitive scores (GCS of at least 1SD below age- and education-adjusted average) showed greater improvement in EDSS after treatment compared with patients with better cognitive function at baseline. GCS scores were also improved after natalizumab [F(1,71)=6.3, P=0.02]. An improvement of at least 0.5SD in GCS was noted in 17% of the patients.
Conclusion: Cognitive impairment predicts therapeutic response to natalizumab and may improve after treatment with natalizumab. Cognitive dysfunction in PwMS may not necessarily imply irreversible brain damage, but may be also due to ongoing inflammation that is amenable to treatment.

Disclosure

All authors have nothing to disclose

EP1540

Social cognition deficits in early multiple sclerosis

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Background: Cognitive impairment and deficits in social cognition (SC) have been reported to affect a highly variable percentage of patients with Multiple Sclerosis (MS). However, SC has not been thoroughly explored in the initial stages of the disease.
Objectives: To study different components of SC including theory of mind, empathy and emotion recognition in patients with early MS.
Methods: Patients were recruited from the outpatient MS clinic at the Raul Carrea Institute for Neurological Research (FLENI) by attending neurologists. Thirty-four relapsing-remitting MS patients, fulfilling 2017 McDonald criteria, with ≤ 2 years disease duration and scores ≤2 on EDSS, were included. Thirty subjects matched for age, gender, and educational level, recruited from a local volunteer group, served as controls. Both groups underwent complete neuropsychological evaluation (Rao BRB). Social Cognition was assessed using the International Affective Picture System (emotional processing), The Mind in the Eyes Test the Empathy Quotient, and the Faux Pas Test. Neuropsychiatric scales were also administered (HADS, Apathy Evaluation Scale).
Results: Groups did not differ significantly in age, sex, educational level or in the neuropsychiatric scales that assessed depression, anxiety and apathy. Patients showed significant deficits in cognitive tests of verbal memory, executive functions and language (Rao BRB). Social cognition assessment showed that patients presented greater difficulties in Reading the Mind in the eyes tests; p = 0.014), in the detection of socially inappropriate behaviors (Faux Pas Test p= 0.009) and a positive bias was observed in the interpretation of neutral images in the emotional reactivity test (IAPS p = 0.023). No differences were observed in the Empathy Quotient performance.
Conclusions: Patients with early MS present disorders in cognitive functions and social cognition. Social cognition deficits are an important component of cognitive functioning and must be taken into account in early MS patients. They have strong impact on social functioning and quality of life. Future research is needed to study the longitudinal course of these disorders.

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Impaired natural viewing behaviour reflects cognitive impairment in multiple sclerosis- an eye-tracking study

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Cognitive impairment can be one of the major deficits multiple sclerosis (MS) patients are suffering from. Still cognitive deficits are not frequently examined and diagnosed due to the limited time of Neurologists and Neuropsychologists. It is well known that even mild cognitive deficits can lead to a loss in quality of life as patients complain about problems in their daily life. Therefore we tested if impaired natural viewing behaviour reflects cognitive impairment in MS. We used the BOiS - Berlin Object in Scene Database (Mohr et al., 2016) which includes photographs of naturalistic scenes with a typical object at two different locations - expected versus unexpected location - and one where the target object is absent. 105 of those photographs were rated into three different categories depending on the difficulty. We measured the reaction times and used eye-tracking in 92 subjects (53 patients with relapse-remitting MS and with progressive multiple sclerosis and 39 healthy control subjects). Reaction times differed between the patients and healthy controls as well between the different difficulty and object location (expected, unexpected and missing). Furthermore, eye-tracking of natural viewing behaviour differentiated between MS patients and healthy subjects and was linked to cognitive impairment. Natural viewing behaviour as measured with eye-tracking can therefore be used as a predictive tool to evaluate which MS patients should undergo a detailed neuropsychological examination.

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EP1542

Neuropsychological correlates of fatigue in multiple sclerosis

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Background: Fatigue is a frequent and debilitating symptom in patients with multiple sclerosis (MS). It could affect up to 90 % of cases during their disease course. Yet, the pathophysiology of MS fatigue remains unclear.

Objectives: This work aims to assess the neuropsychological correlates of MS fatigue.

Methods: Thirty-eight adult MS patients were enrolled. Patients were excluded if they had relapse in the last three months, excessive daytime sleepiness as per Epworth Sleepiness Scale score > 10, clinical depression as per Beck Depression Inventory score > 19 or other neuropsychiatric diagnoses. Patients were classified as fatigued and nonfatigued based on the Modified Fatigue Impact Scale. They underwent a neuropsychological evaluation that included the Symbol Digit Modalities test, the Hospital Anxiety and Depression Scale, and the Toronto Alexithymia Scale.

Results: There was no significant group difference (non-fatigued versus fatigued) with regard to age, gender, education, MS type, expanded disability status score, duration of disease or the progressive phase of illness. Compared to non-fatigued patients, those with fatigue had higher anxiety (3.88±1.93 vs. 6.14±3.47, $p = 0.016$), depression (4.00±2.72 vs. 6.05±2.60, $p = 0.023$) and alexithymia scores (45.35±11.53 vs. 53.43±9.52; $p = 0.023$). Direct correlations were found between fatigue and each of anxiety ($p = 0.001$), depression ($p = 0.000$) and alexithymia ($p = 0.019$).

Conclusions: These results support the existence of common underlying mechanisms for fatigue and anxiety/depression and a bidirectional interaction between these symptoms. In other words, the more the individuals are tired, the more they feel demotivated and melancholic, and the more they become worried and preoccupied with the future. The generation of this ill-being state would contribute to the accentuation of fatigue which would in turn generate new fears and negative thoughts. Thus, individuals would enter a difficult to manage vicious cycle. Our findings also suggest that autonomic hyperarousal and amplification of somatic complaints, generally described in the context of alexithymia, could influence the patients' experience and perception. Saying differently, in alexithymic patients who have difficulty analyzing and describing their own emotions, the underlying sympathetic hyperactivity may increase the tendency of patients to intensify their bodily sensations and thus exaggerate their perception of fatigue.

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EP1543

Study of the relationship between executive functioning and episodic memory performance in multiple sclerosis using the Test of Memory Strategies

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Background: The ability to generate memory strategies is a relevant factor in episodic memory, nevertheless no memory test has been designed to assess the relationship between executive functions (EF) and memory (MEM) in multiple scleroris (MS).
Goals: To evaluate if the Test of Memory Strategies (TMS) allows to assess the relationship between EF and episodic MEM; and to study the relevance of the level of the organization of the material in MEM performance in MS.
Methods: We selected 49 patients with remitting-relapsing MS and 47 healthy controls (HC) matched in age and educational level. MS sample was assessed with a neuropsychological battery and classified in 3 groups: no cognitive impairment (NCI), mild cognitive impairment (MCI) and moderate cognitive impairment (ModCI). TMS was administered to all groups. TMS evaluates incidental and immediate MEM including 5 word lists with increasing external organization presented serially: T1, incidental learning task with no phonemic (PH) or semantic (SEM) relations; T2, explicit learning task with no PH or SEM relations; T3, explicit learning task distributed in two SEM categories randomly presented; T4, explicit learning task distributed in two organized SEM categories; T5, explicit learning task distributed in two organized SEM categories previously announced. We analyse differences for TMS performance among HC and MS groups.
Results: A Group X Level of cognitive impairment ANOVA revealed statistically significant differences ($p < 0.001$) for T3, T4 and T5; *Post-hoc* analysis showed that HC obtained better results than all the patients groups. When considering the degree of cognitive impairment (CI) all MS groups presented a significant decrement of correct answers for T5 ($p < 0.001$); and CI groups obtained significant poorer performance (MCI for T3 and ModCI for T3 and T4, $p < 0.01$)) than NCI.
Conclusion: We find no incidental memory differences between MS and HC. Analysis according to CI revealed that patients with MCI show difficulties to take benefit from semantic categories when randomly presented but no when they are externally organized, suggesting the presence of early EF symptoms; as cognitive decline progresses, the ability to take benefit from external organization and clues also decreases suggesting the existence of memory problems. We conclude that TMS allows to study relationship between EF and MEM and provides relevant information about the course of memory decline in MS.

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EP1544

The 15-15 PASAT 3" approach to study congnitive fatigue in multiple sclerosis

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Introduction: Fatigue is one of the most frequent and interfering symptoms in persons with multiple sclerosis (PwMS), and it has physical and cognitive manifestations. Cognitive fatigue (CF), is difficult to be quantitatively assessed and can be differently explained: due to an extreme punctual cognitive effort or due to maintained long-term extenuating effort. Previous research has suggested PASAT 3" as a measure of cognitive fatigue dividing the test in two halves and comparing both performances.
Objectives: To assess if a new measure of PASAT 3" can be used as a more accurate measure of CF using the first and the last 15 items of the test.
Methods: This is an observational, multicenter, case-control study with PwMS and healthy controls (HC) of the same age and educational level. MS performed a neuropsychological evaluation as part of the clinical assistance routine to define the cognitive profile: no cognitive impairment (NCI), mild (MCI) and moderate cognitive impairment (ModCI). As CF measure we selected the first 15 items (15F) from PASAT3" and compare them with the last 15 items (15L). We considered hits and dyads responses.
Results: 165 PwMS, 71% women with a duration of the disease of 9,9 years and EDSS of 2,2. 50 HC, 58% men showed with similar age (PwMS M=39,8; HC M=36,9) and years of education (PwMS M=14,5; HC M=14,6). HC produced more hits (M=10,6; SD=3,2; $p < .012$) and dyads (M=9,4; SD=4,4; $p < .033$) at 15L than PwMS (hits M=9,2; SD=3,4 and dyads M=7,9; SD=4,4), with no difference at 15F. When considering cognitive profile, all presented a decrement of both hits (NCI 15F M=12,6 vs 15L M=9,8; MCI 15F M=11,1 vs 15L M=9,3; ModCI 15F M=10 vs 15L M=7,7) and dyads (NCI 15F M=11,8 vs 15L M=8,6; MCI 15F M=10,2 vs 15L M=7,8; ModCI 15F M=8,5 vs 15L M=6,5).
Conclusion: This 15-15 PASAT analysis seems to be a good alternative measure for cognitive fatigue that discriminate patients and controls. This model focus on the first and last items of PASAT as we suggest that they might better reflect cognitive effort. Analysis according to cognitive impairment showed that as cognitive decline progresses, the number of correct answers in the last part of the test might suggest a higher rate of cognitive fatigue associated.

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EP1545

A systematic literature review: the relation between cognitive functioning and work outcomes in patients with multiple sclerosis

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Background: The majority of MS patients are unable to retain in the work force. Cognitive dysfunction is increasingly being recognized as an important limiting factor in work participation in patients with Multiple Sclerosis. This literature review provides a description, synthesis and interpretation of the existing literature and identifies gaps and caveats in current knowledge.

Methods: Clinical trials, randomized controlled trials or observational quantitative studies, published between 1970 and April 2017 in which data on cognitive factors associated with employment, work functioning or work-related problems were reported, were included. Papers were manually double checked by two blinded reviewers.

Results: A total of 41 papers were included of which 4 papers concerned prospective, longitudinal studies. The majority of studies reported positive associations between cognitive functioning and work outcomes (37/41 studies; 90%). Positive associations were found between work outcomes and global cognitive functioning (8/9 studies; 89%), language (8/17 studies; 47%), processing speed/ working memory (22/26 studies; 85%), new learning and memory (12/21 studies; 57%), executive functioning (10/16; 63%), intelligence (1/6; 17%) and self-reported cognitive functioning (14/15; 93%). None of the reviewed studies found a relation between visuospatial processing and work outcomes (0/8; 0%). Models including cognitive measures as well as demographic (age, education), neurological (disability, fine motor coordination, disease course), and psychological variables (depression, personality, fatigue) best predicted work outcomes.

Conclusion: By conducting this review we found ample evidence that objective cognitive functioning (specifically processing speed/ working memory and executive functioning) and self-reported cognitive functioning are important independent associates of work outcomes and should be addressed by healthcare professionals. Future research could benefit from a standardized categorization of cognitive tests and a focus on longitudinal changes in cognition and its relation to work outcomes.

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EP1546

Performance on a digital neuropsychological test battery in individuals with relapsing remitting multiple sclerosis and healthy controls. Normative values

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Introduction: The INECO digital neuropsychological test battery is a valid tool for the assessment of attention, episodic memory, working memory and processing speed in Multiple Sclerosis (MS) patients. This battery allows us to make an adequate remote

assessment of patients cognitive status, being more efficient in terms of costs and time.
Objectives: To compare the performance on the INECO digital neuropsychological test battery in individuals with relapsing remitting MS and healthy controls, in order to obtain normative values.
Methods: The INECO digital neuropsychological test battery and a standard neuropsychological assessment was administered to 33 relapsing remitting MS patients and 70 healthy controls in Buenos Aires, Argentina. Mean age: 39,16 years old (9,011). Every subject had at least 12 years of education. We used T test to evaluate the differences between the groups. Alpha score established was 0.05.
Results: Groups did not differ with regard to demographic variables (age, sex and years of education). We found significant differences in the performance on IFS, phonemic verbal fluency, processing speed index (WAIS-III), Rey auditory verbal learning test and Rey complex figure test between MS patients and controls, in the standart assesment. We also found significant differences between the two groups in the performance on computerized test that assessed attention, working memory, processing speed and episodic verbal and visual memory. Normative values were matched by age according to the interval superposition strategy.
Conclusions: The INECO digital neuropsychological test battery is a sensitive tool for the assessment of attention, executive functions and episodic memory in relapsing remitting MS patients. We obtained normative values for adults (18 to 60 years old).

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Correlation of fatigue with cognitive and emotional variables in a Portuguese group of multiple sclerosis patients

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Introduction: Fatigue is a common multi-dimensional symptom of patients with Multiple Sclerosis (MS), characterised by a sense of tiredness, exhaustion or a lack of physical and mental energy that affects physical and cognitive functioning related to their work, social tasks and daily life. Due to high prevalence of fatigue in MS, this study aims to identify its modifiable contributing factors.
Methods: Ninety-five patients (61 females; 34 males) were included. Aged between 17 and 68 years (M= 38.2, DP=11.1), mostly were married (53.7%) and employed (61.1%). The most prevalent refers to relapsing-remitting type (92.6%), with mean (SD) disease duration of 6.5 (5.9) years, median EDSS of 1.5 and median MMSS of 2.0. Fatigue, anxiety/depression, and cognition were assessed with the Modified Fatigue Impact Scale (MFIS), Hospital Anxiety and Depression Scale (HADS) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), respectively. A chi-square test of independence was performed to examine the relation between fatigue and cognitive impairment, and t-test for independent group's analysis was conducted to test differences between patients with or without fatigue (cut-off 37) in BICAMS' tests. Multivariate analysis was run to examine correlations between fatigue and cognitive and emotional variables.
Results: We found that 45 patients had fatigue, 38 anxiety, 21 depressive symptoms and 22 were cognitively impaired. Patients with fatigue were more likely to show cognitive impairment (X^2 (1, N= 95)= 10.27, p< 0.01) as they performed worse than patients without fatigue in all cognitive tests (SDMT (t(93)= 5.41, p= .000), CVLT (t(93)= 4.03, p= .000), BVMT (t(93)= 2.80, p= .006). Analysis showed a negative association between fatigue and all cognitive tests (specially SDMT: r= - 0.449, p= .000) and a positive association between fatigue and anxiety and depression. Regression analysis showed that most relevant predictors of fatigue are SDMT, anxiety and depression.
Conclusion: Our results show that not only cognitive variables, but also emotional factors are related to the presence of fatigue. This highlights the importance of comprehensive psychological intervention in MS, including emotional support that could help patients to cope with symptoms contributing to fatigue, besides cognitive training.

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EP1548
Dynamics of cognitive dysfunction profile in patients with multiple sclerosis based on their disease duration

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Introduction: The profile of cognitive dysfunction in multiple sclerosis (MS) has been thoroughly investigated in the end of the last century. The more recently studied "dual" nature of MS - both a neuroinflammatory and neurodegenerative disorder - and the different significance of these two components in the different stages of MS suggest a dynamic profile of cognitive dysfunction in the course of the disease. Such data, however, is lacking or insufficient.
Aim: The aim of our study is to characterise the profile of cognitive dysfunction in a Bulgarian cohort of MS patients as a function of disease duration.

Methods: 100 MS patients underwent detailed neuropsychological assessment with a battery comprising tests for general cognitive functioning, episodic verbal and visuospatial memory, verbal fluency, attention and executive functions and their results were compared to those of 57 healthy controls (HC). The patients were divided into 3 groups depending on their disease duration - group 1: < 1 year (n = 20), group 2: 1-10 years (n = 43), group 3: >10 years (n = 37).
Results: In the Free and Cued Selective Reminding Test the results in group 1 differed from HC in free ($p< 0.001$), total ($p< 0.001$) and delayed recall ($p=0.001$). Groups 2 and 3 differed significantly from HC not only in free, total and delayed recall, but also in immediate recall ($p< 0.001$ for both) and recognition ($p=0.001$ and $p=0.004$, respectively). Tests for executive functions (Digit Symbol Modalities Test, Trail-Making Test, etc.) and verbal and semantic fluency all detected significant differences from HC even in patients in group 1. Stroop Colour Word Test revealed a significant difference from HC in its 3rd phase for group 1 ($p = 0.019$), but also in its 1st and 2nd phase for groups 2 and 3. The general cognitive functioning scale revealed significant differences from HC in groups 2 and 3 ($p< 0.001$ for both).
Conclusion: The profile of cognitive dysfunction in MS is not static and changes with disease progression - during the first years of disease, when the neuroinflammatory component is the leading cause of damage, patients demonstrate predominantly dysexecutive features, information processing disturbance and deficits in attention, verbal fluency and memory retrieval, while in the more advanced stages of disease, when the neurodegenerative component is the leading cause of damage, this specific cognitive profile is lost and universal deficits in almost all cognitive domains are observed.

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EP1549

Cognitive performance of RRMS patients at the time of diagnosis: one step before the concept of cognitive impairment

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Introduction: Cognitive impairment (CI) affects a large proportion of multiple sclerosis (MS) patients, but the clinical attention to neuropsychological aspects usually begins too late, when CI is, unfortunately, already evident also without formal testing.
Aim: To assess cognitive performance of a group of MS patients without diagnosis of formal CI at the time of MS diagnosis compared with a group of matched healthy controls (HC).
Methods: Twenty-seven MS patients with relapsing-remitting (RR) course (8 CIS and 19 RRMS, 21 F, Age: 35.6±10.9, Education: 14.0±2.2, Disease duration: 3.2±4.0) and 27 matched HC were tested with the Brief Repeatable Battery (BRB; Rao et al., 1990). First, we have ensured that all MS patients had no CI according to the widely accepted classical approach (0 or 1 subtest under the cut-off score of normative data). Second, we assigned a "cognitive performance score" (CPS) considering the *z*-scores of each subtest of the BRB (the higher the value, the higher the cognitive performance). Third, with the same approach, we also calculated a global CPS (global-CPS) as the sum of each CPS of the BRB subtests.
Results: The results showed a significant difference between MS and HC in the global-CPS (p=.01). Considering the CPS of the BRB subtests, we found a significant difference between MS and HC on the Selective Reminding Test - Delayed (SRT-D; p=.01) and the Symbol Digit Modalities Test (SDMT; p=.006).
Conclusions: Despite this group of MS patients did not reach the diagnosis of CI at time of MS diagnosis, we found a significant decrease in their cognitive performance as compared with the HC group either at a global level, or in specific cognitive domains, i.e., verbal long-term memory (SRT-D) and information processing speed (SDMT). These results suggest that a more sensitive approach can improve the detection of slight impaired cognitive performance, already present at the time of MS diagnosis, earlier the formal diagnosis of CI. Advanced technological tools are needed to overcome the limitation of classic neuropsychological testing of MS patients in detecting impaired cognitive performance.

Disclosure

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All the other authors have nothing to disclose.

EP1551

Validation of the Brief International Cognitive Assessment for multiple sclerosis (BICAMS) in a Colombian population

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Introduction: Cognitive impairment (CI) has been recognized as an important factor in multiple sclerosis (MS) in the past few years. It influences employment, activities of daily living, and social and emotional functioning. One brief, reliable and valid tool to assess cognition in MS is the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), which encompasses the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test (CVLT II), and the Revised Brief Visuospatial Memory Test (BVMT-R).
Objectives: Standardizing raw scores of the BICAMS and obtaining regression formulas in order to adjust for demographics in the Colombian Population. Establish test-retest reliability and criterion related validity for the validation.
Aims: Continuing with the international initiative to validate the BICAMS, our aim was to obtain normative data for the Colombian population.

Method: Fifty MS patients and 100 healthy controls (HC) participated in the study. Instead of the CVLT-II, the Colombian validated form, PAM (Free Encoding Verbal Learning and Memory Test) was used. Test re-test measures were obtained in 6 patients. Normative raw data was obtained from the HC group and converted to uncontrolled scaled scores. Stepwise multiple linear regressions were used to obtain an adjusted Z score.
Results: Evidence of criterion validity was obtained, MS group performing significantly worse than HC group in all three tests (SDMT: p= .001, PAM: p= .03, BVMT-R: p< .00; effect sizes: SDMT= 0.61, PAM= 0.33, BVMT-R= 0.90). Test re-test was obtained, finding significant correlations for the SDMT (r=0.928, p=0.008) and the BVMT-R (r=0.83, p=0.037), but not for the PAM (r=0.6, p=0.2). Standardization was done and these scores were then adjusted for age and years of schooling.
Conclusions: CI was found in 50% of our sample, similar to the percentages reported in other validations and the estimated prevalence for CI in MS. In the Colombian validation, the BICAMS proved to be able to discriminate between patients and controls, especially the BVMT-R. The BICAMS proved to be a valid and sensitive tool to screen for CI in MS patients, but the importance of a more comprehensive assessment is highlighted. This study is the first effort to guarantee the use of a reliable and valid tool in Colombia. As a diverse country, the need of a wider and cross-cultural sample is highlighted for future studies.

Disclosure
The authors reported no potential conflict of interest.

EP1552
Spanish adaptation of the multiple sclerosis and vocational accommodations in multiple sclerosis patients

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The Buffalo Vocational Monitoring Survey (BVMS) is a tool to characterize work-challenged patients. Given the lack of an instrument in Spanish, we have proposed: to evaluate the adaptation of the Spanish version of the BVMS; to describe findings from this survey, to analyze the relationships between negative events and clinical and cognitive variables and to investigate the relationship between accommodations and clinical and cognitive variables.
61 MSpatients (93.2%RR-1.7%SP-5.1%PP) were included. 59%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: BVMS Survey; clinical outcomes; EDSS, BDI II & FatigueScale. Cognitive outcomes: *BICAMS* (SDMT-CVLT-BVMT-R); 7/24 Visuospatial Scale, PASAT2"-3" and Verbalfluency. Two factors were obtained: Clinical factor (EDSS-fatigue-depression-Cronbach´s α0.400) and Cognitive factor (SDMT-CVLT-BVMT-R-Cronbach´s α0.765). Psychometric evaluation included a professional translator, face and content validity procedure performed by an expert, a field test to verify the understanding of the contents and external criterion validity.
Regarding external criterion validity, between employees (dependent and self-employed) vs. unemployed (unemployed-retired) significant differences were obtained: Cognitive Factor (p=.022), SDMT (p=.040) , BVMT-R(p=.036), Pasat3 (p=.004), Pasat2 (p=.000) and Fatigue (p=.030), tendency in the Clinical factor (p=.051). Of 65.55% employee, 57.5% are in a dependency relationship, 32.5% are self-employed of informal works and 10% are self-employed composed of university professionals. 14.5% are unemployed of which 55.5% are due to disability. Regarding work problems, 13.5% refer decrease of scheduled work hours, 8.1% removal of job responsibilities, 5.4% asked to work additional hours and 2.7% formal discipline for a mistake. 12% of patients work additional hours per week and 22.5% miss days of work. 2 patients received harassment. Regarding job accommodations, flexible work hours, access refrigerator, memory aids and written job instructions are the most frequently used. Depression (p=.044) differentiate patients with and without negative events. Significant associations were found between accommodations and verbal memory (p=.335) and cognitive factor (p=.407).
This Spanish version is considered a new tool to monitor employment difficulties in Spanish-speaking MS patients.

Disclosure
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Marinangeli Aldana: nothing to declare
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Biomarkers

EP1553
Alternative splicing in multiple sclerosis: a systematic review of the literature and validation in transcriptome data

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Nearly all human genes encode multiple transcriptional variants. Previous studies reported genes with altered RNA splicing patterns in multiple sclerosis (MS). We aimed to utilise cell type-specific transcriptome profiles obtained by high-resolution microarrays to further examine the exon composition of these genes in patients with relapsing-remitting MS.

Following the PRISMA guidelines, we screened the literature for studies on splicing in MS, considering only primary research articles with data on human samples. Moreover, we processed a huge dataset comprising 150 Affymetrix HTA 2.0 microarrays to explore the transcriptomes of five different immune cell populations, which were obtained from the peripheral blood of MS patients. Alternative splicing events (ASE) were detected in these data using the EventPointer software.

We identified 38 MS-related publications that investigated alternative RNA variants of in total 28 genes, including IFNAR2, IL7R and MBP. For 21 of those genes, 52 ASE could be retrieved with p-value < 0.01 when we compared the microarray data of the individual MS patients. Most of the ASE were detected in CD56+ natural killer cells. Among the top genes were NFATC1 and NFAT5, two members of the family of nuclear factors of activated T-cells, for which different mRNA isoforms result from usage of an alternative first exon and skipping of a cassette exon, respectively.

To conclude, analyses at exon level can help to achieve a better understanding of transcriptional blood biomarkers for MS. Our study demonstrates that specific transcript variants expressed in immune cell subsets are suited for patient classification. Their predictive value regarding the individual clinical course of the disease remains to be determined.

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EP1554

Expression levels of apoptosis-related molecules in peripheral blood cells of multiple sclerosis patients

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Background: The pathogenesis of multiple sclerosis (MS) is thought to involve autoreactive T lymphocytes that have the capacity to invade the central nervous system and promote tissue damage. Programmed cell death (apoptosis) of activated autoreactive T lymphocytes is one of the mechanisms involved in the maintenance of the immunological tolerance. A failure in the deletion of potentially pathogenic cells might lead to a major persistence of these cells in peripheral blood. In the present study, we aimed to explore the role of a large panel of pro- and anti-apoptotic factors by measuring the expression levels in peripheral blood mononuclear cells (PBMC) from MS patients with different clinical forms of the disease.

Methods: The mRNA expression levels of BID, BAK, BAX, BAD, BIM, SMAC, BNIP3, NOXA, PUMA (pro-apoptotic molecules), and BCL-2, BCL-XL, BCL-W, MCL-1, FAIM1, FAIM2, LFG, FLIP, FLIP-L, clAP-1, clAP-2 (anti-apoptotic molecules) were measured by real time PCR in PBMC from 12 healthy controls and 29 untreated MS patients [17 patients with relapsing-remitting MS (RRMS), 12 with primary-progressive MS (PPMS), and 6 RRMS patients during the relapses].

Results: The most differentially expressed gene between healthy controls and RRMS patients corresponded to *PUMA* (p53 unregulated modulator of apoptosis), and the expression levels for this gene were significantly down-regulated in RRMS compared to controls (p= 0.019). *BID* (BH3 Interacting Domain Death Agonist) and *BAD* (BCL2 Associated Agonist of Cell Death) expression levels were significantly down-regulated in PPMS patients as compared to healthy controls (p=0.047 and p=0.024 respectively). *BID* expression levels were also significantly decreased in PPMS patients compared to RRMS patients (p=0.0094).

Conclusions: These findings support a role for the pro-apoptotic factors *PUMA*, *BID* and *BAD* in the pathogenesis of MS. Western blot studies are currently in progress to investigate whether differences in mRNA expression levels for these genes are also present at the protein level.

Disclosure

S Malhotra, C Matute-Blanch, M Moreno, L Negrotto and E Sarró report no disclosures.

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J. Rio has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma, Merk Serono, Biogen-Idec, Teva Pharmaceuticals, Sanofi-Aventis, Genzyme, and Novartis.

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.

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EP1555

Serum levels of mir-128-3p are associated to clinical course and disease activity in multiple sclerosis

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Background: MicroRNAs (miRs) are gene transcription regulators, which have emerged as novel candidate biomarkers for multiple sclerosis (MS). The main goal of the study was to investigate the association between miRs expression in serum of patients with MS and the disease course.
Methods: Serum sample of consecutive patients with clinically isolated syndrome (CIS) or MS stored at Verona Laboratory of Neuropathology were analysed. All cases were followed clinically at Verona MS Centre and had a brain MRI performed by a standardized protocol at time of serum collection. Serum samples from subjects with other neurological conditions were used as controls. Based on earlier studies, a panel of ten circulating candidate miRs extracted from serum were analysed by Real-Time PCR. miR-425-5p, which showed the most stable expression across samples in a preliminary screening, was used as normalizer. Non-parametric statistical tests were used to analyse the association between miRs expression and outcomes of interest, including relapse occurrence and expanded disability status scale (EDSS) score change over time.
Results: Serum samples from 72 CIS/MS cases and 17 controls were analysed. Mean age at sample collection was 37 ±12 years. Among cases, 59 had a relapsing course, including 10 CIS patients, and 13 had a progressive disease. Mean follow-up duration was 16 months. No significant differences were found in miRs levels between cases and controls and according to gender, age, and presence of contrast-enhancing lesions on MRI. We found a significant decrease of miR-128-3p levels in patients who had one or more relapses on follow-up compared to cases with no relapses (median ratio 0.82 vs. 1.64; p=0.014); also, there was a significant inverse correlation between miR-128-3p levels and relapse rate (r= -0.44, p=0.008). In addition, miR-128-3p levels were significantly higher in patients with progressive compared to relapsing MS (2.86 vs 0.73, p=0.009). We observed a significant correlation between miR-223-5p levels and EDSS score at 1 year after sample collection (r=0.41, p=0.032). Finally, miR-92a-5p levels were significantly higher in patients with EDSS score increase compared to stable patients (0.1 vs 0, p=0.02).
Conclusions: This study highlights the existing connections between the expression of miRs involved in regulatory mechanisms of the immune system and MS clinical course. In particular, serum levels of mir-128-3p seem to be related to disease activity and progression.

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EP1556

Biomarker discovery in tears of multiple sclerosis patients: a new vision in medicine?

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Introduction: Tears represent an exciting promising fluid for biomarkers discovery. Their easy way to collect, invasiveness, timeless and absence of side effects make them particularly attractive for clinical uses. Indeed, their complex molecular composition is highly regulated depending on several factors including ocular and systemic diseases.
Objectives: Here, we present quantitative proteomics analyses of human tears comparing the protein levels between multiple sclerosis (MuS) patients and healthy controls.
Aims: The aim of this study is to identify some potential biomarker candidates for multiple sclerosis.
Methods: Tears of MuS patients (N=6, 2 males, mean age (±SD): 39.2 years (± 10)) and healthy subjects (N=6, 2 males, 37.7 (± 11.2)) were collected with Schirmer's papers and proteomics quantification analyses were done. Samples were tagged using Tandem Masse Tags (TMTs) reagents then trypsin digestion and off-gel electrophoresis fractionation were performed. Analyses were done using high throughput mass spectrometers coupled to a liquid chromatography, and Proteome Discoverer software (version 2.2) was used to obtain protein identification and quantification (2 unique peptides, 1% FDR at protein and peptide levels, ratio < 0.67 or >1.5, p-value < 0.05). Pathway analysis was done using Reactome database.
Results: Globally, 832 proteins were quantified in human tears, with 105 proteins found as differentially expressed between MuS patients and controls. Pathway analyses highlighted among others the immune system, the transport of small molecules and the metabolism of proteins. Eight proteins were found significantly deregulated in the experiments, and further analyses and verification of several candidates are ongoing.
Conclusions: In these first steps, we were able to highlight in tears of MuS patients some interesting proteins related to the immune response and the survival of neurons. These preliminary results tend to enhance the interest of tears as one of the promising future diagnostic strategies.

Disclosure

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EP1557

Plasma neurofilaments correlate with disability in progressive multiple sclerosis patients

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Background: Cerebrospinal fluid and serum/plasma neurofilaments are markers of axonal damage in various diseases, including Multiple Sclerosis (MS). The dosage of blood NFL is currently being investigated, mostly in Relapsing-Remitting (RR) MS, as a marker of disease activity and of response to treatment, while data on the correlation between blood NFL and disability/disability progression in progressive MS patients is scarce.
Objective: In this retrospective study, we aimed to correlate plasma NFL (pNFL) dosages with disability, disease severity and disability progression in a group of patients with primary (PP) and secondary (SP) progressive MS patients (PP/SP).
Methods and Materials: NFL were dosed using SIMOA (Single Molecule Array, Quanterix, USA) on plasma samples which had been stored away during a previous study, of 91 untreated MS patients: 70 progressive (27 PP and 43 SP), 21 RRMS patients and 10 healthy controls (HC). Longitudinal pNFL dosages were available for nine PP/SP patients. PNFL levels were correlated with patients' clinical data.
Results: Median pNFL dosages were 12.8pg/ml (interquartile range -IQR:10-16) in PP/SP patients, 9.7pg/ml (8.3-11.2) in RR patients and 9.5pg/ml (7.3-11.9) in HC, with significant differences (post-hoc analysis of Kruskal Wallis test) of PP/SP versus RR patients (p=0.007). They correlated with EDSS (rho: 0.34, p=0.001) and MS Severity Score values (rho: 0.27, p=0.01), even after correction for age. In particular, after Bonferroni correction, they correlated with the pyramidal, sensory and ambulation EDSS Functional System scores.
There was no difference in pNFL levels between PP/SP patients with EDSS progression in the preceding year (14% of patients) or during a median follow-up of 27 months (IQR: 20-46) (41%).
In nine PP/SP patients, pNFL levels were tested at least twice, with a median interval between testing of 25 months (range: 12-39). PNFL values increased in all patients from a median of 10.8pg/ml (IQR: 9.8-13.9), to a median of 13.9 (IQR: 11.4-15.4), while EDSS either remained stable (nr=7/9) or increased (nr=2/9).
Conclusions: Plasma NFL levels showed correlation with patient disability and disease severity in PP/SP MS patients and increased over time in patients with repeated dosages. They were, however, not associated with prior or subsequent disability progression as measured by EDSS, which may have a too low sensitivity to change/disease progression in this context.

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Guicciardi C has nothing to disclose in relation to the study.
De Biasi S has nothing to disclose in relation to the study.
Pinti M has nothing to disclose in relation to the study.
Bedin R has nothing to disclose in relation to the study.
Camera V has nothing to disclose in relation to the study.
Vitetta F has nothing to disclose in relation to the study.
Nichelli P has nothing to disclose in relation to the study.
Cossarizza A has nothing to disclose in relation to the study.
Sola P has nothing to disclose in relation to the study.

EP1558

Collection of tear fluid from multiple sclerosis patients for the investigation of oligoclonal IgG bands

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Background/aim: Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. Intrathecal synthesis of immunoglobulin G (IgG), which is a major diagnostic hallmark of MS, can be demonstrated in about 95% of patients by the detection of oligoclonal IgG bands (OCB) in the cerebrospinal fluid (CSF). It has been suggested, that OCB can be found not only in the CSF, but also in the tear fluid of MS patients. However, data on pre-analytical standardization of tear fluid collection and analysis are not well established. Therefore, we aimed to develop a standardized collection method to subsequently allow the investigation of tear fluid samples from MS patients.
Methods: Tear fluid was collected using Schirmer test strips and plastic capillary tubes. The collection methods were established with the help of healthy controls (n=12) and compared regarding feasibility, safety and convenience. In a second step, samples were collected from patients (n=37), whose experiences were recorded on a questionnaire. OCB were analysed in tear fluid, CSF and serum samples from 22 MS patients by isoelectric focusing (IEF) followed by immunoblot.
Results: Both methods were tolerated well and allowed the collection of small volumes of tear fluid without any report of adverse events. The detection method was adjusted to account for the small volume as well as the high protein and low IgG concentration of tear fluid. In first IEF experiments one or more IgG bands with differing pattern when compared to CSF and serum OCB were detected in the tear fluid of 14 out of 20 analysable MS patient samples.

Discussion: The tested sampling methods allowed the collection and subsequent investigation of tear fluid. Despite particular properties of tear fluid, which required adjustments in the analysis method, first results indicate that IgG bands can indeed be detected in the tear fluid of MS patients. The detection of inflammatory signs in tear fluid of MS patients implies interesting possibilities for research and diagnostics. Next steps include the refinement of analytical methods and further sample collection from patients with MS as well as other inflammatory and non-inflammatory neurological diseases.

Disclosure

F.B. has no conflict of interest to declare.
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EP1559
Elevation of Chi3l1 in acute disseminated encephalomyelitis: implications in pathogenesis

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Objective: Chi3l1 is a biomarker related to chronic inflammation. It has been described in cancer and chronic inflammation outside the central nervous system (CNS) and it has been shown to be a prognostic biomarker for CIS conversion to CDMS and disease progression. However, scarce information exists regarding its concentration in acute disseminated encephalomyelitis (ADEM).
Aims: Our purpose was to describe Chi3l1 changes in a series of cases of ADEM and compare its concentration with a cross-sectional cohort of Multiple Sclerosis (MS) patients (Valencia cohort).
Methods: Chi3l1 levels were measured in CSF samples in patients with ADEM (n=4) with ELISA assay. CSF samples were obtained within 15 days from disease onset in three patients, and four months after recovery in one. Clinical data were recorded during admision and in the follow up. The obtained concentrations were compared to median values in MS patients (n=156) and historical controls (HC) (n=20) detected with the same methodology. Variability intra-assay CV% was 6,49 and inter-assay 5,18.
Results: Chi3l1 levels were very elevated in the acute episode in the three reported cases (730,00 ng/ml, 1106,00 ng/ml, and 601,90 ng/ml) with a four-fold increase respect to median values in MS patients (134.7 ng/ml, RRMS 115,35, PMS 171,45 ng/ml) including patients with active inflammation (clinical attack or gadolinium-enhancing lesions) in which median values were not significantly elevated (133.15 ng/ml). In the fourth case, after complete clinical recovery, Chi3l1 returned to HC levels. A biopsy performed in one patient in the acute phase showed a dense inflammatory infiltrate composed mainly by TMEM119+/YKL-40+ microglial cells and less prominent CD4+ lymphocytic component.
Conclusion: Our results indicate that acute inflammation occurring in ADEM patients might be related to innate immune response, expressed as Chi3l1 secretion, and that there is a different profile in the inflammation that takes place in clinical attacks in MS, with possible pathogenic implications. Summed to other clinical variables, Chi3l1 levels could be useful for differential diagnosis at first symptoms.

Disclosure

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EP1560
Longitudinal expression of gluco- and mineralocorticoid receptors and their targets in multiple sclerosis

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Background: The hypothalamo-pituitary-adrenal axis (HPA axis) is activated in multiple sclerosis (MS) patients (Then Bergh *et al.* 1999; Gold *et al.* 2005), apparently related to disease course and progression. Our group showed in a cross-sectional study that gluco-(GR) and mineralocorticoid receptors (MR) are significantly downregulated in MS patients compared to healthy subjects (Bechmann, L *et al.* 2014). Downstream target genes of the GR were differentially up- or downregulated according to disease severity. We meanwhile identified *bona-fide* MR target genes in PBMC (Kuestermann *et al*., in preparation).
Objective: To investigate the longitudinal development of GR, MR and their target genes´ expression in MS and potential effects of disease-modifying treatment.
Methods: Using qPCR technique with total RNA isolated from lysed whole blood, we first compared the mRNA expression of GR, MR and selected downstream targets in MS patients during

a relapse (before the initiation of steroid treatment) with that in patients in remission. Second, we analyzed the expression of these genes in blood samples taken over a period of up to five years, normalized to a baseline value measured before the initiation of the specific treatment. These patients are characterized demographically, clinically and according to disease modifying therapy.

Results: Expression of GR, MR and their target genes´ mRNAs did not differ between MS patients during relapse (n=11) and those of matched MS patients in remission (n=11). This finding allows us to analyze the longitudinal data without excluding patient data collected close to a relapse. Preliminary longitudinal analysis based on the first 100 patients with varying follow-up periods showed a rather abrupt, significant and lasting downregulation of the MR in patients treated with fingolimod (n=39; up to 30 +/-2 months; $p < 0.0001$).

Conclusions: MS relapse does not significantly influence the expression of GR, MR and their target genes. DMT does affect the expression of some of these genes, possibly offering additional explanations of their modes of action, and/or additional options for treatment surveillance.

Disclosure

CG, FK, JO and AU have nothing to disclose. MS has received financial support, through her institution, to attend scientific meetings or for investigator initiated studies from Biogen, Fresenius, Merck Serono, Novartis, Sanofi Genzyme and Teva. SH has received financial support, through her institution, to attend scientific meetings from Bayer and Merck. FTB has received personal compensation for speaking and attending advisory boards from Actelion, Bayer, Biogen, Genzyme, Merck, Novartis, Teva and Roche; financial support, through his institution, to attend scientific meetings or for investigator initiated studies from Actelion, Bayer, Biogen, Genzyme, Merck, Novartis and Teva.

EP1561

Sonographic optic nerve sheath diameter versus optic coherence tomography as a biomarker for disability in patients with multiple sclerosis

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Background: The development of new biomarkers for multiple sclerosis is crucial to improve our ability to predict disease progression and disability. The aim of this study was to study the potential role of optic nerve diameter measurement using ultrasound as a marker of axonal loss, to compare it to optical coherence tomography as a standard biomarker and to elaborate its role in early detection of disability in patients with relapsing remitting multiple sclerosis (RRMS).

Methods: Forty nine patients with relapsing remitting multiple sclerosis (RRMS) with or without history of unilateral optic neuritis were studied for optic nerve sheath diameter (ONSD) using transorbital sonography; retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness measurement using optical coherence tomography (OCT). Age and sex matched healthy controls were recruited as a control group.

Results: RNFL and GCC were significantly thinner in patients group whether in affected eyes ($p < 0.001$) or unaffected eyes ($p < 0.001$). There was no significant statistical difference neither in the optic nerve diameter nor in the optic nerve sheath diameter (ONSD) between affected ($p = 0.319$, 0.760) respectively) and unaffected eyes ($p = 0.396$, 0.335 respectively) of both groups. However, patients with EDSS > 2 had significantly lower ONSD, RNFL thickness and GCC ($p = 0.035$, $p = 0.039$, $p < 0.001$ respectively) as compared to patients with EDSS ≤ 2.

Conclusion: Transorbital sonographic measurement of optic nerve sheath diameter (ONSD) is a potentially valuable marker for early detection of disability in patients with relapsing remitting multiple sclerosis.

Key words: optic nerve sheath diameter, multiple sclerosis, optic coherence tomography

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EP1562

Searching for early CSF biomarkers of primary progressive multiple sclerosis

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Introduction: Up to now diagnosis of primary progressive multiple sclerosis (PPMS) is based on clinical assessment, imaging and cerebrospinal fluid (CSF) analysis with regard to evidence of oligoclonal bands and/or elevated IgG index. However, specific biomarkers that can help to early stratify PPMS from relapsing remitting multiple sclerosis (RRMS) patients and give insights into its pathogenesis are still unknown.

Aims: To identify a specific CSF inflammatory profile associated to PPMS since early phases of disease.

Methods: An extensive analysis of the presence and levels of 69 inflammatory mediators (cytokines and chemokines) and NF-L has been performed on the CSF obtained at the diagnosis from 14 patients (mean age 45.9±9.4 y) with PPMS, 45 (32.4±9.6 y) with RRMS, 7 (37.7±12.1 y) with Clinically Isolated Syndrome (CIS) and 12 (51.7±12.1 y) with non-inflammatory neurological disorders. Data about white and grey matter (WM, GM) lesion volume and cortical lesion (CL) numbers were collected by 3T-MRI.

Results: No significant differences between PPMS and RRMS patients were noticed in IgG index, oligoclonal bands, CSF

lymphocyte count, NF-L levels, CL numbers, WM and GM lesion volume. PPMS had higher mean EDSS respect to RRMS group (3.0 vs 1.7, p< 0.01). Interestingly, CSF of PPMS patients was characterized by a pattern of inflammatory molecules, including CCL11, CCL26, CX3CL1, CXCL2, CCL2, CCL7, CCL15, CCL23, IL-16, significantly overexpressed when compared to RRMS and control group (p< 0.05); among them, CCL2 and CCL15 were found significantly increased also when compared to CIS group (p < 0.05). Higher levels of CXCL13, IL28A and Pentraxin were detected in RRMS compared to PPMS, control group and, except IL28A, CIS patients (p< 0.01). Kegg pathway analysis confirmed that most of molecules characterizing PPMS CSF profile are specifically involved in immune reactions observed in other chronic inflammatory diseases.

Conclusions: At the diagnosis CSF of PPMS patients showed a specific pattern, involved in chronic inflammation: while CXCL13, Pentraxin and IL28A may represent surrogate markers of a relapsing disease, CCL2 and CCL15 should be better assessed as potential PPMS biomarkers. In addition to clinical and instrumental analysis, a detailed CSF profiling obtained at the diagnosis could help to differentiate progressive forms of MS, giving new insights into its pathogenesis and providing useful tools in clinical practice.

Disclosure

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EP1563

The expression in PBMCs of a subset of microRNA is able to differentiate MS patients with lipid-specific oligoclonal IgM bands

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Introduction: The clinical course of multiple sclerosis is heterogeneous and the presence of anti-myelin lipid specific oligoclonal IgM bands (LS-OCMBs) have been defined as an accurate predictor of an aggressive evolution. The detection of this biomarker is performed in cerebrospinal fluid (CSF), a quite invasive liquid biopsy.
MicroRNAs are single-stranded small non-coding RNAs that regulate gene expression and have been reported to be differentially expressed in MS patients both in blood and CSF, suggesting a role in the disease.

Objectives: The aim of the study was to analyze miRNA expression profile in PBMC from MS patients with positive and negative LS-OCMBs in order to evaluate whether a subset of miRNA could reflect the status of LS-OCMBs in a more accessible liquid biopsy.
Methods: Patients were recruited in the Hospital Ramon y Cajal after giving informed consent. Blood samples were obtained and peripheral blood mononuclear cells (PBMCs) were isolated following a standard Ficol gradient separation protocol and frozen.. CSF was obtained to analyze the status of LS-OCMBs as previously described.
RNA was extracted using miRNeasy mini kit and quantity and quality was evaluated using Nanodrop ND-1000 spectrophotometer.
Total RNA (200ng) was labeled using the FlashTag Biotin labelling kit and hybridized to the GeneChip miRNA array 4.0 (Affymetrix) following the manufacturer's protocol.
Microarray data analysis was performed using Transcriptome Analysis Console.
Candidate miRNA were validated by quantitative PCR using TaqMan Advanced microRNA assays.
Results: In microarray exploratory analysis 11 MS patients were included (5 with positive LS-OCMB and 6 without LS-OCMB). 42% of the probes were detected in at least one sample. Twenty probesets showed at least two-fold change (7 upregulated and 13 downregulated) in patients with LS-OCMBs (p< 0.05). Interestingly, this subset of miRNA was able to distinguish patients with LS-OCMBs from those without LS-OCMBs according to a hierarchical clustering analysis.
Validation of the more promising candidates will be performed in a bigger cohort.
Conclusion: The expression pattern in PBMCs of a subset of 20 miRNAs is able to distinguish patients with LS-OCMBs. Thus, it is worth to follow this line of research aiming at establishing a new biomarker of a more aggressive disease course in a more accessible sample.

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EP1564

Comparable sNFL levels in a NEDA-3 cohort of RRMS patients irrespective of different immunomodulatory therapies

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Introduction: Serum neurofilament light chain (sNfL) has been proposed as a promising biomarker for treatment response in relapsing-remitting multiple sclerosis (RRMS) patients. We previously reported in a small cohort i) that sNfL was strongly associated with gadolinium-enhancing lesions and T2 lesion volume in patients with very early MS, ii) that higher baseline sNfL levels at diagnosis predicted brain atrophy levels after 24 months, and iii) that sNfL was reduced under baseline therapy (Siller et al., Mult Scler, 2018). However, it is currently unclear whether each individual patient's levels should be compared longitudinally or whether an absolute threshold can be defined for sufficient treatment control.
Objectives: To evaluate whether sNfL levels differ in relapsing-remitting patients with clinical and radiological response to treatment under lower and higher efficacy drugs.
Methods: From a cohort of 927 RRMS patients, we selected patients with no evidence of disease activity (NEDA-3) at time of blood withdrawal under different disease-modifying therapies (DMTs; interferons, glatiramer acetate, dimethyl fumarate, fingolimod or natalizumab (n = 50-80 patients per DMT group)). sNfL levels were determined using single molecule array technology.
Results: sNfL levels do not vary significantly between RRMS patients fulfilling NEDA-3 criteria receiving interferon (median 3,26 pg/ml [1,07 - 8,84]), glatiramer acetate (median 3,52 pg/ml [0,78 - 12,77]), dimethyl fumarate (median 2,59 pg/ml [0,46 - 14,6]), fingolimod (median 3,4 pg/ml [1,45 - 10]) or natalizumab treatment (median 3,24 pg/ml [1,08 - 7,57]). Patients were divided into quartiles according to their sNfL levels; data will be presented regarding whether high sNfL levels despite being clinically and radiologically stable indicate a risk for future disease exacerbation.
Conclusions: In a cohort of RRMS patients fulfilling NEDA-3 criteria, patients exhibit the same sNfL levels regardless of whether they receive baseline or escalation DMTs.

Disclosure

JP has nothing to disclose
FS has nothing to disclose
FL has nothing to disclose
FZ has nothing to disclose
SB has nothing to disclose

EP1565

Characterizing cytokine changes before and after ocrelizumab infusions and their contribution to infusion related reactions

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Objective: To characterize infusion related reactions (IRRs) in patients with relapsing forms of multiple sclerosis (MS) before and after their first ocrelizumab (OCR) dose following the discontinuation of rituximab (RTX) by comparing associations with B-cell reconstitution and changes in cytokine profiles.
Background: RTX is an anti-CD20 medication that is often used off-label for the treatment of MS. Many of these patients switched to OCR with approval of this new anti-CD20 medication in March 2017. IRRs are common with RTX and have been associated with B-cell reconstitution. Here we examine some of the factors associated with IRRs in patients switching from RTX to OCR.
Methods: Patients at the Rocky Mountain MS Center at the University of Colorado with relapsing forms of MS (n=200) with ≥2 RTX doses were split evenly into 2 cohorts: 1) a comparator arm that continued 2 standard of care doses of RTX, 2) a switch arm (SWT) that transitioned to OCR and received doses on Days 1, 15, and Week 24. For the first 60 SWT patients, plasma samples collected before and after Day 1 and Day 15 infusions, were analyzed using a V-PLEX Human Cytokine 44-Plex kit, using a mesoscale SECTOR Imager 2400. B-cell reconstitution was assessed at OCR Day 1. IRRs were evaluated using the National Cancer Institute's Common Terminology for Adverse Events Scale. SAS was used to perform paired sample T-tests.
Results: Of the first 60 SWT patients, 39 (65%) were female, the mean age was 44.47 (+/-11.4 SD), had MS for 11.49 years (+/-7.8 SD) and had a median EDSS of 3 (2.0-4.3 IQR). They received OCR 235.5 (+/-62.6 SD) days after their last RTX infusion and had received 4.2 courses of RTX. Of these patients, 7 had an IRR on Day 1, of which 1 was grade 1 and 6 were grade 2. (28/58) patients had begun to reconstitute their peripheral B-cells. Seventeen of the 45 cytokines examined significantly changed pre and post OCR infusion on Day 1. Cytokine changes were similar between Day 1 and Day 15, with smaller changes seen at Day 15. Larger changes were observed at Day 1 in patients with B-cell reconstitution. In patients with IRRs, IL-16 (76.6 pg/mL, p=0.019) and IL-27 (359.7 pg/mL, p=0.008) increased significantly, while Eotaxin (-48.6 pg/mL, p=0.032) decreased.
Conclusions: Cytokines changed significantly following OCR infusions. Changes were generally smaller in B-cell depleted patients and on Day 15 infusions. Eotaxin, IL-16, and IL-27 differed in patients who experienced IRRs.

Disclosure

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EP1566
CSF biomarkers of neurodegeration in early multiple sclerosis course

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Introduction: Neurodegeneration (ND) occurs early in multiple sclerosis (MS), and caused clinical deterioration and disability. Biomarkers reflecting this phenomena, such as neurofilament light chain (NF-L), tau and β-amyloid (Aβ), could be measured easily in the cerebrospinal fluid (CSF).
Aim: To evaluate if CSF biomarkers of neurodegeneration predict early MS disability.
Methods: CSF NF-L, Aβ and tau levels were determined with commercial enzyme-linked immunosorbent assay in 45 newly-diagnosed MS patients (30 females). Baseline disease-courses were: three radiological (RIS) and 15 clinical isolated syndrome (CIS), 24 relapsing-remitting (RR) and 3 primary of secondary progressive (PR)-MS. Our disability outcome was the MS severity score (MSSS) at the last follow up (minimum 1 year after disease onset). We estimated differences between CSF biomarkers in baseline MS courses and disability with ANOVA.
Results: First, only CSF NF-L differed significantly among MS courses (p=0.004). In fact RIS showed the lowest levels (CSF NF-L mean 206 ng/ml ± standard deviation 220) if compared to CIS (1209±509), RR (1616±741), and PR-MS (1714±27). On contrast, none of the CSF biomarkers was related to MSSS at last follow up. Of note, we excluded a correlation among tau or Aβ with NF-L in the CSF.
Conclusions:
• NF-L are the unique biomarker of neurodegeneration related to MS forms. Their levels increased progressively with MS-course severity reflecting the higher axonal damage in PR-MS.
• CSF NF-L, Aβ and tau failed to predict early MS disability: short-term outcome could not reflect the natural disease history.

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Cantello R : nothing to disclose,
Comi C: nothing to disclose

EP1567
Serum neurofilament light chain in MS: association with clinical and MRI measures

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Recent studies have focused on neurofilament light chain (NfL) as a diagnostic and prognostic biomarker in multiple sclerosis (MS). NfL levels in cerebrospinal fluid (CSF) and in serum show a strong correlation, enabling the use of blood samples, which can be collected promptly in a non-invasive manner. In MS, CSF and serum NfL have been associated with neuronal damage, disability and magnetic resonance imaging (MRI) characteristics, but replication in larger, independent cohorts is needed.
Our aim was to investigate the association of serum NfL, a biomarker of axonal damage, with demographic, clinical and MTR parameters.
Our study population consisted of 116 MS patients, for whom serum samples at the time of diagnostic lumbar puncture (LP) as well as clinical data were available. For a subset of 58 patients, volumetric and magnetization transfer ratio (MTR) MRI parameters, reflecting neurodegeneration and demyelination, respectively, were obtained throughout the disease process (median years after diagnostic LP (range): 4 (0-10)). NfL levels in serum were measured using a previously described electrochemiluminescence (ECL) protocol.
Serum NfL levels in 116 MS patients did not correlate with gender, age or clinical parameters such as age at onset, disease course, and Multiple Sclerosis Severity Score (MSSS) ($p > 0.05$). Serum NfL levels were negatively correlated with median ($\beta_0 = -0.35$, $p=0.02$) and peak height ($\beta_0 = -0.40$, $p=0.01$) MTR in normal appearing gray matter (NAGM), and with white matter volume ($\beta_0 = -0.40$, $p=0.006$). There was also a positive correlation between serum NfL levels and lesion volume ($\beta_0 = 0.39$, $p=0.02$). The observed associations between serum NfL levels and MRI measures may support feasibility and usefulness of serum NfL in MS clinical management. Longitudinal studies will be required to understand whether they could be useful to measure disease severity and progression.

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Other authors report no conflict of interest.

EP1568
Hemostasis biomarkers in multiple sclerosis

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Objective: To investigate the plasma levels of hemostasis components in multiple sclerosis (MS) and their association with clinical and MRI outcomes.
Methods: We studied 138 MS patients (85 with relapsing-remitting, RR-MS and 53 with progressive, P-MS) with mean age of 54 years; 72.5% female; median EDSS 3.5; mean disease duration 21 years) and 42 age- and sex-matched healthy individuals (HI). All subjects were examined with 3T MRI and clinical examinations. Plasma levels of hemostasis factors (procoagulant, factor XII, FXII) and inhibitors (tissue factor pathway inhibitor (TFPI), thrombomodulin (TM), heparin cofactor II (HCII), disintegrin-like and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13), and plasminogen activator inhibitor 1 (PAI-1) were evaluated by magnetic Luminex assays and ELISA. Associations between hemostasis plasma levels and clinical and MRI outcomes were assessed.
Results: Lower ADAMTS13 levels were found in MS patients compared to HI (p=0.008), and in MS patients presenting with cerebral microbleeds compared to those without (p=0.034). Higher PAI-1 levels were found in MS patients compared to HI (p=0.02). TFPI levels were higher in the P-MS subgroup compared to RR-MS patients (p=0.011) and compared to HI (p=0.002). No significant associations between hemostasis plasma levels and clinical or MRI outcomes were found.
Conclusions: Decreased ADAMTS13, particularly in MS patients with cerebral microbleeds, increased PAI-1 and TFPI levels were observed in MS patients, which deserves further investigation. No relationship between hemostasis plasma levels and measures of disease severity was detected. This article is protected by copyright. All rights reserved.

Disclosure

As I′m a resident of masters degree my monthly income is about 100 $. It would be very good if you will give me travel grant.

EP1569
Blood-brain barrier-activation induced by immunoglobulin G in multiple sclerosis

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Background: Breakdown of the blood-brain barrier (BBB) is a key pathological feature of multiple sclerosis (MS). We previously reported the effect of sera from MS patients on the BBB dysfunction. We also published the association between blood-brain barrier (BBB) dysfunction and glucose-regulated protein 78 (GRP 78) autoantibodies in neuromyelitis optica (NMO).
Objective: The purpose of this study is to clarify the effect of immunoglobulin G (IgG) from MS patients on the BBB-endothelial cell activation. We observed the association among the clinical phenotype/disease activity, positivity of GRP78 antibodies and BBB disruption in MS.
Methods: We purified serum IgG from 38 sera with MS patients [9 MS in the acute phase (acute MS), 14 MS in the secondary/primary progressive phase (progressive MS), 15 MS in stable stage (stable MS)]. IgGs from 10 healthy volunteers and 11 disease controls were used as controls. IgG was exposed to the human brain microvascular endothelial cells (TY10) and the amount of nuclear NF-κB p65 positive cells as a marker of endothelial cell activation was analyzed using a high-content imaging system. Presence of GRP78 antibodies from patient IgGs was detected by western blots. Positivity of CSF oligoclonal IgG band (OCB) from MS patients was also evaluated.
Results: IgG in progressive/acute MS group significantly induced the nuclear translocation of NF-κB p65 compared to those from stable MS group and healthy/disease control group. There is no significant difference in the positive rate of GRP78 antibodies among progressive MS, acute MS, stable MS, disease controls and healthy controls. No association was observed in the number of nuclear NF-κB p65 positive cells induced by IgG between positive and negative for OCB in MS patients.
Conclusion: Endothelial cell activation induced by IgG incubation was observed in not only NMO but also MS patients and associated with acute/progressive MS stage. The positivity of GRP78 antibodies is not associated with BBB disruption in MS, unlike NMO, suggesting that unknown molecules other than GRP78 antibodies that contribute to BBB breakdown may be present in MS sera.

Disclosure

nothing to disclose

EP1570
gMS-classifier1 does not predict disability progression in multiple sclerosis

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Background: Anti-alpha-glucose IgM antibodies (gMS-Classifier1) have been proposed as biomarkers in multiple sclerosis (MS). There are hints of gMS-Classifier1 as predictors of expanded disability status scale (EDSS) progression in relapsing remitting multiple sclerosis.
Objective: The aim of this study was to test the ability of the gMS-Classifier1 to predict disability progression measured by changes in the EDSS score in MS patients with long-term follow-up.
Methods: Four Multiple Sclerosis centers collected blood samples and clinical data of patients with a final diagnosis of clinically isolated syndrome (CIS), relapsing remitting MS (RRMS) or secondary progressive MS (SPMS) between 1993 and 2007. Disability progression was defined as sustained progression of at least 1.0 EDSS point over the baseline EDSS. Serum samples (n=358) were analysed for different anti-glycan antibodies. If one of the four antibodies was above the cut off value, patients were

considered positive for the gMS-Classifier1. We explored the association of gMS-Classifier1 status with EDSS progression.
Results: gMS-Classifier1 status at baseline did not predict EDSS progression during follow-up.
Conclusions: The gMS-Classifier1 may not have any predictive value for disability progression in MS.

Disclosure

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Peter N. Riskind reports no conflicts of interest
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Charlotte Teunissen served on the advisory board of Fujirebio and Roche, received research consumables from Euroimmun, IBL, Fujirebio, Invitrogen, and Meso Scale Discovery, and performed contract research for IBL, Shire, Boehringer, Roche, and Probiodrug
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EP1571

Characterization of serum neurofilament, a biomarker for axonal damage, in the SYNERGY study as a complement to opicinumab zreatment effect in MS

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Introduction: Serum neurofilament (Nf) is a marker of axonal damage that correlates with MS disease activity and is modulated by anti-inflammatory MS therapeutics; however, the application of Nf in emerging remyelination therapeutics is not established. Opicinumab blocks LINGO-1, a negative regulator of myelination and axonal regeneration, and recent results from the SYNERGY study (NCT01864148) revealed an increased percentage of clinical improvement responders in the 10 mg/kg and 30 mg/kg cohorts. Post-hoc analyses further identified a subgroup that showed a greater and sustained clinical effect.
Objectives: To evaluate serum Nf light and heavy chain (NfL and NfH) levels in the 10mg/kg and placebo cohorts from SYNERGY to determine their potential utility as biomarkers of remyelination and patient stratification for opicinumab treatment effect.
Methods: High-sensitivity technologies were used to measure serum NfL (Simoa) and NfH (Ella) at baseline, week 36 and week 72 of the 10 mg/kg opicinumab and placebo cohorts. The following analyses were performed: (i) association of Nf with demographics, baseline and post-treatment imaging and clinical outcomes, including progression and improvement response; (ii) characterization of treatment-related effects on Nf and (iii) evaluation of Nf levels to stratify treatment responders from non-responders.
Results: Exploratory analyses indicated that baseline NfL and NfH levels are weakly correlated with age, baseline imaging parameters and selected clinical measures and seem to be influenced by prior MS treatment as levels are modestly higher in the treatment naïve individuals. NfL appears to be modestly associated with disease progression and improvement response, as NfL is slightly higher in progressors and non-responders at all time points. Furthermore, a trend of seemingly greater treatment-related NfL decline was observed in non-progressors and improvement responders. Interestingly, baseline NfH is not associated with clinical outcome and no treatment-related change in NfH levels was observed
Conclusions: Preliminary findings demonstrated that serum NfL, but not NfH, levels were associated with improvement responders and non-progressors and warrants further investigation of serum NfL as a potential biomarker of interest to assess remyelination. It will be critical to further understand the synergistic and relative impact of concomitant immunomodulatory agents and novel remyelination therapeutics on NfL.

Disclosure

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EP1572

Multicenter sensory and motor evoked potentials: definition of improvement beyond measurement variability in single subjects

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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 suggest cut-offs to define improvement as a significant reduction of latency in single subjects.

Methods: 21 patients with MS (mean age: 47.3 years, median EDSS: 3.0, 74% relapsing MS, 26% progressive MS) were evaluated at two time points (tp) within a 30 day window with median and tibial SEP and upper (UL) and lower limb (LL) MEP in three centers[1-3]. Five neurophysiologists independently marked all curves using custom server-based software (EPMark). N20, P40, mean (mn) and shortest (sh) cortico-muscular-latencies (CxM) and a modified quantitative EP-score (mqEPS=sum of z-transformed results from each test/number of tests; unit= mean standard deviation) were analyzed.

Using mixed effects linear models (outcome: tp 1 and 2 combined) total variance and its components were estimated. The standard error related to intra-subject longitudinal variability (SE_{long}; assuming 2 central readers) was used to determine the measurement variability *D* with a margin *z* above which a difference is not attributable to *D* in 95% of cases, using: $D=SE_{long}*z_{95}$, with $z_{95}=1.645$ (95^{th} percentile of standard normal distribution, one-sided).

Results: Proportions of patients with none, 1-2, 3-4 or >4 pathological tests were 41%, 23%, 27% and 9%, respectively. For MEP, median and tibial SEP, rater variability was < 7%, 10% and 16% of total variance, respectively. Variability of SEP is partly explained by ambiguity in peak definition as tp2 rating was done blinded to tp1 results. In MEP, *D* ranged from 2.1 to 3.0ms (MEP-UL shCxM: D=2.4ms, mnCxM: D=2.1ms; MEP-LL shCxM: D=3.0ms, mnCxM: D=2.2ms), in SEP from 1.0 to 4.9ms (N20: D=1.0ms, P40: D=4.9ms), in mqEPS: D=0.94. Whether improvement (I) is to be defined as any difference beyond *D* (I>D) or as (I>C+D) with C denoting a minimal required additional change for security depends on the study setting.

Conclusion: Our results allow the definition of improvement in single EP tests (one limb, one modality) and may be used to define responders to remyelinating drugs, for example as subjects with improvement in at least one test. Using the mqEPS avoids bias in case of improvement in one test but deterioration in the others.

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EP1573
IgM MOG antibodies associated with cerebral lymphoma and CLIPPERS syndrome

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Introduction: The pathophysiological and clinical role of antibodies to myelin-oligodendrocyte-glycoprotein (MOG-abs) is still not fully understood. In this context we report the case of a 61-year-old patient presenting with neurological symptoms and positive serum IgM MOG-abs.

Case report: A 61-year-old female patient developed episodes of vertigo, which worsened significantly along with double vision, lack of coordination and weight loss. Primary assessment included MRI and CSF analysis. MRI showed unspecific white matter lesions with focus in the pons and cerebellar peduncles without gadolinium enhancement. CSF analysis revealed a mild lymphoplasmacellular pleocytosis without detection of any tumour cells. As an inflammatory demyelinating disorder appeared possible a screening for MOG-abs complemented the diagnostic approach. Serum MOG-ab were detected with an initial titer of 1:160, however, this MOG-ab-response was mainly of the IgM isotype (1:2560), most likely also detected by the IgG(H+L) secondary antibody used, whereas no IgG(Fc) specific response was detected. After alternating periods of improvement due to high-dose methylprednisolone and relapses with brainstem symptoms, the therapeutic regime was changed to continuous, oral low-dose corticosteroids. As MRI was repeated a new, strongly gadolinium enhancing lesion in the basal ganglia, highly suspicious for CNS lymphoma was revealed, which was verified by biopsy and

histopathology. The following therapy with rituximab, azathioprine and methotrexate was unfortunately not successful, thus palliative treatment was decided.
Conclusion: The present case challenged by its differential diagnoses, which included inflammatory, like CLIPPERS-syndrome, and neoplastic disorders. The exclusive IgM-isotype MOG-ab-response might be a false positive result, which fits well to the resent observation, that secondary antibodies to human IgG can also detect IgM-abs. While the absence of demyelination in the biopsy argues against a pathophysiological role, the clinical relevance of MOG-ab response is unclear. Finally, we have analysed 10 additional patients with CNS lymphoma for MOG-abs, but all of them were negative for IgG MOG-abs, whereas two were positive for IgM MOG-abs.
This case report demonstrates the possible pitfalls of MOG-ab testing and indicates that borderline positive MOG-ab results should be confirmed by a second immunoassay using either human IgG(Fc) or IgG1 specific secondary antibodies.

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EP1575

Long-term prognostic value of anti myelin antibodies in multiple sclerosis

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Background: Although evidence in clinically isolated syndrome (CIS) suggests that the presence of anti-myelin Abs can predict the clinical conversion to multiple sclerosis (MS), the relevance of anti-myelin antibodies (Abs) in MS patients remains largely unexplored.
Objective: To test the prognostic value of anti-myelin Abs in patients with MS in longer-term.

Methods: Sera were collected after the first clinical episode suggestive of MS and tested by Western blotting for the presence of anti-anti-myelin oligodendrocyte glycoprotein(MOG) and anti-myelin basic protein(MBP) IgM Ab. Patients were classified accordingly as anti-MOG+ve /anti-MOG-ve and anti-MBP+ve / anti-MBP-ve. We collected clinical data and considered as clinical endpoints: a) the number of patients with confirmed EDSS worsening of at least 1 point; b) the number of patients reaching EDSS=4.0. Possible risk factors for the reaching EDSS=4.0 were estimated using forward stepwise logistic regression and considering in the model the presence of MOG Abs, MBP Abs, age, sex, baseline EDSS, the involvement of ≥1 functional systems and the recovery after CIS.

Results: Out of 34 patients [18 (52.9%) women, mean age 30.7±8.0] 14 (41%)were anti-MOG+ve and 16 (47%) anti-MBP+ve at baseline. The mean follow-up (FU) was 17.9±2.9 years.

At the end of the FU, only 3 patients did not present a clinical relapse. One patient died during the observation period as consequence of serious infection.Thirty patients (88.2%) underwent MS specific treatment: 18 patients started interferon-beta, 7 glatiramer acetate, 2 dimethyl fumarate, 2 natalizumab and 1 fingolimod. Twenty-two patients (65%) presented an EDSS worsening: median EDSS baseline was 1.0 [0-1.5] median EDSS at FU was 2.5[1.5-5.875] ($p< 0.001$).

At the end of FU, anti-MBP+ve patients presented higher EDSS score and lower number of fully ambulatory patients compared to anti-MBP-ve (mean EDSS increase 3.4±2.4 *vs.*1.4±2.0 p=0.02, and 7 (44%) vs 14 (75%) p=0.04 respectively). No differences were found in patients anti-MOG+ve compared to patients anti-MOG-ve. Patients anti-MBP+ve showed an increased risk of reaching the EDSS=4.0 (OR 6, 95%CI 1.2-30, p=0.03).

Conclusion: We suggest that the presence of MBP IgM Abs after a first clinical episode increases long-term risk of disability and may represent a negative prognostic factor for disease course.

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EP1576

Quality controls in biobank samples: effects of pre-analytical factors on blood samples used in gene expression studies

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Background: Biobanks are acquiring a crucial role in research activities. Accurate studies to evaluate the quality of samples collected and exchanged are essential. Gene expression profiling in peripheral blood mononuclear cells (PBMC) is a widely used tool in clinical diagnostics and health research: therefore, the identification of processes influencing RNA stability is mandatory. Pre-analytical phase represents a crucial step for the whole testing process.

Goals: This study was designed to evaluate the influence of pre-analytical variables, time and temperature, on blood samples used in gene expression studies. Our study was focused on samples collected in EDTA tubes. TEMPUS tubes were also tested, representing the gold standard for RNA stabilization. Endpoints to characterize RNA stability were RNA yield and purity, and gene expression levels.

Methods: Blood specimens collected in EDTA tubes (n=10 subjects) were processed for PBMCs isolation immediately after blood drawn (T0) and following 2, 4, 6 hours and ON incubation either at RT and 4°C. Blood samples collected in Tempus Tubes (n=5 subjects) were processed at T0 and following 5 days incubation, at RT and 4°C.

Resultant RNA yield and quality were determined. Gene expression analysis was performed by Real Time PCR on 8 candidate genes (CD14, IL10, TNF, TNFAIP3, NR4A2, CD20, CD19, MxA) and 4 housekeeping (HK) genes (GAPDH, HPRT1, B2M, CASC3).

Results: 1)RNA from Tempus Tubes resulted stable across the experimental conditions. 2)RNA yield and purity from EDTA tubes were slightly reduced after ON incubation. 2)RNA expression was affected according to the HK-gene and to the specific target gene: B2M and CASC3 resulted the better HK-genes; CD19, CD20, MxA were the more stable genes, as a higher instability was observed for TNFAIP3 and NR4A2. This effect was stronger after 6 hours of ex-vivo incubation. 4)Inter-individual variation was also observed.

Conclusions: This study showed the importance of evaluating effects of pre-analytical processes in gene expression studies. RNA levels from EDTA tubes resulted influenced in a gene-, housekeeping-, and subject- related manner. When generic blood collection device are used, time-course studies are mandatory to evaluate the stability of genes of interest, and the better HK-gene. Our results confirmed that Tempus Tubes assure RNA stabilization, strongly suggesting to use this tubes or analogue special devices for gene expression studies, and to biobank samples.

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EP1577

Differential effects of dimethyl fumarate on peripheral blood mononuclear cells of relapsing-remitting multiple sclerosis patients and prognostic implications

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Background: Dimethyl fumarate (DMF) is a fumaric acid ester approved for the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Several descriptive studies have shown that DMF affects adaptive immunity by shifting the balance between an inflammatory to a tolerogenic profile in Peripheral Blood Mononuclear Cells (PBMCs). However, little is known about DMF effects on innate immunity
Objective: To improve our understanding of DMF-induced changes in monocyte and lymphocyte subpopulations and to establish a possible association with response to treatment that could predict No Evidence of Disease Activity (NEDA) status at 2 years.
Methods: PBMCs from 10 healthy controls and 22 RRMS patients were analysed by flow cytometry at baseline and after 12 months of DMF treatment. Specific antibodies were used to identify different subsets of monocytes and lymphocytes. Clinical outcomes NEDA3 and NEDA4 were measured at 1 and 2 years of follow-up and patients were divided into two groups based on their NEDA status. The non-parametric Mann-Whitney test was used to compare clinical and cytometry data before and after 12 months of treatment as well as the differences between the two groups. The Bonferroni's correction for multiple comparisons was used considering as significant p-value < 0.0005. Correlations between cell populations and response to treatment were established using a negative binomial regression model.
Results: Mean age of our sample of patients was 41+/-9.6 years, presenting similar conditions of disability and disease activity. In accordance with previous findings, DMF treatment produced an increase in the number of naïve T cells and a significant reduction in the number of effector, central memory and IFN-gamma+ T lymphocytes, and of memory and regulatory B lymphocytes. In addition, we have newly found that DMF reduces the number of IL2+ producing T cells. After 2 years, 65% of patients were NEDA3 and only 1 patient was NEDA4. Interestingly, we have found a decrease in the number of intermediate monocytes after 1 year of DMF treatment, only present in patients who were EDA3 at 2 years (9.9%+/-3.8 at baseline versus 4.9%+/-0.9 after 1 year of DMF treatment, p< 0.0008), while NEDA3 patients were resistant to this decrease.
Conclusions: DMF exerts an immunomodulatory effect on adaptive immunity but also on innate immunity, producing differential changes in the intermediate monocyte subset than can be associated with an optimal response to treatment.

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The other authors do not have any conflicts of interest to report.

EP1578

MicroRNAs and their use as biomarkers in clinically isolated syndrome and multiple sclerosis

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Introduction: Multiple Sclerosis (MS) is the most common demyelinating disease in Denmark. MS is thought to be caused by a mixture of an overreactive proinflammatory immune response and a missing anti-inflammatory immune response which leads to infiltration of immune cells to the central nervous system (CNS) and a local destruction of myelin sheaths, oligodendrocytes and the blood-brain barrier (BBB). MicroRNAs (miRNAs) are short, non-coding RNA molecules that are involved in many biological processes including the immune system.
Objectives: So far, no specific MS biomarkers have been identified. Several studies have investigated the involvement of miRNAs in MS. In this study, we review studies that have measured miRNA levels in patients with clinically isolated syndrome (CIS)

and MS patients with different disease courses and compare across disease groups as well as controls, furthermore miRNA levels in patients and controls following MS treatment and in different media such as whole blood, plasma, serum, blood leukocytes, white matter and cerebrospinal fluid.
Aims: The aim of this study is to investigate the use of miRNAs as biomarkers in MS diagnostics, predict treatment efficacy and determine disease prognosis of MS patients.
Methods: A structural litterature search was conducted in the bibliographic database PubMed using relevant keywords. Studies with subjects younger than 18 years of age, in vitro studies, solely animal studies, studies investigating other demyelinating diseases and certain foreign language studies were excluded.
Results: Many miRNAs were found to be dysregulated in MS patients. The most commonly dysregulated and investigated miRNAs included miR-155, miR-223, miR-146, let-7, miR-181, miR-30, miR-143, miR-15, miR-26 and miR-326. Several miRNAs were dysregulated when comparing MS patients with healthy subjects as well as when comparing with other disease controls or between different MS disease courses. Furthermore, several miRNAs in the investigated media. Additionally, a change in miRNA expression was observed following both first- and second-line treatments against MS as well as autologous hematopoietic stem cell transplantation (AHSCT).
Conclusions: Since MS is a multifactorial disease with different disease courses, unknown etiology and various results in the different studies, it is not possible to conclude whether miRNAs can be used as MS biomarkers. Further large controlled studies with well-established cohorts should be conducted.

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EP1579
Circulating microRNAs as biomarkers in multiple sclerosis

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Introduction: Biomarkers that could be used in early diagnosis of multiple sclerosis (MS), segregation of disease subtypes and discrimination of the aggressive disease course from the benign one are urgently needed. Circulating microRNAs (miRNA) have great biomarker potential, due to their exceptional stability in body fluids and relative ease of collection and quantification. Aberrant miRNA expression levels were previously reported in multiple MS studies, with less attention paid to circulating miRNAs, especially to their longitudinal stability.
Previously we reported miR-191-5p and miR-24-3p to be overexpressed in relapsing-remitting (RRMS) and primary progressive (PPMS) MS, while miR-128-3p showed tendency towards the predominant expression in PPMS.
Objectives: Study association of miR-24-3p, miR-191-5p, miR-128-3p and miR-223-3p to disability accumulation and disease activity over the 4-year follow-up cohort, as well as to evaluate their correlations to MRI findings.
Aims: Assess the stability of specific miRNA expression in longitudinal study to highlight its promising biomarker potential.
Methods: The expression of miR-24-3p, miR-191-5p, miR-128-3p and miR-223-3p were analyzed in sera samples of 32 RRMS, 15 SPMS, 15 PPMS and 19 CIS patients at the baseline, 2 and 4-years after the study enrollment, as well as in 30 HC.
Results: We have detected longitudinal variability in circulating miRNA expression levels, in RRMS, PPMS, SPMS and CIS patients. These miRNAs were stable, when studied in HC.
Conclusions: Our results indicate an abnormal expression and longitudinal variability of microRNAs in MS. While our MRI result are under analysis now, we believe that our findings will be of interest to ECTRIMS conference participants.

Disclosure

Julia Vistbakka: nothing to disclose, Irina Elovaara: nothing to disclose, Terho Lehtimäki: nothing to disclose, Marja-Liisa Sumelahti: nothing to disclose, Sanna Hagman: nothing to disclose

EP1580
Looking for prognostic factors in MS: the simultaneous absence of IgGOB and spinal cord lesions at diagnosis identifies a less aggressive disease course

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Introduction: On the basis of the 2018 Diagnostic Criteria for Multiple Sclerosis (MS) cerebrospinal fluid-restricted Oligoclonal IgG Bands (IgGOBs) can be used as markers of dissemination in time (DIT) of inflammation. However, DIT criterion can be acquired on the basis of MRI findings and, thus, MS diagnosis can be achieved in the absence of IgGOB.
Objective: To evaluate whether the absence of IgGOB might mark a less aggressive disease course, independently of the number and site of lesions supporting the dissemination in space (DIS) criterion.
Methods: All patients who underwent CSF examination for diagnostic purposes (T0) between January 2016 and April 2016 at the MS Centre in Padua, were retrospectively analysed and included in this study if the following criteria were respected: i) clinically isolated syndrome suggestive of MS; ii) disease duration $\leq$3 months; iii) MS diagnosis in agreement with the 2017 McDonald criteria; iv) at least 24 months of clinical and radiological follow-up. Brain and spinal cord MRI were acquired at baseline and annually (12 months=T1, 24 months=T2), while clinical evaluations were performed biannually. Clinical relapses and appearance of new/enlarging T2 lesions defined disease activity.
Results: 70 patients completed the 2-year follow-up. IgGOB were detected in 46/70 (66%) patients while 34/70 (48.5%) had gadolinium enhancing lesions. Survival analysis revealed a mild effect of IgGOB ($p< 0.05$) in predicting disease activity in the overall cohort. When only MS patients with no IgGOB were considered,

survival analysis revealed an association with the number of typical site involved ($p< 0.05$). Indeed, patients with less than 3 typical sites involved had less frequently disease reactivation in the following 24 months (0% vs 50%, $p=0.009$). Finally, while Kaplan-Mayer analysis revealed a higher probability of disease activity in presence of brainstem ($p=0.03$) or spinal cord lesions ($p< 0.001$) at baseline, Cox analysis confirmed only the latter association (O.R. 26.6, IC95% 2.7-257.0, $p=0.005$). None of these associations was observed in MS patients with IgGOB.

Conclusion: Our findings indicate that the diagnosis of MS in the absence of CSF IgGOB requires a careful evaluation of brain and spinal cord MRI. Moreover, the simultaneous absence of IgGOB and spinal cord lesions identifies patients with a less aggressive disease course.

Disclosure

Puthenparampil Marco received travel grant from Novartis, Almirall, Genzyme, Biogen Idec, Teva and Sanofi Aventis; he has been consultant for Genzyme and Biogen Idec. Martina Saiani and Marta Pengo received travel grants from Teva, Novartis and Genzyme-Sanofi. Miante Silvia reports grants from Novartis, grants from Genzyme Sanofi, grants from Biogen Italia, grants from Almirall, grants from Teva, grants from Merck Serono, outside the submitted work. *Rinaldi Francesca* serves as an advisory board member of Biogen-Idec and has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, Teva and Bayer Schering Pharma. *Perini Paola* has received funding for travel and speaker honoraria from Merck Serono, Biogen Idec, Sanofi-Aventis, and Bayer Schering Pharma and has been consultant for Merck Serono, Biogen Idec and Teva. Gallo Paolo has been a consultant for Bayer Schering, Biogen Idec, Genzyme, Merck Serono and Novartis; has received funding for travel and speaker honoraria from Merck-Serono, Biogen Idec, Sanofi-Aventis, Novartis Pharma and Bayer-Schering Pharma, Teva; has received research support from Bayer, Biogen Idec/Elan, MerkSerono, Genzyme and Teva; and has received research grant from the University of Padova, Veneto Region of Italy, the Italian Association for Multiple Sclerosis, the Italian Ministry of Public Health.

Immunomodulation/ Immunosuppression

EP1581

The link between epigenetic regulators, neurotrophins and treatment efficacy in patients with multiple sclerosis

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Multiple Sclerosis (MS) is an neuroinflammatory and neurodegenerative autoimmune disease of the central nervous system (CNS) with considerable heterogenity in all aspects, including response to therapy. A number of disease modifying drugs (DMD), such as interferon beta (IFN- β), glatiramer acetate (GA) and Fingolimod (FTY) available for disease management. However, a considerable number of patients to achieve adequate response at therapeutic doses of IFN-β, GA and FTY.

Epigenetic regulators such as sirtuin 1 (SIRT1) is member of the histone deactylase (HDAC) family. SIRT1 can regulate transcription, energy metabolism, DNA repair, aging and the functions of T helper 17 (Th17) cells. SIRT 1 was found significantly decreased during relapses and increased levels were seen in responders to GA treatment. In literature there haven' t been any study about the effects of IFNβ and FTY according to serum levels of SIRT1.

On the other hand, investigations on neurotrophins, specifically brain derived neurotrophic factor (BDNF) concentration in patients undergoing GA and IFNβ treatment have conflicting results. Levels in GA and IFNβ treated patients have been reported as decreased, increased and unchanged when compared to controls. There haven't been any study about FTY treatment.

In this study we investigated the effects of different therapies on SIRT1 and BDNF serum levels and their subsequent neuroprotective outcomes. In addition, we undertook the analysis of serum SIRT 1 and BDNF levels in responder and non-responder MS patients. For this reason; IFNβ, GA, FTY responder and non responder MS patients serum samples were collected and measured with enzyme linked immunosorbent assay (ELISA) method. IFNβ treated responder group had significantly higher BDNF serum levels than all other groups. Levels of SIRT1 in GA treated responder group is remarkably higher than all other groups. Consequently our findings suggest that SIRT1 and BDNF could be a possible biomarker to evaluate responsiveness to GA and IFNβ treatments.

Although experimental studies support BDNF mediated neuroprotection of GA in demyelinating conditions, we could not find similar results in vivo. Further studies, on the protective roles of SIRT1 and BDNF in MS patients and their therapy responsiveness are required.

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EP1582

Siponimod increases brain-derived neurotrophic factor (BDNF) levels in cortical neuronal cultures and naïve healthy mice

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Background: Siponimod is a potent, oral, selective sphingosine 1-phosphate (S1P1,5) receptor modulator. Recent preclinical data suggest direct neuroprotective effects of siponimod in the central nervous system that are independent of peripheral immune effects. Stimulation of brain-derived neurotrophic factor (BDNF) synthesis

by neurons has been proposed as one of the potential underlying mechanisms for the central effects of the reference S1P1/3/4/5 modulator, fingolimod.
Objective: To investigate the effects of siponimod on BDNF expression in cortical neuronal cultures and in naïve healthy mice.
Methods: Cortical neuronal cultures were stimulated with siponimod or phospho-fingolimod (100 nM) at different concentrations. Extracellular signal-regulated kinase (ERK1/2) phosphorylation was analysed after 30 minutes and the changes in the BDNF levels were analysed after 24 hours incubation with the study compounds. The effect of siponimod on BDNF expression was also analysed in vivo. C57BL/6 (naïve healthy) mice of 6-7 weeks of age were treated daily (intraperitoneal [i.p.] administration) for 14 days with siponimod, fingolimod, AUY954 (a S1P1 selective agonist), NIBR213 (a S1P1 selective antagonist) or saline. Changes in BDNF levels in the cortex, hippocampus, striatum and cerebellum regions of the brain were determined by the ELISA techinique.
Results: The addition of siponimod to the cortical neuronal cultures led to an increase in BDNF levels and ERK1/2 phosphorylation. These observations were further confirmed in the in vivo study. After 14 days of i.p. administration of siponimod, increased levels of BDNF were observed in the cortex, hippocampus and striatum regions but no effect was observed in the cerebellum. Similar results were obtained with AUY954 and fingolimod treatment whereas NIBR213, the S1P1 selective antagonist, had no effect on BDNF levels in any of the brain regions.
Conclusions: These data show that siponimod stimulates BDNF synthesis in certain brain regions, including the cortex and thus support the direct central effects of siponimod in MS. This effect is at least in part mediated by the S1P1 agonism.

Disclosure

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EP1583
Explaining long-term depletion of memory B lymphocytes after cladribine treatment

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Objective: To determine the mechanism by which cladribine leads to long-lasting depletion of memory B lymphocytes in people with multiple sclerosis (pwMS).
Background: Cladribine is a synthetic purine nucleoside analogue with high efficacy in relapsing MS. Cladribine is selectively toxic towards lymphocytes in vivo, and leads to long-lasting memory B cell depletion. Here, we explore the mechanistic basis of this apparent cell type-specific toxicity.
Results: Cladribine was toxic to stimulated and unstimulated lymphocytes in a dose-dependent and deoxycytidine kinase (DCK)-dependent manner over a physiological dosing range (0 - 1x105 nM). Toxicity was most pronounced for naive B cells, followed by memory B cells, followed by T cells. High DCK expression and low ADA expression correlated with susceptibility to cladribine-induced cell death.
Conclusions: Cladribine kills all lymphocyte subsets in vitro with a predilection for naïve B cells. Depletion of the circulating naïve B cell pool removes the precursors for the generation of new memory cells. This 'roadblock' mechanism may explain delayed reconstitution of the memory B cell pool in pwMS following treatment with cladribine. A high DCK:ADA expression ratio appears to partly determine the cell type-specific toxicity of cladribine.

Disclosure

Competing interests: Dr Baker reports being a founder and consultant to Canbex Therapeutics and receiving research funds from Canbex Therapeutics, Sanofi-Genzyme, and Takeda in the past 3 years. Prof Giovannoni reports receiving fees for participation in the advisory board for AbbVie Biotherapeutics, Biogen, Canbex, Ironwood, Novartis, Merck, Inc, Merck Serono, Roche, Sanofi Genzyme, Synthon, Teva, and Vertex; speaker fees from AbbVie, Biogen, Bayer HealthCare, Genzyme, Merck Serono, Sanofi-Aventis, and Teva; and research support from Biogen, Genzyme, Ironwood, Merck, Inc, Merck Serono, and Novartis. Dr Schmierer reports being a principal investigator of trials sponsored by Novartis, Roche, Teva, and Medday; involved in trials sponsored by Biogen, Sanofi-Genzyme, BIAL, Cytokinetics, and Canbex; and receiving speaking honoraria for lecturing and advisory activity and/or meeting support from Biogen, Merck, Inc, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. All authors with the exception of TX have presented at the ECTRIMS annual congress on one or more occasions.

EP1584
Alemtuzumab in highly active MS: effectiveness in real life and the need of immunological profiling

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Background: long-term effectiveness data shows that more than two cycles of alemtuzumab (Alem) are often required to treat some multiple sclerosis (MS) patients. Cases of activation of the disease occurring in the first years of treatment are increasing.
Methods: We retrospectively studied a court of 15 MS patients starting therapy with Alem between August 2015 and March 2017 at the Multiple Sclerosis Center of Montichiari, Brescia and at the Multiple Sclerosis Center of Treviso (Italy).
Results: all 15 patients received 2 treatment courses at a 12-month interval with a mean follow-up from second Alem treatment cycle of 11 (5-19) months. Patients had a median disease duration of 7.5 years and they switched to Alem from other DMTs (natalizumab:

6, fingolimod: 4, dimethyl fumarate: 2, interferon beta-1a: 2) for treatment failure. Overall, 9 subjects experienced lack of response to Alem with clinical and/or radiological disease activity after the first therapeutic course (MRI activity after mean 7,8 months from treatment; relapses after mean 8,2 months from treatment). Two of them (showing a less active disease before Alem start) stabilized after the second treatment course, 6 patients lacked the full control of the disease after the second course. Two patients with clinical and radiological stability after the first cycle, reactivated after the second one, in contrast with reported data of possible uselessness of second Alem course in case of MS stabilization during the first year. In our patients the relapse-rate was 0.75/year after the first course of Alem and 0.33/year after the second one. Autoimmunity was observed 11 months after the first course in one patient (thyroiditis), 11 months after the second course in two patients (thyroiditis and eczema) and 13 months after the second course in one patient (alopecia, arthralgia).

Conclusions: high proportion of our highly active MS patients treated with Alem failed a complete response after the first and/or the second treatment course. Autoimmunity was observed precociously in 4/15 patients. The immunological profile at baseline and during treatment (kinetic of B and T cells recovery) could condition the efficacy of the drug, the risk of autoimmunity developement or suggest a different administration schedule.

Disclosure

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EP1585

Switching inactive MS patients under BRACE therapies to teriflunomide due to injection-related problems

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Background: In clinical practice, inactive relapsing-remitting multiple sclerosis (RRMS) patients under interferons and glatiramer acetate (collectively known as BRACE therapies) are often reluctant to be kept under an injectable drug when oral alternatives are available. A recent subgroup analysis from TEMSO and TOWER studies showed that patients previously treated with BRACE therapies presented a reduction in relapse rate and in the disability progression after switching to teriflunomide. However, in these patients, MS was active in the 24 months prior to teriflunomide start.

We aimed to evaluate if switching inactive patients under BRACE therapies to teriflunomide maintained their inactive-status or if it was associated with an increase in disease activity.

Methods: We designed a case-control study including all adult patients with the following inclusion criteria: RRMS, inactive under BRACE therapies for at least 2 years according to Lublin criteria, that were subsequently switched to teriflunomide due to injection-related problems (exposure group) or maintained under the injectable DMT (control group), and had a minimum follow up of 6 months. We analyzed the risk of relapse and disability progression between groups using Kaplan-Meier survival curves with the log-rank test and Cox regression.

Results: Of 48 patients included, 32(66.7%) were women, with a mean age of 45.4(± 11.1) and a median disease duration of 11.0 (IQR 9.0) years. The median EDSS at baseline was 1.0 (IQR 1.0). Patients had been under BRACE therapies for a period of 2-16 years. Eleven (22.9%) patients switch to teriflunomide. Switching to teriflunomide did not associate with a higher risk of relapse (HR: 3.528, 95% CI 0.220-56.445; p=0.373) or a higher risk of disability progression (HR:0.317, 95%CI:0.414-15.236; p=0.317) during a median follow-up period of 24 (IQR 0.0) months.

Conclusion: Teriflunomide seemed a good alternative in inactive RRMS patients under BRACE therapies reporting injection-related problems. The transition of these patients to teriflunomide was not associated with a higher risk of relapse or disability progression in our sample. Further studies with larger samples and including radiologic assessments would be useful to confirm if patients controlled with BRACE therapies can be safely switched to teriflunomide in case of injection-related problems.

Disclosure

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EP1586

Comparison of fingolimod and teriflunomide on the basis of relapse, magnetic resonance imaging and cognition following the switch from injectables in patients with stable multiple sclerosis

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Introduction: Unacceptable tolerability may be the reason for considering treatment switch from platform madications to oral agents in multiple sclerosis (MS). Both fingolimod and teriflunomide can be used effectively. used in multiple sclerosis (MS). Early relapse outcomes in long-term stable patients switching from IFNb and GA to oral madications have been stimulating issues.
Aims: To compare relapse possibilities and cognitive and magnetic resonance imaging (MRI) issues in patients switching injectables to fingolimod or teriflunomide.
Methods: RRMS patients who were stable at least one year with paltform injectables were recruited. Annual relapse rate, disability progression, number of new T2 lesions and new T1 lesions (black holes), and symbol digit modalities test scores were compared in switchers (previously stable MS patients switching from platform injectables) and stayers (patients remaining on IFNβ/GA).
Results: A total of 406 switchers were matched to 324 stayers. There was no difference in the proportion of patients recording at least one relapse in the first year (3.4% switchers, 2.9% stayers; $P = 0.085$). The mean annualized relapse rate ($P = 0.19$) and EDSS progression (0.09) were also comparable. There was no significant difference between two groups on the basis of new T2 lesion (p=0.14) and new T1 lesion (p=0.754). İnformation prossessing speed measured by SDMT was also did not change in this period for both groups (p=0.08)
Conlusions: Our results indicated that there was no evidence of disease reactivation in terms of relase possibility, MRI activitiy and cognitive status within the first year in patients switching to oral therapy when they were previously stable, and both fingolimod and teriflunomide had similar results in this respect.

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EP1587

Long-term remission of tumefactive relapsing multiple sclerosis after alemtuzumab rescue treatment in an adolescent patient

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Background: tumefactive demyelinating lesions may be a diagnostic and therapeutic challenge [1], especially in pediatric patients [2]. Alemtuzumab showed efficacy in a fulminant form of multiple sclerosis (MS) [3].
Method: case report of an adolescent with tumefactive relapsing MS who underwent a sustained remission after alemtuzumab therapy.
Results: in February 2015, a 16 years old male, without remarkable previous clinical history, had a subacute sensorimotor right hemiparesis associated with headache and vomiting. Brain MRI showed five lesions (including corpus callosum) with ring-shaped enhancement, one with a tumor-like appearance with pronounced perilesional oedema. Spinal cord MRI, CSF, evoked potentials, autoantibody screening (including anti-NMO and anti-MOG) were normal. He was treated with an intravenous (iv) methylprednisolone course (ineffective), then with two courses of plasma exchange (partial recovery), finally with two Rituximab courses 15 days apart, with slow clinical improvement. In April 2015 brain MRI showed partial regression of one lesion, but worsening of the pseudotumoral one, associated with a further deterioration of symptoms. In May 2015 a second CSF analysis was negative, as well as the work up for lymphoproliferative diseases (total body CT, testicles ultrasound, eye fundus examination). In May 2015 cyclophosphamide was started (9 courses monthly), without a significant remission of disease activity. In July 2015 brain MRI showed inflammatory activity in almost all lesions with increased left fronto-temporal perilesional oedema. The patient presented marked dysarthria that was treated with iv methylprednisolone, with only partial recovery. In autumn 2015, problems of memory and attention arose. In February 2016 brain MRI showed a further reduction of posterior lesions, but new, large pseudotumoral bifrontal contrast-enhancing lesions appeared. Brain biopsy confirmed the diagnosis of inflammatory demyelinating disease compatible with MS, excluding other mimickers (neoplasm, lymphoma, vasculitis, ADEM or infection). Alemtuzumab was then started in March 2016, with a sustained clinical improvement and complete remission of any activity at subsequent brain MRI. No adverse events were observed.
Conclusions: alemtuzumab led to a long-term remission in a young patient with tumefactive relapsing MS, confirmed by neuropathological examination. Alemtuzumab should be considered early in the therapeutic algorithm of these forms.

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EP1588
Cyclophosphamide in multiple sclerosis: a real-life study on 222 patients

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Introduction: Cyclophosphamide (CYP) is an immunosuppressive drug, commonly used in Multiple Sclerosis (MS) in some French MS centres. While this drug seems to be efficient to treat inflammation in Relapsing Remitting (RR) MS, several randomized controlled trials have been conducted in progressive MS but with contradictory results. Here, we analyzed the efficacy and safety of the use of CYP in real life in a French cohort of MS patients.
Methods: All MS patients that had received CYP between 1989 and 2016 in Nantes, were included. Expanded Disability Status Scale (EDSS), relapses, gadolinium enhancing lesions and adverse events were collected.
Results: 222 MS patients were included (115 Secondary Progressive MS, 66 Primary Progressive MS and 41 RRMS). The mean age at baseline was 46,92 years old. Treatment by CYP was started 13 years after the beginning of the disease. 83 patients were naïve of drugs before starting CYP. Mean treatment duration by CYP was of 12.27 months, with a mean cumulative dose of 6.76 g. Mean annualized relapse rate (ARR) decreased from 0,89 (before treatment) to 0,27 at one year and 0,48 at two years ($p< 0.0001$ for both comparisons vs baseline). Mean EDSS at baseline was 5,60 and increased significantly to 6,01 two years after the beginning of the treatment ($p < 0,0001$). However, EDSS was stabilized (n_s= 53/124) or improved (n_i= 31/124) in 67 % patients at 12 months and 50% (n_s= 39/117, n_i= 20/117) at 24 months. Mean enhancing lesions on Magnetic Resonance Imaging before CYP was 0.64 and decreased to 0.15 one year after the beginning of the treatment ($p< 0.05$).14 patients stopped CYP for adverse events, 144 for planned arrest, 30 for inefficacy, 8 for others reasons. 94 patients presented some adverse events that were mainly infectious (21,65%), vomiting (16,19%) and asthenia (9,91%).
Conclusion: This immunosuppressive drug seems to be efficient on the inflammatory components of the disease but without major effects on disability progression. A sub group analysis (on the differents forms of MS) will be performed to better understand these results.

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EP1589
Patient initiation of fingolimod treatment in younger patients with multiple sclerosis in clinics and in the Gilenya@Home Program

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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 during fingolimod initiation. FDO can be conducted in clinics; with the Gilenya@Home program, most US patients initiate fingolimod at home. Side-effect reporting differs among settings due to extra precautions taken at home. FDO data for younger vs older patients are worth analysis.
Objectives: Assess FDO findings in younger (≤30 years) vs older (>30 years) patients initiating fingolimod at home or in the clinic.
Methods: Retrospective, anonymized patient FDO safety data were collated from Gilenya@Home (Oct 2014-Jul 2017) and Gilenya assessment network clinics (Jul 2010-Dec 2016). Extended monitoring (EM) was conducted per product label or if HR was ≤45 bpm at 6 hours. Patients were transferred to an emergency room (ER) for overnight monitoring if required. Cardiac safety data (HR, first-degree [1°] or second-degree [2°] atrioventricular [AV] block) and additional monitoring (EM, ER) were compared for patients aged ≤30 vs >30 years.
Results: Data were collated for 5060 in-home visits and 14,873 in-clinic FDO procedures (with available date of birth), of which, 756 (14.9%) and 2109 (14.2%), respectively, were in patients aged ≤30 years. Baseline pre-dose HR (mean±standard deviation) was similar for in-home patients aged ≤30 vs >30 years (75.2±12.9 vs 74.8±12.1 bpm), as was HR at 6 hours post-dose (65.1±10.7 vs 64.0±12.9 bpm). HR for younger vs older in-clinic patients were similar at baseline (74.3±11.3 vs 74.2±11.4 bpm) and discharge (68.3±10.0 vs 67.8±10.0 bpm). Percentage of patients with 1°AV block was similar between younger and older patients in the in-home (2.0% vs 2.5%) and in-clinic (0.1% vs 0.5%) settings, respectively. Occurrence of 2°AV block was low in all groups (in-home: 0% vs 0.1%; in-clinic: 0.1% vs 0.1%). Proportion of patients requiring EM was similar for younger and older patients

(in-home: 9.0% vs 10.3%; in-clinic: 2.2% vs 2.7%) settings. A smaller percentage of younger vs older patients attended the ER (in-home: 0.1% vs 0.3%; in-clinic: 0.3% vs 1.0%).
Conclusions: Safety outcomes were as expected for patients initiating fingolimod, regardless of age and in-home or in-clinic setting. Younger patients appeared less likely to require ER monitoring during FDO.

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, Jamie Weiss and Nina Jaitly are employees of Novartis Pharmaceuticals Corporation.

EP1590
Effects of MS treatments on the phenotypic and functional characteristics of B cells

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Objective: To analyze whether commonly used multiple sclerosis (MS) disease-modifying drugs may induce changes in B cell subset distribution and/or cytokine production capacities of B cells.
Methods: We prospectively enrolled RRMS patients naive of any disease modifying drugs. Blood samples were collected at baseline, and 3, 6 and 12 months after initiation of treatment. To determine both peripheral blood B cell subset distribution and functions, a phenotypic analysis by cytometry was performed. The proportions of IL-6- and of IL-10-producing B cells were measured, after polyclonal stimulation, to assess pro-inflammatory and anti-inflammatory functional properties of peripheral blood B cells. Changes in either lymphocyte subset numbers or percentages (as appropriate) were analysed by building a mixed model of repeated measurements for each lymphocyte subset (SAS® 9.4 software).
Results: Of the 46 RRMS patients included: 18 were treated by beta-interferon (IFN-β), 17 by dimethylfumarate (DMF) and 11 by teriflunomide (TFM). Although no significant decrease in total B cell counts could be considered in either of the 3 treatment groups, significant changes were evidenced in B cell subset distribution. IFN-β initiation was associated with an increase of transitional B cell ($p< 0.001$) and a decrease of marginal zone B cell ($p< 0.003$) proportions from the 3rd month of treatment. IFN-β also induced an increase of the IL-10-producing B cell proportion from the 6th month ($p< 0.001$), without any change of the IL-6-producing B cells. DMF initiation was associated with a decrease of all memory B cell subset ($p< 0.001$) proportions from the 6th month, and with an increase of the mature naive B cell proportion at 12 months ($p=0.005$). No variation in IL-10 or IL-6-producing B cell proportions was observed. Under TFM initiation, no significant modification of the B cell subset distribution was observed, while both the IL10- and IL-6-producing B cell proportions decreased ($p=0.02$ and $p=0.04$ respectively) at 12 months.
Conclusions: TFM is associated with a decrease in pro- as well as anti-inflammatory B cell properties. Conversely, IFN-β and DMF induced significant changes in B cell subset distribution, which were, for IFN-β, notably associated with changes in functional properties leading to an increase of potentially regulatory IL-10-producing B cells. These effects on B cells appear early with IFN-β and delayed with DMF.

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EP1591
Synthesis and preliminary testing of siRNA targeting the T Cell receptor β-chain - A proposed therapy for the treatment of autoimmunity

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As of 2018, the United States National Institutes of Health estimate that over half a billion people worldwide are affected by

various autoimmune disorders. Though these conditions are prevalent, treatment options remain relatively poor, relying primarily on various forms of immunosuppression which carry potentially severe side effects and often lose effectiveness overtime. Given this, new forms of therapy are direly needed. We propose the use of small interfering RNA (siRNA) for the T-cell receptor β-chain gene (TRB) as a highly targeted, novel means of therapy for the treatment of autoimmune disorders. To meet this goal, the conducted research aimed to develop methods to produce siRNA for TRB. Additionally, this research included testing of said siRNA for its effects on the TRB gene and cell viability.

Jurkat (T-lymphocyte) cells were lysed and their mRNA isolated. After reverse transcription, C-tailing coupled with modified conventional techniques was applied in order to create siRNA specific for TRB. Additionally, siRNA synthesis using a previously reported multi-primer method was attempted (though was unsuccessful). Synthesized siRNA was subsequently coated with lipofectamine to facilitate transfection. The coated siRNA molecules were then applied to Jurkat cells at concentrations of 2 and 20 picomolar and incubated for 72h. Gene knockdown was quantified by qPCR, while cell viability was quantified both by direct counting and MTT assay.

While we were unable to synthesize siRNA for TRB using a previously reported "multi-primer method", synthesis using C-tailing was successful. The encapsulated siRNA constructed in this manner demonstrated an ability to knockdown expression of TRB by more than 99.8% at concentrations of both 2 and 20 picomolar while having no observed effect on T-cell viability. This data suggests that siRNA for TRB may potentially be an effective, novel means of therapy in the treatment of autoimmune disorders.

Disclosure

Nicholas Magazine: nothing to disclose

EP1592

Characterization of myelin peptide-coupled red blood cells

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Background: The development of safer and more efficient immune therapies remains an important unmet medical need in patients with autoimmune diseases. Induction of antigen-specific immune tolerance can be achieved via injection of cells chemically coupled with target antigens. Preclinical studies with peptide-coupled splenocytes have suggested „cross-tolerance" as the main mechanism of action for inducing tolerance (1), whereby peptide-coupled cells undergo apoptosis and are processed by macrophages in the spleen to represent the antigens in a tolerogenic way. Much less is known using peptide-coupled red blood cells (RBCs) instead of peptide coupled splenocytes.

Goals: Objectives of this project are to analyze the effects of the coupling procedure on RBCs *in vitro* and investigate the biodistribution of peptide-coupled RBCs *in vivo*.

Methods and Results: Treatment with the cross-linker ethylcarbodiimide (EDC) led to a reduced deformability of peptide-coupled RBCs as observed by ektacytometry. Electron microscopy analysis revealed only minor morphological changes following treatment with EDC.

In addition, coupling of RBCs initiates physiological changes such as a rapid influx of cytosolic calcium and phosphatidylserine exposure, both hallmarks of programmed cell death in RBCs, called eryptosis.

Both deformability and morphological changes of peptide-coupled RBCs appear to influence the *in vivo* biodistribution and direct these cells to specific organs. To identify the cellular origin involved in the uptake of peptide-coupled RBCs, we injected fluorescently-labelled peptides coupled to RBCs intravenously in BALB/c mice and analysed the biodistribution, both *in vivo* and *ex vivo*. Bioluminiscence imaging data indicates the liver as one of the major organs involved in the uptake of peptide-coupled RBCs. Histological analysis confirmed the aforementioned findings, demonstrating uptake of peptide-coupled RBCs by liver macrophages/Kupffer cells.

Conclusion: RBCs exhibit hallmark characteristics of eryptosis following peptide coupling and these are efficiently taken up by macrophages/Kupffer cells in the liver following their intravenous administration.

1: Miller SD et al, Nat Rev Immunol 2007.

Disclosure

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A. Lutterotti

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M. Hohmann, T. H. Ludersdorfer, M.J. Docampo, C. Sellés-Moreno, P.C. Englezou, J. S. Goede, J. Deuel, F. Guffanti, M.Broggini, E. Scanziani and M. Sospedra

Nothing to disclose.

EP1593

Dissection of the distinct susceptibility of hematopoietic precursors and immune cells to cladribine

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Cladribine (2CdA) is deoxyadenosine antimetabolite activated by sequential deoxycytidine kinase (dCK) phosphorylation causing cell death through apoptosis and necrosis. This is reverted by cytosolic 5' deoxynucleotidase (NT5C2). Thus, high dCK/NT5C2 ratios in lymphocytes reflect 2CdA-specific lymphopenic effect. Clinical trials have shown a difference in timing of immunoreconstitution for different lymphocyte subsets in multiple sclerosis (MS) patients, suggesting that a differential susceptibility to 2CdA by these subsets and/or of their lymphoid progenitors is linked to dCK/NT5C2 ratio variability. Moreover, dCK expression and activity are enhanced during lymphopoiesis and in activated lymphocytes. On this basis, our objective is to assess the enzymes involved in 2CdA metabolism *in vitro* in selected immature cells, including hematopoietic stem cells, and common lymphoid (CLP) and myeloid progenitor cells (CMP) from healthy donors, as well as in activated mature lymphoid and myeloid cellular subsets isolated from the peripheral blood of healthy donors upon 2CdA stimulation.

Flow cytometry analysis using pre-validated rabbit anti-dCK and anti-NT5C2 polyclonal antibodies showed a positive dCK/NT5C2 MFI ratio in B cells, T cells and monocytes, with mean values of 5.19, 3.28 and 2.17, respectively. Within B-cell subsets, dCK and NT5C2 expression was highly heterogeneous, with plasma cells displaying the highest MFI, but no significant differences were observed in the respective B-cell dCK/NT5C2 ratios (B memory dCK MFI mean = 10580, NT5C2 MFI mean = 3206, ratio = 3.30; B mature dCK MFI mean = 7496, NT5C2 MFI mean = 2356, ratio = 3.18; B transitional dCK MFI mean = 7364, NT5C2 MFI mean = 2451, ratio = 3.00; plasma cells dCK MFI mean = 16901, NT5C2 MFI mean = 2451, ratio = 2.47).

These data support our suggestion that 2CdA affects specific immune cell subsets differentially.

Disclosure

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Federico Carlini, Federico Ivaldi, Nicole Kerlero de Rosbo and Antonio Uccelli: nothing to disclose

Ursula Boschert: Head of Neuroimmunology at EMD Serono, Inc., USA

Andrea Visconti: Medical Affairs Department, Merck Serono, Italy

EP1594

Multiple sclerosis relapse resolution with corticosteroid alternatives: a retrospective claims analysis of us health plan data

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Background: Multiple sclerosis (MS) relapse adversely impacts short-term functioning, and accumulation of associated residual deficits results in neurological disability. As such, relapse resolution represents a critical measure of treatment effectiveness. While corticosteroids (CS) are routinely used to treat relapse, alternatives are available where CS are inappropriate (e.g. non-response/intolerance), including repository corticotropin injection (RCI; H.P. Acthar® Gel), intravenous immunoglobulin (IVIG), or plasmapheresis (PMP).

Objectives: To characterize relapse episodes and relapse resolution with CS alternatives

Methods: Analyses were conducted using administrative health insurance claims data from HealthCore from 1/1/06-11/30/16. A relapse was defined per convention as: 1) hospitalization with a principal diagnosis OR outpatient visit with any diagnosis of MS (ICD-9/10-CM=340.xx/G35) plus 2) receipt of RCI, IVIG, or PMP ≤30 days. Relapses ≤30 days were considered one episode, with the end date as the date of the last relapse plus 30 days. Continuous enrollment was required. IVIG and PMP treatments ≤7- and ≤14- days of the initial treatment were considered a course. Relapse resolution was evaluated based on all treatments received during the first episode, including CS; the first treatment was used for group assignment, i.e. RCI or PMP/IVIG. Treatment was assumed ineffective and the relapse unresolved, if another treatment followed. Comparative effectiveness analyses were conducted, using chi-square tests for categorical variables and t-tests for continuous variables.

Results: Approximately 60.2% (n=240) and 39.8% (n=159) of patients first received RCI and PMP/IVIG during their first episode, with mean number of days of 38.1 and 47.4 for each ($p< 0.001$). Relapse resolution differed by treatment ($p< 0.001$); 78.3% and 56.0% of patients receiving RCI and PMP/IVIG did not require additional relapse treatment. For RCI, 17.9% and 3.8% of patients required 1 and 2+ additional treatments to resolve their relapse, vs. 27.0% and 17.0% for PMP/IVIG.

Conclusions: RCI resolved the relapse episode more quickly and at a significantly higher rate, vs. PMP/IVIG, and can be self-administered. Consistent with prior findings, treatment effectiveness is greater with RCI vs. PMP/IVIG and RCI may be considered first for appropriate patients. Claims limitations apply.

Disclosure

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Xian Zhang is currently employed by HealthCore, which is a consultancy whose activities on research projects were funded by

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Nancy Ho Mahler, is an employee and stockholder of Mallinckrodt Pharmaceuticals (MNK), a life sciences company, Bedminster, New Jersey, USA. MNK provided funding for this research.
Royce Waltrip is an employee and stockholder of Mallinckrodt Pharmaceuticals (MNK), a life sciences company, Bedminster, New Jersey, USA. MNK provided funding for this research.
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EP1595

Peginterferon beta-1a every 2 weeks demonstrated better clinical outcomes than glatiramer acetate once-daily in patients with RRMS: propensity score matching of phase 3 data from ADVANCE and CONFIRM

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Introduction: Peginterferon beta-1a and glatiramer acetate (GA) are both approved first-line therapies for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS). These therapies have been studied in different clinical studies, and head-to-head efficacy comparisons are lacking. Propensity score matching (PSM) is a statistical method that allows the assessment of differences in treatment effects by modelling the relationship between confounders and treatment assignments (eg, in different clinical trials), such as ADVANCE and CONFIRM.
Objectives: Compare subcutaneous (SC) peginterferon beta-1a 125 mcg every 2 weeks vs SC GA 20 mg/mL once-daily on clinical efficacy endpoints at 2 years in patients from ADVANCE and CONFIRM using PSM.
Methods: PSM (1:1) based on key baseline characteristics (age, baseline expanded disability status score [EDSS], years from onset of symptoms, number of relapses in prior year, and gender) was performed on 512 ADVANCE peginterferon beta-1a patients and 350 CONFIRM GA patients. Outcomes included annualised relapse rate (ARR), which was assessed using negative binomial regression, and 12-week and 24-week confirmed disability worsening (CDW), which were evaluated using the Kaplan-Meier method and Cox proportional hazards modeling.
Results: After matching, 336 each of peginterferon beta-1a and GA patients were included. At 2 years, patients treated with peginterferon beta-1a had a significantly lower ARR (0.204 vs 0.282; rate ratio 0.724; P=0.0453), a significantly lower probability of 12-week CDW (10.0% vs 14.6%; hazard ratio (HR) 0.625; P=0.0476), and a numerically lower probability of 24-week CDW (7.7% vs 10.6%; HR 0.684; P=0.171) compared with patients treated with GA.
Conclusions: In this PSM analysis using data from two recent phase 3 trials, peginterferon beta-1a every 2 weeks showed significantly better clinical outcomes in terms of relapses and 12 week disability worsening compared to GA once-daily in patients with RRMS over 2 years.

Disclosure

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EP1596

Ocrelizumab in an expanded cohort of primary progressive MS patients: safety outcomes and clinical/paraclinical follow-up

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Background: Ocrelizumab, a humanized monoclonal antibody targeting CD20+ B cells, has recently been approved by EMA for a subset of primary progressive MS (PPMS) patients. According to regulators, patients should be treated if strict clinical and paraclinical criteria are met (i.e.: early PPMS in terms of disease duration, level of disability, and MRI activity). Although efficacy and safety has been well established in in early PPMS patients, most patients in clinical practice do not fulfill all of the above criteria. Additionally, safety and efficacy outcomes in longstanding, non-ambulating or older PPMS patients have yet to be studied and compared with those of PPMS patients fulfilling EMA criteria.
Aims: To evaluate, in a single center real life MS clinic, safety and efficacy of ocrelizumab treatment using clinical and paraclinical parameters.
Methods: PPMS patients were enrolled in the ocrelizumab compassionate use program before EMA pronouncement on prescription restrictions. Patients were infused with ocrelizumab and underwent MRI scan before ocrelizumab administration in order to detect radiological activity. All patients were followed, according to good clinical practice guidelines, with serial EDSS,

BICAMS, patient reported outcomes (PRO), MRI, OCT, and laboratory assessment.
Results: 34 patients were included in the analysis (F/M ratio 22/12, mean age 52 (range 36-66) years). The median follow-up was 4.5 months (range 1.2-14). Mean and median disease duration at ocrelizumab initiation were 12.4 and 9.3 years, respectively. Median pre-treatment EDSS was 6.0 (range 2.0-7.5). 10 patients (29%) were treatment-naïve at ocrelizumab treatment onset. Infusion related AE were experienced by 4 patients and serious AE (SAE) by 1 patient. Radiological activity was found in 6 patients. Only 4 out of 34 patients (12%) fulfilled all EMA criteria for PPMS treatment with ocrelizumab but there was no significant difference in terms of AE and SAE between the two groups of patients (p=0.32 for AE).
Conclusions: Ocrelizumab induction regimen appears to be safe in our real-life cohort of patients with longstanding disease, greater age and disability than those enrolled in clinical trials and absence of radiological activity.

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EP1597

Efficacy of teriflunomide in a progressive multiple sclerosis cohort in the CLIMB study

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Introduction: The Effect of teriflunomide in a progressive multiple sclerosis (MS) population is not well characterized
Objective: We wished to explore the side effect profile and efficacy of teriflunomide in a group of patients with primary (PPMS) and secondary progressive (SPMS) multiple sclerosis.
Aims: To describe side effects and efficacy in a PPMS and SPMS as measured by timed 25 foot walk (T25FW) and expanded disability status scale (EDSS).
Methods: We conducted a single-center retrospective observational analysis of medical records and available comprehensive longitudinal investigation in MS database (CLIMB) information for patients labelled by clinicians as having PPMS or SPMS at a tertiary academic center with teriflunomide from 2012-2017. Patients also were required to be ≥ 40 years old and an EDSS ≥ 3.5 at the initiation of treatment with teriflunomide. EDSS and 25-foot walk time in the year before treatment and after treatment were analyzed. Analysis of T25FW prior to start and one year after start was compared with Wilcoxon rank sum testing.
Results: Twenty-nine patients were included in the study. Mean EDSS did not differ prior to teriflunomide start and after one year (n=29, 6.29 vs 6.33, p=0.98.) Mean T25W also did not differ prior to teriflunomide start and at one year (n=19, 10.5s vs. 10.8, p=0.85.) Teriflunomide was generally well tolerated without serious tolerability or safety concerns in this small population.
Conclusions: Patients did not worsen over the course of one year as measured by EDSS and T25FW while on teriflunomide. Further characterization of this population and comparison to other cohorts is needed.

Disclosure

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EP1598

Real-world data on alemtuzumab treatment of relapsing multiple sclerosis: a two-year prospective one center study

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Introduction: Alemtuzumab (ALZ) belongs to the pulsed immune reconstitution therapies for relapsing-remitting multiple sclerosis (RRMS). In clinical practice ALZ is used as a second or third line treatment of RRMS and thus the real-world population treated with ALZ is different from the populations participated in the pivotal studies of ALZ.
Objective/Aim: We aimed to assess basic characteristics and therapeutic effects on clinical and imaging parameters of disease activity for RRMS patients selected for ALZ.
Methods: RRMS patients were consecutively included. Patients were clinically assessed with Expanded Disability Status Scale (EDSS), occurrence of clinical relapses and with cerebral MRI at baseline and at month 6, 12, 18 and 24.
Results: 51(30 females) RRMS patients, mean age 38±7.2 years and mean disease duration at baseline 7.4±5.6 years, were included. Prior to baseline 6(12%) patients had first line treatment, 38(74%) had second line and 7(14%) were treatment naive. Reasons to switch to ALZ were breakthrough disease activity

despite disease modifying therapy (DMT) in 23(45%) patients, side effects in 3(4%), positive JC virus test during natalizumab in 18(35%) and highly active disease from disease onset in 7(14%). All patients received the first course of ALZ, 50(98%) the second, 9(18%) a third and 1(2%) a fourth course. Median EDSS at baseline was 2(range 0-7.5), at month 12, 1.5(range 0-7) and at month 24, 1.5(range 0-7,n=42). In total 40/51(78%) patients had no relapse. Baseline MRI revealed high lesion load; 36(71%) had T2 lesions >20, 12(23%) had T2 lesions 10-20 and 3(6%) had T2 lesions 1-9. 36(71%) had no contrast enhancement. Upon follow-up at 6, 12, 18 and 24 months, 42(82%) patients, 39(76%), 39(89%,n=44) and 39(93%,n=42) had no new or enlarged T2 lesions. Corresponding number with no contrast enhancement was 48(94%), 41(80%), 44(100%) and 38(90%). Between baseline and 12 months of follow-up 8(16%) patients had Clinical Disability Worsening (CDW), 8(16%) had Clinical Disability Improvement (CDI) and 28(55%) met No Evidence of Disease Activity (NEDA), between 12 and 24 months of follow-up, corresponding number was 2(5%,n=42), 3(7%) and 29(70%).

Conclusion: This real word population confirms that ALZ as second or third line treatment effectively reduced disease activity with CDI or stability in 92%, and NEDA in 51% at 24 months of follow-up. The study population is currently followed to collect long-term efficacy and safety data of ALZ.

Disclosure

SS and LN has nothing to disclose. MA has received compensation for lectures and/ or advisory boards from Biogen, Genzyme, and Novartis. JL has received travel support and/ or lecture honoraria from Biogen, Novartis, Teva and Genzyme/ SanofiAventis; has served on scientific advisory boards for Almirall, Teva, Biogen, Novartis and Genzyme/ SanofiAventis; serves on the editorial board of the Acta Neurologica Scandinavica; has received unconditional research grants from Biogen, Novartis and Teva. CM has received honoraria for lectures and advisory boards from Biogen, Merck, Novartis and SanofiAventis.

EP1599

Effect of RAM589.555 on viability, proliferation and expression of brain derived neurotrophic factor of primary mouse microglia and astrocytes in vitro

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Background: Targeting of RNA Polymerase-1 (POL1) machinery is a new strategy for suppression of multiple sclerosis (MS) relapse activity. Oral administration of POL1 inhibitor, RAM-589.555 ameliorates PLP-induced experimental autoimmune encephalomyelitis (EAE) by suppression of activated autoreactive lymphocytes. RAM-589.555 can cross the blood brain barrier and access the central nervous system (CNS). However, its immunomodulatory effects on CNS-resident glial cells have not yet been elucidated.

Objectives: To assess whether RAM-589.555 can modulate microglia and astrocytes.

Methods: $CD11^+$ microglia and $GLAST^+$ astrocytes were isolated from mouse pups, cultured according to Miltenyi Biotec protocol and activated with 100 ng/ml lipopolysaccharide (LPS) and tumor necrosis factor a (TNFa), with various concentrations of RAM-589.555 for 48 hrs. Viability and proliferation were examined by XTT and BrdU assays, respectively. Brain derived neurotrophic factor (BDNF) was measured in supernatants by ELISA and the leading marker of POL1 pathway, pre-ribosomal RNA (pre-rRNA) was tested by RT-PCR.

Results: Viability and proliferation of LPS-activated microglia was not affected at 25-200 nM of RAM589.555 while significantly reduced at 400 nM by 70% and 45% ($p< 0.05$), respectively. Viability and proliferation of TNFa-activated astrocytes were not affected by RAM589.555. Pre-rRNA expression decreased gradually with elevated concentrations of RAM589.555 both in microglia and astrocytes. RAM589.555 did not alter the levels of secreted BDNF by microglia and by astrocytes (6.7±0.8 and 11.8±2.0 pg/ml in un-treated cultures vs. 9±0.7-11±1.9 and 11.6±1.6-14.3±1.8 pg/ml with 25-400 nM RAM589.555 in microglia and astrocytes, respectively; $p>0.05$).

Conclusions: RAM589.555 is non-detrimental neither for astrocytes nor in 25-200 nM for microglia while highest RAM589.555 dose impairs the microglial viability and proliferation, probably due to higher proliferation rate of microglia. Notably, the neuroprotective potential of microglia and astrocytes is not impaired by RAM589.555.

Disclosure

RZF: nothing to disclose
MG: nothing to disclose
AA:nothing to disclose

EP1600

Evaluation of efficacy of glatiramer acetate treatment for multiple sclerosis in Japan

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Introduction: Glatiramer acetate (GA) has been established as a first-line therapy in multiple sclerosis (MS) for more than 20 years in Western countries. In contrast, in Japan, interferon beta (IFN-β) has been the only disease-modifying drug (DMD) for MS for over 10 years. Later, fingolimod and natalizmab, second-line therapies, were introduced prior to GA. GA became available only 2 years ago. It is thus very important to evaluate the efficacy of GA as a therapeutic for MS patients in Japan.

Objective: To evaluate the effectiveness and usefulness of GA in MS patients in Japan.

Methods: We conducted a retrospective evaluation of the clinical background, clinical course, and side effect profile of GA in patients with MS. GA was administered between December 2015

and February 2018 in our hospital. We observed their clinical course until February 2018.
Results: One hundred and one patients with MS (35 men, 66 women) received GA treatment. Mean Expanded Disability Status Scale at the introduction of GA was 3.5, and the mean period from the onset of MS was 9.2 years. Other DMDs were used before the administration of GA in 57 cases, with 44 and 8 patients receiving one and two types of DMDs, respectively. Five patients received GA after receiving IFN-β, fingolimod, and natalizmab. GA treatment has been continued in 61% of the 101 patients and stopped in 39%. Although 91 (90%) of the 101 patients treated with GA had adverse events (AEs) upon administration of the drug, only 8 patients stopped GA treatment because of AEs. In 46 patients who continued GA for more than 1 year, the annualized relapse rate before GA administration was 0.76, and that after GA administration was 0.37, indicating that GA suppressed recurrence with a significance of $p < 0.01$. GA was effective in cases where patients were IFN-β-non-responders or in those where other DMDs were discontinued due to side effects. In addition, in certain cases, a stable clinical course was obtained after GA administration, even in those that failed to achieve a satisfactory outcome after treatment with IFN-β, fingolimod, and natalizmab.
Conclusion: GA is a promising treatment of choice for Japanese patients with MS.

Disclosure

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EP1601

Disease modifying treatments (DMTs) in Germany - changes in treatment patterns

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Background: The German MS-Register, initiated in 2001 by the German MS society (DMSG), has undergone a major technical revision between 2014 and 2016. Detailed information on disease-modifying drug treatment for multiple periods per patient is now collected.
Objective: To provide insights how the availability of new treatment options changed treatment patterns.
Methods: For a subset of patients (relapsing-remitting MS, receiving DMT treatment in their last visit, detailed information on DMT available, N=4,239) historical and current DMTs where exported from the database. Patients were attributed to one of the following three groups according to DMT starting date: 1) before 2006 [N=794], 2) after 2006 but before 2011 [N=1,482] and 3) beginning in 2011 [N=1,963]. The dates where chosen based on the emergence of major new treatment options after market authorization.
Results: For the 1st group the most frequently used initial DMTs were interferons (IFN) (76.9%), followed by glatirameracetate (GLAT) (15.9%), azathioprine (AZA) (3.9%) and others (3.1%). Secondary treatment option were mostly (other) IFN (28.2%) followed by GLAT (13.6%), natalizumab (NAT) (10.7%), fingolimod (FYD) (7.5%) and others. 25% patients with initial DMT before 2006 are either still on the initial DMT or have discontinued the treatment.
In the 2nd group initial DMTs were still primarily IFN (67.2%) and GLAT (24.1%). NAT was used as first line treatment in 4.4% of patients. Secondary treatments for the 2nd group were mostly IFNs (22.7%) followed by FYD (12.2%), GLAT (11.9%) and NAT (11.4%). 24.9% are either still on the initial DMT or have discontinued the treatment.
In the 3rd group initial DMTs were again mostly IFNs (68.7%) followed by GLAT (22.8%) and NAT (3.4%). Secondary treatment option were in the majority of cases IFNs (21.8%) followed by FYD (11.5%), GLAT (10.9%), NAT (10.1%) and dimethyl fumarate (DMF) (6.2%). 28.7% of the patients in this group are either still on the initial DMT or have discontinued the treatment.
Conclusion: The availability of new treatment options significantly changed the prescription patterns in Germany. Our analysis showed that in line with the guidelines most patients are initially treated with IFN or GLAT. Depending on the duration since initial DMT start secondary DMTs differed quite a lot. Interestingly, throughout all three groups, a substantial proportion of patients (approximately 25%) did not switch treatment.

Disclosure

- *Peter Flachenecker* has received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen, Genzyme, Merck-Serono, Novartis, Roche and Teva. He has participated in pharmaceutical company sponsored trials by

Almirall, Biogen Idec and Novartis. None resulted in a conflict of interest.

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- *Judith Haas* has received compensation from Almirall, Allergan, Biogen, Bayer, HOFFMANN La Roche, Merck, Novartis, Octapharma and Teva.
- *Christoph Kleinschnitz* has received personal compensations for giving lectures and attending advisory boards from Biogen, Merck Serono, Bayer, Teva, Novartis, Medday, Mylan, Genzyme, Almirall, and Roche.
- *Dieter Pöhlau* received institutional research grants and personal honoraria as speaker from Almirall, Biogen Idec, Bayer, Genzyme, Merck Serono, Novartis, Sanofi and TEVA.
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- *Uwe K. Zettl* received institutional research grants and personal honoraria as speaker from Almirall, Biogen Idec, Bayer, Merck Serono, Novartis, Roche, Sanofi and TEVA.
- *Kerstin Eichstädt*, *Firas Fneish*, *Otto Rienhoff* and *Alexander Stahmann* have nothing to disclose.

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EP1602

Disease-modifying therapy of paediatric onset multiple sclerosis. A nationwide Danish cohort study

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Introduction: Paediatric onset multiple sclerosis (POMS) is rarer than adult-onset disease, and can represent challenges in the diagnosis and treatment.

Aims: The aim of the study was to describe the cohort of persons with disease onset before the age of 18 and to characterize the treatment of POMS in Denmark since 1996, when disease-modifying therapy (DMT) became available, until data were sourced in February 2018.

Methods: The complete cohort of 134 POMS patients treated with a DMT before the age of 18 years was extracted from the nationwide Danish Multiple Sclerosis Registry and followed until the age of 25 years. Baseline characteristics were tested in a multivariate regression analysis to predict annualized relapse rate (ARR); and in a Cox proportional hazard model to predict time to confirmed Expanded Disability Status Scale (EDSS) score worsening and improvement.

Results: Persons with POMS started their first DMT at 16.0±1.8 years and were followed for 6.4±2.9 years. In total, 100 patients (75%) switched to another DMT during follow-up, of whom 55 escalated to a second line therapy. Only 29 (22%) persons with POMS continued on their first DMT, with mean treatment duration of 71.2 months (range 7.4-198.6).

ARR was reduced from 1.8±1.1 prior to start of first DMT to 0.27±0.3 during the whole follow-up period. Males had a significantly lower ARR during follow-up compared to females (0.12 (95% confidence interval (CI): 0.073-0.19) vs. 0.37 (95% CI: 0.29-0.46), p=< .0001). Disease duration at treatment start of < 2 years was associated with lower ARR compared to ≥ years (0.16 (95% CI: 0.12-0.21) vs. 0.28 (95% CI: 0.19-0.40), p=0.0063). Relapse-free survival on first DMT was significantly lower among females than males (p=0.020). Risk of confirmed EDSS worsening among patients with an EDSS baseline ≥2 was decreased with 60% compared to patients with an EDSS baseline of < 2 (HR=0.40, 95% CI: 0.20-0.79). The chance of EDSS improvement was nearly 2-fold increased among females compared to males (HR=1.87 (95%CI: 0.94-3.74)), and an EDSS baseline ≥ 2 was associated with a 3-fold hazard of improvement (HR=3.14 (95% CI: 1.72-5.73)).

Conclusions: Predictors of disease activity on DMT were sex, disease duration and EDSS at treatment start.

Disclosure

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Morten Blinkenberg: has served on scientific advisory boards for Genzyme, Roche, Biogen Idec, Merck Serono, Novartis and Teva; has received speaker honoraria from Genzyme, Biogen Idec, Merck Serono, Bayer Schering, Novartis, Teva and Roche; has received consulting honoraria from the Danish Multiple Sclerosis Society, Biogen, Teva, Biogen Idec, and Merck Serono; has received funding for travel from Genzyme, Roche, Biogen Idec and Merck Serono.

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Per Soelberg Sørensen: Sorensen PS. has received personal compensation for serving on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; and has received speaker honoraria from Biogen, Merck Serono, Teva, Sanofi-Aventis, Genzyme, and Novartis.

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EP1603

Skin warts during fingolimod treatment in patients with multiple sclerosis

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Background: Fingolimod is associated with different infections including lower respiratory tract, herpes virus, cryptococcal meningitis, histoplasmosis, progressive multifocal leukoencephalopathy, atypical mycobacterial infections, Kaposi sarcoma and reactivation of hepatitis C. However, to the best of our knowledge, skin wart infections with fingolimod have not been previously reported.
Objectives: To describe five cases of skin warts in MS patients treated with fingolimod at the American University of Beirut Medical center (AUBMC) MS Center (MSC).
Methods: We reviewed all MS patients treated with fingolimod at our MSC and identified patients who developed skin warts during treatment. We also reviewed a control group of patients treated with different interferons matched for age and sex.
Results: Of 159 patients treated with fingolimod at our MSC, 5 (3%) developed skin warts. In 159 patients treated with different interferons and matched for age and sex, no cases of skin warts could be detected.
Case 1: A 32 year old woman with relapsing-remitting multiple sclerosis (RRMS) was started on fingolimod in January 2012. In July 2016, she developed warts in her genital area, diagnosed by a dermatologist as condyloma acuminatum, a wart-like lesion caused by human papilloma virus (HPV). This was confirmed by an HPV positive pap test. She was shifted a month later to dimethyl fumarate. The genital warts resolved completely within 2 months of discontinuing fingolimod.
Case 2: This 34 year old woman with RRMS was shifted to fingolimod in August 2016. Seven months later, she developed genital warts which recurred despite treatment. Pap test was positive for HPV 52 (high oncogenic risk) as well as HPV 6 and HPV 61 (lower oncogenic risk). Fingolimod was discontinued and the lesions resolved completely within a month.
Case 3: A 38 year old female with RRMS was started on fingolimod in June 2015. Few months after starting fingolimod, she developed warts over her nose. Her dermatologist resected the lesions twice and she was kept on fingolimod.
Conclusions: In conclusion, we report five patients who developed skin warts during fingolimod therapy, especially HPV-related, for an overall incidence of 3%. No warts were reported in a control group of patients treated with different interferons and matched for age and sex. Larger cohorts are needed to confirm this proposed higher susceptibility of fingolimod-treated patients to HPV infections.

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EP1604

A new place for mitoxantrone in the treatment of multiple sclerosis

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Background: Mitoxantrone (MTX) can be used in the treatment of various clinical stages of multiple sclerosis (MS). In 2000, MTX was approved by the US Food and Drug Administration for the treatment of aggressive relapsing - remitting (RRMS), secondary progressive (SPMS) and progressive-relapsing MS. MTX still remains the only agent for the treatment of both RRMS and SPMS. A difficult challenge is to indicate a subgroup of MS patients who are on the borderline of RRMS and SPMS in everyday clinical practice. The average delay in the diagnosis of SPMS is about 3 years, and the beginning of this MS variant is most likely among patients who achieved 4 points in the Expanded Disability Status Scale (EDSS). In fact, some patients with RRMS and this degree of disability have already experienced transition to SPMS.
Objective: To evaluate the efficacy of MTX on disability progression in MS patients, with particular distinction of individuals from the borderline of RRMS and SPMS.
Methods: We conduct a retrospective assessment of 100 Caucasian MS patients treated with cyclical intravenous MTX infusions at a dose of 12 mg /m². All patients underwent a clinical neurological examination during every cycle of treatment. Treatment efficacy was evaluated by comparing EDSS score between the baseline and the end of MTX therapy.
Results: The study group consist of 64 women and 36 men in mean age of 44.3 ±10.8 years. The 36 patients were distributed into RRMS, 36 into SPMS and 28 into PPMS with respect to disease course. The mean disease duration was 9,5 ±7,1 years. The mean time to transition from RRMS to SPMS was 12.1 ±6.4 years. The mean time of MTX treatment was 1,9 ±0,6 year. The mean number cycles of MTX infusion was 6,8 ±1,97 and the median total drug dose was 140 mg. We observed a decrease in the median EDSS score from 4.0 at baseline to 3.5 at the end of MTX infusion in RRMS subgroup and increase from 4.5 to 5.25 in PPMS subgroup. In the subgroup of patients with SPMS, the median EDSS score at baseline was 5.0 and remained stable during the treatment period. The median time to improve on the EDSS scale was 3 months. Among patients with confirmed disability progression ≥1.0 EDSS point, there was no RRMS patient, 8 patients had PPMS and the remaining 2 had SPMS (p=0,0004).
Conclusion: Apart from approved indications, mitoxantrone should be considered for the treatment of MS patients who are on the borderline of RRMS and SPMS.

Disclosure

Nothing to disclose.

EP1605

Teri-CARE study design and baseline characteristics of the full study population: assessing changes in quality of life in teriflunomide-treated patients

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Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing forms of MS. The Teri-CARE study will investigate quality of life (QoL) in patients with relapsing remitting MS (RRMS) treated with teriflunomide 14 mg in real-world clinical practice in Spain.
Objective: To describe the study design of Teri-CARE and report baseline patient characteristics for the full study population.
Methods: Teri-CARE is an ongoing prospective, observational, non-interventional study conducted at 48 hospitals in Spain. Eligible patients were 18-65 years of age, had RRMS, were treated with teriflunomide 14 mg for ≤4 weeks before enrolment, and had no relapse within 30 days before study entry. Clinic visits are expected to take place at baseline and every 6 months thereafter for up to 2 years. The primary endpoint is measuring the change in QoL over treatment time, measured using the Multiple Sclerosis Impact Scale-29 (MSIS-29). Secondary endpoints include measuring patient-reported outcomes (fatigue, depression, health-related productivity, urinary disorders, health resource utilisation, and treatment satisfaction), efficacy outcomes (annualised relapse rate, disability evaluation using the Expanded Disability Status Scale [EDSS], and MRI lesion analysis), treatment adherence, resource use, employment status, and safety.
Results: A total of 327 patients have been enrolled, 230 (70%) are female, with a mean age of 43.1 years (standard deviation [SD] = 10.4). The mean (SD) time since first diagnosis of MS is 7.1 (7.2) years and mean (SD) time since most recent relapse onset is 3.5 (4.3) years. The mean (SD)/median (range) baseline EDSS score is 1.7 (1.5)/1.5 (0 to 8.0). A total of 93 patients (28%) had T1 Gd+ lesions at baseline and 208 (64%) had received at least one prior disease modifying therapy.
Conclusions: Teri-CARE will provide valuable information on QoL outcomes in teriflunomide-treated patients with RRMS in the real-world setting in Spain.

Disclosure

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EP1606

Teriflunomide reduces spontaneous lymphoproliferation of peripheral blood mononuclear cells from patients with human T-lymphotropic virus (HTLV)-1-associated myelopathy/tropical spastic paraparesis

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Background: Human T-lymphotropic virus (HTLV)-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) is a rare chronic progressive myelopathy with no approved therapies. Peripheral blood mononuclear cells (PBMCs) from patients with HAM/TSP demonstrate spontaneous lymphoproliferation in short-term culture without exogenous stimulators.
Objective: To explore whether teriflunomide, a dihydroorotate dehydrogenase inhibitor that reduces the proliferation of activated lymphocytes and is approved for the treatment of relapsing forms of MS, can reduce spontaneous proliferation of PBMCs from patients with HAM/TSP ex vivo.
Methods: PBMCs from patients with HAM/TSP were grown in culture with 0, 25, 50, or 100 μM teriflunomide. Lymphocyte proliferation was measured at Days 3 to 5 using tritiated thymidine incorporation and carboxyfluorescein diacetate succinimidyl ester dye dilution assays. Digital droplet polymerase chain reaction was used to measure HTLV-1 proviral load and *tax* (HTLV-1 transcription factor) messenger RNA (mRNA) expression before and after PBMC culture, with and without teriflunomide.
Results: In culture, teriflunomide did not affect cell viability. A dose-dependent reduction in spontaneous proliferation of PBMCs (specifically CD8+ T cells) was observed with 25 (30% inhibition), 50 (45% inhibition), and 100 μM (80% inhibition) of teriflunomide. There was no change in HTLV-1 proviral load or *tax* mRNA expression in these short-term cultures.
Conclusions: Ex vivo, teriflunomide reduced spontaneous lymphoproliferation of PBMCs, specifically CD8+ T cells, from patients with HAM/TSP, without changing proviral load or *tax* mRNA expression. These results suggest that teriflunomide inhibits abnormal T-cell proliferation associated with HTLV-1 infection. Further studies are needed to assess possible long-term effects of teriflunomide in HTLV-1-associated neurological disease.

Disclosure

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EP1607

Anti-inflammatory responses by oral administration of iNKT cell ligand OCH in healthy human and multiple sclerosis: results of investigator-initiated, first-in-human phase 1 study

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Although current disease-modifying drugs for Multiple sclerosis (MS) significantly improved prognosis of the patients, there are several problems to be solved including limited efficacy, risk of severe infectious diseases, injection related side effects etc. Orally available more effective and safer drugs are awaited. Diminished regulatory component of the immune system are reported in MS. We previously reported that oral administration of a sphingosine-truncated analog of α-galactosylceramide, OCH, selectively induced IL-4 production from iNKT cells, thereby preventing the development of experimental autoimmune encephalomyelitis (EAE) (Nature 2001). To develop OCH as a therapeutic agent for MS, we have completed a first-in-human phase 1 study of OCH in 15 healthy subjects (HS) and 9 patients with relapsing remitting MS. To assess the effect of OCH *in vivo*, flow cytometer and DNA microarray analyses were conducted for peripheral blood samples obtained before and after oral OCH treatment. First of all, we have confirmed tolerability of OCH in both HS and MS patients. Pharmacokinetics/pharmacodynamics study revealed that absorption of OCH from gut is better in human than primates and rodents. We have observed several immune-related changes in the blood of the HS and MS: (i) a significant increase of Treg [CD45RA-Foxp3+ effector/activated regulatory T cells] at 6 h, (ii) upregulation of immunoregulatory genes (MAFB and IL4I1) at 6 and 24 h, (iii) downregulation of immune-activating genes (NR4A2, FOS, and FOSB) at 6 and 24 h, and (iv) downregulation of GZMB and killer cell immunoglobulin-like receptors. The results are promising and we are now in preparation for a phase 2 study.

Disclosure

W Sato received speaker honoraria from Takeda Pharmaceutical Co., Ltd. D Noto reports no disclosures. M. Araki received honoraria from Chugai Pharmaceutical Co., Ltd.; Novartis Pharmaceuticals; Biogen Japan; Bayer Holding Ltd; Takeda Pharmaceuti-cal Co., Ltd. T. Okamoto received funding for a clinical trial from Takeda Pharmaceutical Co., Ltd. Y. Lin received speaker honoraria from Asahi Kuraray Medical, Ltd. T. R Saga, Y Hirakawa, H Yamaguchi report no disclosures. T Yamamura served on the scientific advisory board for Biogen Japan, Chugai Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd and received travel funding and/or speaker honoraria from Mitsubishi Tanabe Pharma, Novartis, Nihon, Santen, Abbott Japan/Eisai, Biogen Japan, Dainippon Sumitomo, Bayer Holding, and Astellas Pharma Inc., and Takeda Pharmaceutical Co., Ltd., and received research support from Ono, Chugai, Teva, Mitsubishi Tanabe Pharma, Asahi Kuraray Medical, and the Ministry of Health, Labor, and Welfare of Japan.

EP1608

Neuroblastoma cell line and lymphocytes talk for cladribine influenced apoptosis and inflammation pathways in multiple sclerosis (MS): an "*in vitro*" study

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Background: MS is characterized by autoreactive lymphocytes and inflammation in the Central Nervous System (CNS). In this context, many therapies act to defeat the mechanism but few of them are able to cross Blood Brain Barrier (BBB). Cladribine (CdA) is a purine analogue molecule able to pass BBB, but no data available about its effects in CNS and on neurons.
Aim: We evaluated apoptotic and inflammation pathway in Healthy Donors (HDs) and MS patients lymphocytes and neuroblastoma cell line (SHSY5Y) co-cultures with and without CdA stimulation "in vitro", in order to study neurons response to therapy and to autoreactive cells.
Methods: 20 HDs (43,6±20,1; 10F) and 20 naive MS pts (45,5±21,4; 11F) age and sex matched were enrolled in our study. Co-cultures were assessed and stimulated with 20 nM of CdA for many time points (4 and 24 hours); co-cultures control (no CdA) were considered too.
Flow cytometric analysis was used to assess, at first, apoptosis on both cellular types.
Cellular lysates were analyzed for pro and anti-apoptotic molecules (Bax; Smac/DIABLO; Bcl-2; Cyt-c) in Western Blot. Co-culture supernatants (stimulated or not with CdA) were examinated for pro and anti-inflammatory cytokines (OPN; IL-6; TNF-□; IFN-γ; IL-4; IL-23) with ELISA test.
Results: In vitro experiments showed an increase of MS lymphocytes apoptosis during CdA treatment, if compared to basal cultures ($p \leq 0{,}0025$) and related to HDs ($p \leq 0{,}001$). Anti-apoptotic proteins showed higher expression in MS if compared to HDs ($p \leq 0{,}0001$) and it was reduced during treatment ($p \leq 0{,}0001$). The same was showed in HDs cells. Anti-inflammatory proteins were increased during CdA treatment in MS lymphocytes co-cultures supernatants if compared to basal ($p \leq 0{,}001$) while pro-inflammatory molecules were reduced ($p \leq 0{,}0005$). Neurons, alone or in co-cultures, were not affected by therapy for apoptotic pattern, since pro-apoptotic proteins were not involved.
Conclusions: These data suggest that CdA likely reduces the viability of peripheral and central lymphocytes by apoptosis. No apoptotic signal in neurons was detected.

Disclosure

Prof. Maria Trojano has served on scientific Advisory Boards for Biogen, Novartis, Roche and Genzyme; has received speaker honoraria from Biogen Idec, Sanofi-Aventis, Merck Serono, Teva,

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Dr Paolicelli has received honoraria for consultancy and/or speaking from Biogen Idec, Merck-Serono, Sanofi-Aventis, TEVA, Bayer-Schering, Novartis and Genzyme.
MR, MM, CDG, CP, AF, AV have nothing to disclose.

EP1609

Dimethyl fumarate treatment differentially impairs frequency and function of activated, mature B cells

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Introduction: Dimethyl fumarate (DMF) is commonly used for treatment of multiple sclerosis (MS). Its effects on the peripheral immune system and especially on B lymphocytes are not entirely understood. B cells are increasingly recognized to play a crucial role in the pathogenesis of MS though, acting both as antigen-presenting cells (APC) for the activation of T cells as well as by provision of immune cell-polarizing cytokines. Hence, we investigated whether and how DMF modulates B cell phenotype and function in treatment of MS.
Methods: We analyzed peripheral blood mononuclear cells from 30 DMF- and 31 non-DMF treated control patients by flow cytometry; six individual patients were analyzed before and 6 months after DMF treatment initiation. Frequency of T cells, monocytes and B cells was assessed. B cell subsets were evaluated for surface expression of CD19, CD20, CD24, CD27 and CD38, identifying various maturation stages of B cells. We determined expression of activation markers (CD25, CD69, CD95), molecules involved in antigen presentation (CD40, CD80, CD86, MHC-II) and the production of cytokines (IL-6, IL-10, TNF) by monocytes and B cells.
Results: As reported previously, the frequency of $CD8^+$ T cells was decreased in DMF-treated patients, with a compensatory increase in $CD4^+$ T cells. The frequency of monocytes was elevated with a yet diminished production of pro-inflammatory cytokines. While the frequency of B cells was unchanged, we observed a lower frequency of mature, activated and memory B cells as well as plasmablasts. Furthermore, we observed a reduced production of pro-inflammatory TNF and IL-6 as well as a lower expression of activation markers. Conversely, we determined an increased frequency of naïve and early transitional B cells. DMF reduced the expression of CD40, CD80 and CD86, whereas MHC-II expression was significantly upregulated upon initiation of DMF treatment.
Conclusions: Our study reveals that the compartment of B lymphocytes is substantially affected by DMF treatment, with a pronounced impairment of activated and mature B cell phenotypes. These findings are in line with the hypothesis that DMF primarily targets immune cells with a high metabolic turnover. While impairment of B cell differentiation by DMF likely translates into clinical benefit, current investigations aim to clarify how the observed increase in MHC-II expression by B cells affects their APC function.

Disclosure

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EP1610

Effect of dimethyl fumarate on the development of type-II innate immune cells and CNS-infiltration of M1 macrophages

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Dimethyl fumarate (DMF) is an oral agent for the treatment of relapsing-remitting multiple sclerosis (RRMS). The therapeutic effect of DMF has been suggested to involve neuroprotection and immunomodulation. In this study, we investigated the effect of DMF on the development of pathogenic T helper cells, type-II innate immune cells, and CNS-infiltration of pathogenic (M1) and regulatory (M2) macrophages in MOG35-55-induced experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice. DMF treatment decreased the proliferation of T cells, including MOG specific T cells, in the mesenteric lymph node (MLN) and spleen, accompanied with less differentiation of pathogenic Th17 and GM-CSF-producing Th cells. Furthermore, DMF induced a type-II innate immune response in the periphery, and significantly decreased the cell number of inflammatory macrophages (M1) and anti-inflammatory macrophages (M2) in the CNS infiltrates. The decrease in CNS-infiltrates including M1 macrophages resulted in less demyelination and axonal loss. This study suggests that DMF can promote type-II innate response and suppress the CNS-infiltration of M1 macrophages.

Disclosure

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EP1611

Peginterferon beta-1a safety and efficacy in real-life clinical setting: a prospective, multicenter follow-up study

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Introduction: Peginterferon beta-1a is a pegylated form of interferon beta, with a prolonged pharmacokinetic profile enabling more convenient, less frequent dosing than nonpegylated interferon beta therapies for MS. Its efficacy was established in the 2-year, phase III ADVANCE study. So far, there are scarce data evaluating the safety and efficacy in real world.
Objectives: The aim of this multicenter, prospective, post-marketing study was to address the safety and the efficacy of Peginterferon beta-1ain a cohort of relapsing-remitting MS (RRMS)patients.
Methods: RRMS patients referred to 8 MS Center located in Central Italy and starting peginterferon beta-1atreatment between June 2015 and March 2018 were prospectively included.
Neurological examination, EDSS assessment and magnetic resonance imaging (MRI) were performed at baseline and during follow-up visits according to the routine clinical practice.
The primary end point of the study was the proportion of patients with no evidence of disease activity (NEDA-3) at 1-year and 2-year of follow-up. The definition of disease activity entailed at least one of the following: clinical relapse, 24 weeks confirmed disability progression based on increases in EDSS, MRI evidence of new and/or enlarging T2 hyperintense lesions and/or gadolinium enhancing lesions.
Results: Out of 141 MSRR patients startingpeginterferon beta-1atreatment during the study period 36 were men (25.5%) and 105 were women (74.5%). Mean age at the start of the treatment was 42.1±9.8 years. Mean follow-up duration was 21.2±8.3 months (range, 1-35 months). At the start of peginterferon beta-1a,35 patients were naïve and 106 switched by another treatment.
Out of 137 patients with safety available data, adverse events (AEs) were reported in 102 patients (74.5%). The most commonly reported AEs over 2 years were influenza-like illness in 86 (62.8%) patients and injection site reactions in 53 (38.7%). No serious AEs were reported.
Cumulative proportion of patients free from any disease activity was 72.3% (95%CI: 66.3-78.9)at 1-year follow-up and 68.8% (95%CI: 61.4-75.7)at 2-year follow-up. Cumulative proportion of patients free from any disease activity was lower in naïve patients (60.0%; (95%CI: 56.2-67.4)than in patients switched by another treatment (76.4%; (95%CI: 71.3-81.2)
Conclusions: Our post-marketing experience provides further evidence of safety and efficacy of peginterferon beta-1a.

Disclosure

RT has served on advisory boards and/or received honoraria for speaking or consultation fees from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Teva. Principal investigator in clinical trials for Biogen, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva,
GDL nothing to disclose.
MD has served on advisory boards and/or received honoraria for speaking or consultation fees from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Teva.
BA nothing to disclose.
GC nothing to disclose .
MM nothing to disclose.
MA nothing to disclose.
GD nothing to disclose.
CDM nothing to disclose.
DF nothing to disclose.
RC nothing to disclose.
MR nothing to disclose.
CT nothing to disclose.
MG nothing to disclose.
MDG nothing to disclose.
PC nothing to disclose.
LP has served on advisory boards and/or received honoraria for speaking or consultation fees from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Teva.
CM nothing to disclose.

EP1612

Analysis of therapeutic regimens and treatment switch patterns in specific clinical forms of multiple sclerosis using big data

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Objective: Drug switching in MS patients due to tolerability issues or lack of efficacy is a common finding. The objective of this research is to study the distribution trends of the approved disease modifying therapies (DMTs) and treatment switch patterns amongst the MS population in the United States.
Methods: Data-Driven metrics proprietary to IQVIA, spanning over a period of 5 years (2013-2017), were used to inform this research: Medical (DX), Pharmacy (RX) Claims data, and Primary Market Research Data. These data were leveraged to determine the drug consumption rate for all patients by refill rate of prescription and CPT codes. A tolerance of 5 days, as treatment holiday, was considered, for patients to refill a prescription. This information, enabled indicating treatment paths for multiple drugs.
Results: A total of 420,000 MS patients were considered for this analysis. Of the total patients diagnosed with MS, 76,3% received

a DMT, while less than a quarter were untreated, mainly patients with progressive forms of MS. The proportion of patients switching to another DMT within the first year of initiating therapy is estimated, not to exceed 21%. The average switch rates increase up to 32.6% of the patients, 3 years after starting therapy. The switch rates were higher in patients with injectable treatments (highest for copaxone) compared to orals (lowest for fingolimod). The lowest treatment switch was observed in patients with clinically isolated syndromes (CIS) at around 11% of patients switching to a new DMT.

Conclusions: Drug switches are not uncommon in MS patients for multiple reasons. Switching to a new DMT remains relatively low after the first year, attaining a third of the patients after 3 years of therapy. Lowest switch rates were observed in patients treated with orals compared to injectables. CIS patients tend to switch to new DMTs less frequently compared to other clinical forms.

Disclosure

All authors are full time employess of IQVIA, NO other disclosures.

EP1613

Pharmacokinetics and pharmacodynamics of PEGylated interferon beta-1a in patients with relapsing-remitting multiple sclerosis in the randomized double-blind placebo-controlled study

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Introduction: Interferon beta-1a **(**IFN-β1a) medicines are widely used as the first-line therapy in relapsing-remitting multiple sclerosis (RRMS). PEGylated interferon-beta-1a (PEG-IFN-β1a) is expected to have better efficacy, decreased frequency of administrations and increased patient compliance.

Airms: To evaluate pharmacokinetics (PK) and pharmacodynamics (PD) of the original PEG-IFN-β1a medicine after intramuscular administrations in patients with RRMS in the double-blind placebo-controlled study.

Methods: During the first year, all patients (n=399) will be randomized (2:2:2:1) and administered with either PEG-IFN-β1a 180 μg or PEG-IFN-β1a 240 μg or Avonex® 30 μg or placebo. The PK/PD analysis was performed using blood samples obtained during the first 12 weeks of treatment of 70 patients.

Results: Intramuscular administration of PEG-IFN-β1a in a single dose of 180 μg or 240 μg provides approximately 30 and 40 times higher exposure ($AUC_{0\text{-}168}$ and $AUC_{0\text{-}336}$) and approximately 25-40 times higher C_{max} values compared to Avonex® 30 μg. The peak serum concentrations were reached after 48 hours in PEG-IFN-β1a groups and after 12 hours ($p<0.05$, test Mann-Whithney) in Avonex® 30 μg group. We observed a monophasic decline and a median half-life of 70, 82 and 53 hours in PEG-IFN-β1a 180 μg, PEG-IFN-β1a 240 μg and Avonex® 30 μg, respectively. No accumulation was observed. Elevated neopterin levels were sustained for 7-14 days in PEG-IFN-β1a arms, with the statistically significant increase in $AUC_{0\text{-}168}$ and $AUC_{0\text{-}336}$ in PEG-IFN-β1a groups over Avonex® ($p<0.05$, test Mann-Whithney).

Conclusion: These data confirm the statistically significant difference in PK and PD parameters of PEGylated and non-PEGylated interferon beta-1a in patients with RRMS. As expected, PEGylation of IFN-β1a can improve the dosing regimen reducing the frequency of administration compared to Avonex®. Morever the higher amplitude of neopterin elevation in PEG-IFN-β1a groups supports higher PD effects and, potentially, better efficacy of the pegylated product.

Disclosure

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A. Zinkina-Orikhan and Y. Linkova are employees for BIOCAD Company.

EP1614

Experience with Secukinumab in multiple sclerosis

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Introduction: Secukinumab is a monoclonal antibody fully human anti-human interleukin-17A (IL-17A) that neutralizes the bioactivity of human IL-17A. Secukinumab is used in autoinmune disseases like psoriasis and rheumatoid arthritis. There is evidence on the role of IL17 in the pathogenesis of multiple sclerosis, and

there is clinical evidence of safe, well-tolerated, and significantly reduced MRI lesion activity through a phase II study
Objectives: To describe two clinical cases of patients with Multiple Sclerosis treated with Secukinumab
Metarial and methods: We present two cases of patients with Multiple Sclerosis treated with Secukinumab and affected by other autoimmune pathologies. The treatment decision is made through multidisciplinary management.
Results: Patient1. A 22-years-old man with B27 positive seronegative polyarthritis who develops an aggressive multiple sclerosis after the use of anti-TNF. The patient, who was treated for a year with Tozilizumab and Metotrexate with poor response in both diseases, is currently free of neurological and rheumatic disease after a 3 years treatment with Secukinumab.
Patient 2. A 23-years-old woman affected by undifferentiated spondyloarthropathy HLAB27 negative with insufficient response to Salazopyrin, Motrexate and Golimumab, who starts aggressive Multiple Sclerosis and who has been stable after a 8 months treatment with Secukinumab.
None of the patients presented adverse side effects to the treatment.
Conclusions: Secukinumab might be a good therapeutic alternative in multiple sclerosis patients with rheumatological comorbidities, and allows effective management without adverse effects and without the need for concomitant immunosuppression. Multidisciplinary management is essential in these cases

Disclosure

Virginia Meca-Lallana disclose neither conflict of interest in the elaboration of this abstract

EP1615

Immunomodulatory molecules on plasmacytoid dendritic cell is associated with decreased neurofilament light in the cerebrospinal fluid of patients with multiple sclerosis treated with natalizumab

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Background: Natalizumab (NTZ) is a humanized monoclonal antibody anti-leukocyte α4 subunit of the integrins α4β1 and α4β7, which are expressed in the cell membranes of activated T- and B-lymphocytes. Consequently, the administration of NTZ inhibits the transmigration of auto-reactive lymphocytes into the central nervous system in patients with multiple sclerosis (MS). Since this antibody remains in the peripheral blood for days or months, studies demonstrating its possible immunomodulatory effects are necessary.
Objectives: To investigate whether NTZ treatment alters the immunomodulatory molecules on the surface of plasmacytoid dendritic cells and modifies the levels of neurofilaments in the CSF of MS patients.
Methods: Blood samples from patients with multiple sclerosis under NTZ treatment and from healthy donors were collected. CSF samples were obtained from patients under NTZ therapy. Serum and PBMCs were separated to perform flow cytometry and ELISA techniques.
Results: Plasmacytoid dendritic cells from patients treated with NTZ expressed increased levels of HLA-G, PD-L1 (CD274) and CCR7 and normal levels of HLA-DR in the peripheral blood, and pDCs expressing these molecules were also present in the cerebrospinal fluid. Moreover, the level of neurofilament light (Nfl) was normal in the CSF of these MS patients compared to those of healthy controls and untreated MS patients.
Conclusion: Our results demonstrated that, in addition to the property of inhibiting the migration of lymphocytes into the central nervous system, circulating NTZ exerts an important down-regulatory effect on inflammatory responses within the CNS, which is associated with decreased neurodegeneration, as demonstrated by normal levels of Nfl.

Disclosure

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EP1616

A retrospective observational study of rituximab in multiple sclerosis patients in Cyprus

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Background: Rituximab, a chimeric monoclonal anti-CD20 B-cell depleting agent has shown promising results in the treatment of multiple sclerosis (MS). Since the publication of the first randomized controlled trials in patients with Relapsing-Remitting Multiple Sclerosis (RRMS) and Primary-Progressive Multiple Sclerosis (PPMS) it has been used off-label in heterogeneous cohorts of MS patients.
Objective: To evaluate the efficacy and safety of rituximab given off-label to Cypriot patients with MS.
Methods: Clinical data for 30 MS patients (16 male, 14 female) treated with off-label rituximab at the Cyprus Institute of Neurology and Genetics were retrospectively collected and reviewed. Outcome data (relapse rate and EDSS progression) as well as adverse effects were recorded.
Results: Out of the 30 patients included in this study 10 were diagnosed with RRMS (mean age at diagnosis 23.8±6.3), 17 with Secondary Progressive MS (32.2±5.6) and 3 with PPMS (42±27.7). The median (range) EDSS pre-treatment was 4.5 (2.5-7.5), 6 (3.5-8) and 6(5-8) for RRMS, SPMS and PPMS patients respectively. Before rituximab initiation, 2 patients were treatment naive, 7 were

treated with natalizumab, 6 with interferons, 11 with fingolimod and 4 with other immunosuppresive therapies. Patients were treated with 500 or 1000 mg rituximab IV every 6 months following an initial dose of 2000 mg subdivided into two infusions given within a 2-week interval. Seventeen out of the thirty patients included in this study have recently commenced rituximab infusions (< 12 months) and hence have a very short follow up period. The median (range) follow up period for the remaining 12 patients is 18 (13-63) months. Only one patient with SPMS discontinued treatment due to disease progression.Rituximab infusions were generally well tolerated; there were only six grade 3 or 4 adverse events recorded, including respiratory tract infections, cytopenias and drug-induced psoriasis. Following rituximab administration, all patients with RRMS (with a follow-up period of >12 months) remained relapse-free and had a stable or slightly improved EDSS score. Patients with SPMS had a significant reduction in their relapse rate and a stabilization or slight improvement of their EDSS scores.

Conclusion: Our results are in agreement with larger retrospective studies in which it was demonstrated that rituximab was well tolerated and effective in treating RRMS and SPMS patients by reducing relapse rate and stabilizing disease.

Disclosure

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Neuroprotection and Repair

EP1617

The $S1P_5$ receptor is not down-modulated in response to selective agonists

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Novartis Pharma AG, Basel, Switzerland

Background: The sphingosine-1-phosphate (S1P) receptor subtype 5 ($S1P_5$), mainly expressed on oligodendrocytes and brain endothelial cells, influences neuronal myelination processes and integrity of the blood-brain barrier. Further, evidence suggest this receptor as a potential therapeutic target to prevent and/or reverse the progressive demyelination that causes multiple sclerosis (MS). However, it is not clear whether such pro-myelination effects are triggered by $S1P_5$ signaling or rather by $S1P_5$ down-modulation (i.e. internalisation and degradation) as seen with the $S1P_1$-mediated effects on lymphocytes.

Objective: The study assessed the ability of established $S1P_{1/5}$ agonists (fingolimod, siponimod and ozanimod) to induce down-modulation versus selective human (h) $S1P_1$ (AUY954) and $hS1P_5$ (UC-42-WP04) receptor agonists.

Methods: Chinese Hamster Ovary cells overexpressing $hS1P_1$ or $hS1P_5$ receptors were tagged at the N-terminal (extracellular). The $hS1P_1$ (Myc tag), mu-$S1P_5$ (Myc tag) or $hS1P_5$ (FLAG tag) receptors were generated using an anti-Myc/FLAG-epitope antibody and incubated for 1–3 hours with an agonist (0.0001-1 μM). Receptor internalisation was measured using a flow cytometry assay, which quantified the levels of surface expression of tagged-receptors. In this assay, a reduction in fluorescence indicated disappearance of the tagged receptor from the cell surface.

Results: Under such experimental conditions, no $S1P_5$ down-modulation was observed in response to fingolimod, siponimod or ozanimod up to 1 μM. As expected, all agonists down-modulated the $S1P_1$ receptor internalisation in a dose-dependent manner, with doses inducing mean effective concentration of 50% (EC_{50}) and 90% (EC_{90}) within the 1-5 nM range and 10-70 nM range, respectively. Moreover, no reappearance of $S1P_1$ receptor was observed within 3 hours after washout, confirming long term down-modulation. In comparison, S1P and AUY954 down-modulated the $S1P_1$ but not the $S1P_5$ receptors, whereas UC-42-WP04 had no impact on both $S1P_1$ and $S1P_5$ receptors.

Conclusion: These observations suggest that, in contrast to the $S1P_1$ receptor, the $S1P_5$ receptor is not subjected to agonist-induced down-modulation. Consequently, $S1P_5$ downstream signaling should be considered when studying the direct pro-myelination and neuroprotective effects of $S1P_{1/5}$ selective agonists, such as siponimod.

Disclosure

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EP1618

Optimising Siponimod (BAF312) oral administration for long-term experimental studies in mice

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Background: Siponimod is a selective sphingosine 1-phosphate (S1P1,5) receptor modulator under development for the treatment of multiple sclerosis (MS). It significantly reduces disability progression in secondary progressive MS patients. Exploration of its central mode of action requires long-term studies in preclinical models of progressing chronic demyelination. However, as long-term studies are often impacted by stress responses inherent to repeated treatments by daily oral gavage, alternative administration methods are warranted.

Objective: To compare dose-related siponimod blood concentrations and pharmacological efficacy achieved in mice after administration via drinking water or drug-loaded diet.

Methods: C57BL/6J mice (6-10 weeks-old, females, n=3-6/group) were either treated for 2 weeks with siponimod dosed in drinking water to achieve 0.3, 1.5 or 3 mg/kg bodyweight or were fed over 2 weeks with siponimod-loaded pellets at 0.03, 0.01, 0.003 or 0.001%. Blood samples were collected in short intervals and at termination to assess the siponimod concentrations in blood

and the lymphocyte counts (using Vet ABC™ or ADVIA™ haematology analysers).
Results: Administration of siponimod via drinking water resulted in dose-dependent siponimod blood concentrations of 0.6, 0.4 and 0.1 μM with doses of 3, 1.5 and 0.3 mg/kg body weight, respectively. However, a large time-dependency was observed and a small reduction in blood lymphocyte counts (20%) was observed in the 3 mg/kg group alone. After administration via siponimod-loaded pellets at 0.03, 0.01, 0.003 and 0.001%, siponimod blood concentrations were within the 12.5, 5.1, 1.4 and 0.5 μM range, while circulating lymphocyte counts were reduced by 81%, 56%, 50% and 39%, respectively.
Conclusions: These results suggest the use of siponimod-loaded diet as a robust alternative to daily oral gavage to achieve efficacious siponimod blood exposures in long-term mouse disease models. These, the first results in an experimental autoimmune encephalomyelitis model, confirm efficacy for siponimod-loaded diet at ≥0.003%.

Disclosure

*Michael Dietrich, Christina Hecker, Marc Bigaud, Philipp Albrecht are equally contributing first/senior authors. This study was funded by Novartis Institutes for Biomedical Research, Basel, Switzerland. Christian Beerli, Claire Moebs, Pamela Ramseier, Catherine Afatsawo, Marc Bigaud are employees of Novartis Institutes for Biomedical Research, Basel, Switzerland. Michael Dietrich reports personal fees and non-financial support from Novartis and non-financial support from Biogen. Christina Hecker: nothing to disclose. Philipp Albrecht reports personal fees, grants and non-financial support from Biogen; grants, personal fees and non-financial support from Allergan; personal fees and non-financial support from Bayer; personal fees and non-financial support from Merck; grants, personal fees and non-financial support from Merz Pharmaceuticals; grants, personal fees and non-financial support from Novartis; grants, personal fees and non-financial support from Roche; grants, personal fees and non-financial support from Teva; grants, personal fees and non-financial support from Ipsen.

EP1619

Phase 2 AFFINITY trial evaluates opicinumab in a targeted population of patients with relapsing multiple sclerosis: rationale, design and baseline characteristics

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Introduction: Opicinumab is a human monoclonal antibody against LINGO-1, a negative regulator of oligodendrocyte differentiation and axonal regeneration. Data from the phase 2 SYNERGY study identified a dose (10 mg/kg) and a subpopulation (defined by disease duration and baseline MRI characteristics) that were associated with an enhanced treatment response and thus merit further investigation.
Objectives: To present the rationale for and design of the AFFINITY study (NCT03222973) and participant baseline characteristics.
Methods: AFFINITY is a phase 2, 72-week, multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy/safety of opicinumab (intravenous 750 mg every 4 weeks) versus placebo as an add-on to disease-modifying therapies (DMTs) in a targeted population with relapsing MS. Inclusion criteria include: age 18-58 years with relapsing-remitting or secondary progressive MS; disease duration ≤20 years; Expanded Disability Status Scale (EDSS) 2.0-6.0; clinical relapse between 24 weeks-24 months or brain MRI evidence of disease activity ≤24 months; stable on interferon beta, dimethyl fumarate, or natalizumab for ≥24 weeks; and characteristics on magnetisation transfer ratio and diffusion tensor imaging-radial diffusivity suggestive of lower myelin content and more preserved tissue integrity in brain T2 lesions. The primary endpoint is the Overall Response Score, an integrated assessment of disability improvement and worsening based on the EDSS, Timed 25-Foot Walk (T25FW), and 9-Hole Peg Test (9HPT; dominant and non-dominant). Secondary endpoints include the proportion of patients with confirmed improvement in disability measures including EDSS, T25FW, 9HPT, 3-Second Paced Auditory Serial Addition Test, and Symbol Digit Modality Test.
Results: The study was started in September 2017, and enrolment is ongoing. AFFINITY is expected to enrol ~240 participants at ~150 sites in ~25 countries. Baseline demographic, disease and MRI characteristics of enrolled participants will be presented.
Conclusions: AFFINITY will further investigate the efficacy and safety of opicinumab as an add-on therapy to anti-inflammatory DMTs in a subpopulation of patients with MS (disease duration ≤20 years, lower myelin content and more preserved tissue integrity) with potentially enhanced responses to opicinumab.

Disclosure

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B. Zhu, P. Wolstencroft, K. Johnson, S. Liu, I. Chang, A. Deykin, and S. Sheikh are employees of and hold stock/stock options in Biogen.
P. A. Calabresi has received consulting fees from Biogen and Disarm Therapeutics; is associate editor of The Journal of Clinical Investigation; and has received research support/grants to his institution from Annexon Biosciences, Biogen, MedImmune, Novartis and Sanofi.
G. Giovannoni is on advisory boards for AbbVie Biotherapeutics Inc., Almirall, Atara Biotherapeutics, Biogen, Merck, Merck Serono, Novartis, Roche, Sanofi-Genzyme and Teva; has received speaker fees from AbbVie Biotherapeutics Inc., Biogen, Genzyme,

Merck, Merck Serono, Sanofi-Genzyme and Teva; is co-editor in chief of Multiple Sclerosis and Related Disorders; and has received research support unrelated to study from Biogen, Genzyme and Novartis.
R. Kapoor has received personal fees and/or travel support from Biogen, Genzyme and Roche; and is on clinical trial steering committees for Biogen.
R. Naismith has received consulting/speaker fees from Acorda, Alkermes, Biogen, EMD Serono, Genentech, Genzyme, Novartis and Teva.
H-P. Hartung has received speaker fees/travel expense reimbursement from and is on steering committees/advisory boards for Biogen, Geneuro, Genzyme, Merck, Medimmune, Novartis, Octapharma, Opexa, Receptos, Roche, Sanofi-Aventis and Teva.
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EP1620

Effect of MD1003 (high dose pharmaceutical grade biotin) on dexterity, cognitive, and quality of life measures in a cohort of patients with non-active progressive multiple sclerosis

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Background: MD1003, prescribed in France under a temporary authorization for the treatment of progressive multiple sclerosis (PMS), achieved sustained reversal of MS-related disability in some patients (pts) with a non-active form of the disease in the MS-SPI study (Tourbah et al., 2016).
Objective: To assess in a real-world setting the effectiveness of a 12-month treatment with MD1003 on dexterity, cognition, and quality of life (QOL) measures, as well as in more traditional measures (expanded disability status scale [EDSS], timed 25-foot walk test [T25FWT], in a cohort of pts with non-active PMS from one clinical Centre.
Methods: A cohort of 103 pts with non-active PMS (mean age 56 +/-9.5 yrs; median EDSS 6.5 (4-7.5); disease duration 18.8 +/-9yrs) treated with MD1003 300 mg/day were followed at Baseline, 3, 6 and 12 months. The cohort was divided into 3 groups according to baseline EDSS: group A (EDSS 4-5.5; n=16), B (EDSS 6-6.5; n=60), and C (EDSS 7-7.5; n=27). All groups were assessed for EDSS, T25FWT, 9-hole peg test (9NHPT), symbol digit modality Test (SDMT) and QOL using physical score of Multiple Sclerosis Impact Scale-29 (MSIS-29PHYS). Repeated measures analysis of variance (ANOVA) was used to analyze data. T- tests for paired samples was used for comparison 2 to 2.
Results: After 12 months of treatment, cohort showed significant improvement of dexterity, cognition and QOL ($p< 0.05$). Group A showed significant improvement in 9-HPT from Baseline to 6 ($p< 0.01$) and Baseline to 12 Months ($p< 0.001$). Group B showed significant improvement in MSIS-29PHYS and SDMT from Baseline to 3 (respectively: $p< 0.001$; $p< 0.05$), Baseline to 6 (respectively: $p< 0.001$; $p< 0.05$) and Baseline to 12 Months (respectively: $p< 0.001$; $p< 0.05$). Only the MSIS-29PHYS improved significantly from baseline to 6 Months in Group C ($p< 0.01$). After 12 months, 7/102 pts discontinued treatment because of lack of efficacy (n=6) and adverse event (n=1).
Conclusion: A 12-month MD1003 treatment for non-active PMS was well-tolerated in most pts in our cohort. At M12, improvement from baseline in cognition, QOL, and dexterity was significant in the cohort. Improvement tended to be greater for patient groups with Baseline EDSS 6-6.5. Clinical therapeutic evaluations could be adapted to disability score to detect improvement in PMS. Further research are needed to precise what kind of clinical measures could be proposed for pts with PMS.

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P Hautecoeur:
A Kwiatkowski:
B Lenne:"nothing to disclose"
MA Guyot: "nothing to disclose"
B Lenne: "nothing to disclose"

EP1621

Disability stabilization in multiple sclerosis under teriflunomide treatment

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Background: Teriflunomide is a treatment approved for relapsing Multiple Sclerosis (MS). However, data on patients with progressive forms of MS enrolled in registrative trials showed a stabilization of disability.
Objective: To evaluate the course of disability before and under treatment with teriflunomide in patients with relapsing progressive form of MS (PMS).
Methods: Among patient treated with teriflunomide at the MS Centre of San Raffaele Scientific Institute, we selected patients with PMS and at least annual clinical evaluation in the 2 years before and the 2 years after treatment start.
Results: We selected 30 patient with PMS, 73% of which presented signs of inflammatory activity in the year before treatment start. Mean age of patients was 50 years and 63% were female. Mean disease duration was 19 years and mean baseline EDSS was 5.5. In the two years before teriflunomide start mean EDSS worsened from 4.9 to 5.5. On the contrary, during teriflunomide start mean EDSS remained stable. Delta EDSS between 2 years before and baseline was significantly different from delta EDSS between baseline and 2 years after ($p=0.025$).
Conclusions: Based on evidence from registrative trials suggesting potential effect of teriflunomide on disability, we started treatment in 30 patients with PMS, in most cases presenting persistent inflammatory activity. Our data, even if obtained in a small

real-practice setting, showed a significant stabilization of EDSS, even in patients who presented worsening disability in the 2 years before treatment start.

Disclosure

F. Sangalli, M. Radaelli, L. Moiola, B. Colombo, F. Esposito report consultancy, speaking fees and/or travel expenses from Biogen, Merck Serono, Genzyme, Novartis. 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. M. Pisa and G. Dalla Costa have nothing to disclose.

EP1622

Treatment with dimethyl fumarate enhances cholinergic transmission in multiple sclerosis

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Introduction: Dimethyl fumarate (DMF) exerts antinflammatory effects in multiple sclerosis (MS) by activating the Nrf2 antioxidant pathway, which is also stimulated by acetylcholine via alpha-7 nicotinic acetylcholine receptors. In animal models, Nrf2 potentiates cholinergic synaptic transmission. Increased cholinergic tone has been associated with better prognosis in MS. Central cholinergic functioning can be tested non-invasively in humans by Short-latency Afferent Inhibition (SAI), a paired-pulse transcranial magnetic stimulation (TMS) protocol in which motor evoked potentials are conditioned by peripheral nerve electrical stimulus delivered before magnetic stimulation of motor cortex.

Aim of the study: To test whether treatment with DMF modulates cholinergic pathways in relapsing-remitting multiple sclerosis (RRMS) compared to Interferon-β 1a (INF-β 1a).

Methods: Patients starting DMF (20; DMFG) or INF-β 1a (20; INFG) and healthy subjects (20; HSG) were enrolled. SAI was recorded in patients and controls at baseline and, in patients only, after 6 months of treatment. Patients treated with DMF also underwent autonomic function testing, to further explore peripheral and central cholinergic tone.

Results: At baseline, SAI was similar in patients and in controls (p=0.983). Treatment with DMF significantly increased SAI (p=0.01), while INF-β 1a had no effect (p=0.80). At the cold face test, DMF treatment also increased reflex bradycardia (p=0.013), and reduced diastolic blood pressure variation (p=0.010), further indicating its ability to stimulate cholinergic transmission.

Conclusion: DMF treatment of MS patients is associated with changes of central and autonomic cholinergic tone. Increased SAI was founded in DMF treated patients, but not in INF-βG, confirming the specificity of DMF effect. This may represent a novel mechanism of action accounting for DMF efficacy in RRMS, with possible implications for neuroinflammation and neuroprotection. Future studies are needed to confirm these data and to explore the potential effect of DMF in restoring normal cholinergic transmission in cognitively impaired MS patients.

Disclosure

Dr. Albanese received honoraria for traveling from Almirall, Biogen, Merck Serono, Novartis,and Teva. She is involved as subinvestigator in clinical trials for Bayer Schering, Biogen Idec, Novartis, Merck Serono, Sanofi-Genzyme, Teva, Roche.

Dr. Boffa received travel funding from Almirall, Merck Serono, Sanofi-Genzyme and Teva.

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. Landi received travel funding from Biogen, Merck Serono, Sanofi-Genzyme and Teva, honoraria for speaking from Sanofi-Genzyme and Teva, and consultation fees from Merck Serono and Teva. She is subinvestigator in clinical trials being conducted for Biogen, Merck Serono, Novartis, Roche and Teva.

Dr. Lauretti 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, Biogen Idec, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, Teva.

Dr. Mataluni received travel funding from Almirall, Biogen, Novartis and Sanofi-Genzyme; honoraria for speaking from Biogen. She is subinvestigator in clinical trials being conducted for Biogen, Merck Serono, Novartis, Roche and Teva.

Dr. Mercuri has nothing to declare.

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Dr. Rocchi has nothing to declare.

Dr. Simonelli has nothing to declare.

EP1623

Remyelination promoting therapies in multiple sclerosis animal models: a systematic review and meta-analysis

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Introduction: An unmet but urgent medical need is the development of myelin repair promoting therapies for Multiple Sclerosis (MS). Many such therapies have been pre-clinically tested using different models of toxic demyelination such as cuprizone, ethidium bromide, or lysolecithin and some of the therapies already entered clinical trials.
Objectives: Keeping track on all these possible new remyelinating therapies and their efficacy has become difficult with the increasing number of studies. In this study, we aimed at summarizing the current evidence on such therapies and at providing an effect estimate of tested interventions.
Methods: We did a systematic review and subsequent random-effect model meta-analysis.
Results: We show that 88 different therapies have been pre-clinically tested for remyelination. 25 of them (28%) already entered clinical trials. Our meta-analysis also identifies 16 promising therapies which did not enter a clinical trial for MS so far: Apotransferrin, Benztropine, Epimedium flavonoids, Estrogen receptor agonist G1, Iloprost, Indazol chloride, N6-cyclohexyladenosine, Neurotrophin 3, Ninjin'yoeito, Olesoxime, Pigment epithelium-derived factor (PEDF), Plateled derived growth factor (PDGF), Sildenafil, siRNA against Nogo-receptor, Sonic hedgehog, and Tocopherol derivate TFA-12.
Conclusions: We identify 16 promising pre-clinically tested therapies that have not entered a clinical trial for MS so far. These should be tested for a potential future clinical use. We also show that failure in bench to bedside translation from certain therapies may in part be attributable to poor study quality. By addressing these problems, clinical translation might be smoother and possibly animal numbers could be reduced.

Disclosure

No disclosures.

EP1624

A prospective study of disease modifying therapy and retinal atrophy in multiple sclerosis

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Background: Retinal atrophy may be an early indicator of progression in relapsing-remitting multiple sclerosis (RRMS). It is unclear whether rates of retinal atrophy are affected differentially by disease modifying therapies (DMT). Here, we present the protocol and preliminary results for a prospective cohort study analyzing retinal nerve fiber layer (RNFL) thickness on dimethyl fumarate (DMF) therapy compared to other DMT.
Methods/Design: One hundred patients with the diagnosis of RRMS will undergo Ocular Coherence Tomography (OCT) every 6 months over 2 years. Participants will be assigned to first-line DMT, second-line DMT, and DMF groups based on the medication they have spent the greatest number of days on. The primary outcome is change in RNFL thickness. Secondary outcomes include change in macular thickness and macular volume. Tertiary outcomes include relapse, new T2/gadolinium-enhancing lesions on brain MRI, and changes in the Expanded Disability Status Scale (EDSS). Statistical analysis is performed using linear mixed effects models, with correction for inter-eye correlation. We controlled for age, ethnicity, disease duration, baseline RNFL thickness, and baseline EDSS.
Results: Data collection is underway with 100 patients recruited. In a preliminary analysis of 33 patients with at least one year of follow-up, the three treatment groups were balanced for most baseline parameters, except for decreased baseline RNFL and macular volume in patients on DMF. There is a trend towards increased RNFL thinning in subjects on DMF and second-line DMT compared to first-line DMT ($p=0.18$ and $p=0.092$, respectively). Non-Caucasian ethnicity is a significant predictor of RNFL thinning.
Conclusion: No statistically significant difference in RNFL thinning was observed across treatment groups in this preliminary analysis. Analysis will be repeated when all 100 patients have at least one year of follow-up. Using OCT measurements as early surrogate markers for MS progression, results from this study will aid in selection of treatment for MS patients.

Disclosure

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Edward Margolin: received grant funding from Biogen to conduct this study

EP1625

Frequency and description of relapses in a cohort of progressive multiple sclerosis patients treated with high dose biotin

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Background: With the increased use of high dose biotin in the treatment of progressive multiple sclerosis (MS) following the MS-SPI study in 2016, case series describe potential pro-inflammatory effect following its initiation. Its specific imputation remains not yet determined.

Objective: To describe in real-life conditions characteristics of relapses during the treatment with high dose biotin and try to identify any associated parameters.
Methods: We conducted a prospective monocentric observational study by collecting demographical and clinical data of multiple sclerosis patients treated with high dose biotin (300 mg/day) from September 2015 to February 2018. In case of relapse event, MRI evaluation was realized before prednisolone therapy.
Results: A hundred and seven progressive MS patients treated with high dose biotin for at least 3 months were included in our study. Five patients (4.67%) presented a relapse following well-conducted treatment in the 8 to 11 months after initiation. These patients were relapse-free for the 5 previous years, without inflammatory activity documented by MRI available in 4 out 5 patients. These consisted of 3 women and 2 men, 1 primary progressive and 4 secondary progressive, aged 51 to 60 (mean 54.8) with a disease duration of 9 to 28 years (mean 18.2) and baseline EDSS of 3.5 to 6.5 (median 5.6). None of the patients had had recent disease modifying therapy change. Inflammatory activity was radiologically documented with new MRI T2 and gadolinium-enhancing brain lesions in all 5 patients. No factor was associated with the risk of relapse in an univariate analysis. Relapses were considered as a side effect of treatment and biotin was discontinued in 4 out of 5 patients. Two patients fully recovered and 3 patients had a worsening of EDSS of 0.5, 1 and 2.5. Anti-CD20 therapy was started in all patients with this new inflammatory activity.
Conclusion: Our study found a ratio of 4.67% of relapses in a progressive multiple sclerosis population without previous inflammatory activity. If pro-inflammatory effect of high dose biotin is to be confirmed, future research will be warranted to identify a specific patient profile at risk.

Disclosure

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Dr. Ruet or her institution received honoraria for consulting, speaking at scientific symposia, serving in advisory board or research support from Biogen Idec, Medday, Merck Serono, Novartis, Roche, Sanofi-Genzyme, Teva (all with approval by general director of the Hospital of Bordeaux and the University of Bordeaux).
Drs. Liegey, Deloire, Moroso, Louiset and Guerard : nothing to disclose.

Long-term treatment monitoring

EP1626
Long-term effect of natalizumab in a French cohort of patients with RRMS: TYSTEN cohort

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Introduction: Long-term evolution of multiple sclerosis (MS) has been studied in several cohorts without treatment or on immunomodulatory drugs. However, long-term follow-up on new generation drugs is missing. Natalizumab (NTZ) is among the most effective treatment in relapsing-remitting multiple sclerosis (RRMS) but it remains unclear if NTZ improves the long-term course.
Objective: To describe the long-term effect of NTZ on patients with a RRMS and to investigate potential predictive factors on long-term outcomes.
Methods: Patients starting between April 2007 and April 2012 in Alsace region in France were included and followed to April 2017. Data were used to estimate the median time until secondary progressive multiple sclerosis (SPMS) conversion and reaching Expanded Disability Status Scale (EDSS) score 6.0 using Kaplan-Meier method. Hazard ratio (HR) were defined by Cox model.
Results: 325 patients were included after a mean disease duration of 8.7 years. The mean follow-up was 83 months and 59 months on NTZ. The annualized relapse rate decreased by 79.5% and 41.9% of patients had no evidence of disease at 2 years. The median time until SPMS conversion and reaching EDSS 6.0 were 26 years and 34 years respectively. For SPMS, predictive factors were initial EDSS (HR=1.56, 95%CI: 1.33-1.84, p< 0.0001), MS duration before NTZ (HR=1.04, 95%CI: 1.01-1.08, p=0.03), MRI worsening at 2 years (HR=1.86, 95%CI: 1.05-3.31, p=0.03) and medication possession ratio of NTZ (MPR; HR=0.99, 95%CI: 0.98-0.99, p=0.03). For EDSS 6.0, predictive factors were initial EDSS (HR=2.68, 95%CI: 1.94-3.71, p< 0.0001), EDSS worsening at 2 years (HR=3.94, 95%CI: 1.92-8.09, p=0.0002) and MPR (HR=0.98, 95%CI: 0.97-0.99, p=0.0007).
Conclusion: Compared to previous studies without treatment, NTZ seems to delay the progressive phase and high disability. Some predictive factors could be an assistance in the therapeutic decision making. These results need to be confirmed in larger and longer studies.

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EP1627
Integration of ocrelizumab safety data from the German study CONFIDENCE into the global post-marketing safety studies MANUSCRIPT and VERISMO

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Background: Ocrelizumab (OCR) is a recombinant, humanised, monoclonal antibody that selectively targets CD20+ B cells. OCR demonstrated superior efficacy in patients with relapsing multiple sclerosis (RMS; OPERA I/II [NCT01247324]/[NCT01412333]) versus interferon (IFN) β1a, and primary progressive multiple sclerosis (PPMS; ORATORIO [NCT01194570]) versus placebo. The proportions of patients with adverse events (AEs) or serious AEs (SAEs) were similar in the OCR, IFNβ1a or placebo groups. Pooled trial data indicated an imbalance in malignancies between the OCR and control arms, which was driven by a higher number of female breast cancer events in the OCR group. Further data are needed to characterise the long-term safety of OCR in the post-marketing setting.
Objective: To further assess and characterise the long-term safety profile, including malignancy and serious infections, in patients with MS using OCR in a real-world setting.
Methods: In VERISMO, a US Food and Drug Administration post-marketing requirement prospective, observational, cohort study of patients with MS from the US and Germany initiating OCR treatment, patients will be followed to determine the incidence rates of breast cancer and total malignancy. The European Medicines Agency post-authorisation safety study, MANUSCRIPT, is an international, longitudinal surveillance study of patients with MS initiating OCR treatment or exposed to other approved disease-modifying therapies, also investigating incidence rates of malignancies, serious infections and SAEs. Both VERISMO and MANUSCRIPT studies will incorporate safety data from the 3,000 patients (from approximately 250 neurological centres in Germany) included in the long-term prospective CONFIDENCE study. The CONFIDENCE study will characterise the safety and effectiveness of OCR in patients with RMS and PPMS newly treated with the drug in the real-world setting.
Results: The CONFIDENCE study has started; first patient in occurred in April 2018. The VERISMO and MANUSCRIPT studies will run for 7-10 years, evaluating the risks of malignancy, serious infections and SAEs from first exposure to OCR until the event, censoring, death, loss to follow-up or study end. An overview of the design of both post-marketing studies will be presented.
Conclusions: The post-marketing studies VERISMO and MANUSCRIPT will further characterise the safety profile of ocrelizumab in patients with MS newly exposed to the drug, with a focus on malignancy and serious infections.

Disclosure

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H. Berthold is an employee of Roche Pharma AG
P. Dirks is an employee of Roche Pharma AG
J. Evershed is an employee of Roche Products Ltd.
K. Gunzenhauser is an employee and shareholder of F. Hoffmann-La Roche Ltd.
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EP1628

A comparison of efficacy of subcutaneous interferon beta-1a 44 µg, dimethyl fumarate and fingolimod in the real-life clinical practise, a multicenter observational study

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Background: Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease affecting the central nervous system. Interferon (IFN) beta-1a 44ug, dimethyl fumarate (DMF) and fingolimod are well-established medications for the treatment of relapsing-remitting MS (RR MS). The aim of the project (analysis from registry ReMuS) was to compare the efficacy of IFN beta-1a 44 µg, DMF and fingolimod in patients with RR MS. This treatment began within ninety days after relapse in real world evidence in the Czech Republic.
Methods: A total of 279 patients with RR MS, who experienced one relapse after the treatment with IFN beta-1a 22 µg given 3 times weekly, IFN beta-1a 30 µg given once weekly, IFN beta-1b 250 ug given every other day, teriflunomid 14 mg given daily, glatiramer acetate 20 mg given daily, or glatiramer acetate given 40 mg given 3 times weekly, as well as those who switched the treatment to IFN beta-1a 44ug, DMF or fingolimod, were included into the study. The observed parameters were annualized relapse rate (ARR), time to the first relapse, proportion of relapse free patients and change in EDSS at 1-year of treatment.
Results: We found out a significant improvement in the observed outcomes during one-year observation. A comparison of IFN beta-1a 44ug group (83 patients) vs. DMF and fingolimod group (196 patients) showed a more significant improvement in the observed parameters (ARR and change of EDSS) in DMF and fingolimod group. When we used method propensity score matching (83 patients IFN beta-1a 44ug group vs. 83 patients DMF and fingolimod group), the sustained improvement in the observed parameters persisted before and after the change of the treatment in both groups but no significant differences were observed between the groups.
Conclusion: IFN beta-1a 44ug, DMF and fingolimod are effective in the escalation of the treatment (parameters - change of EDSS and time to the next relapse).

Disclosure

The authors declare that there is no conflict of interest.

EP1629

The BELTRIMS registry: real-world safety and efficacy of DMTs in Belgium

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Introduction: In 2012, a working group from the Belgian Study Group for Multiple Sclerosis (BSGMS) created the first Belgian registry of multiple sclerosis (MS) patients, who starting a new disease modifying treatment (DMT). No such registry existed in Belgium yet.

Objectives: To describe real-world side-effects and efficacy data based on data extracted from a prospective registry of Belgian MS patients. To compare these data to existing literature. To continuously add data to this registry.

Aims: We aim to collect data independent from pharmaceutical companies in a single registry, as opposed to having different registries for each new DMT. In doing so, we anticipate to detect unknown or rare side-effects, to collect real-life efficacy data and to capture pregnancy outcomes.

Methods: Neurologists who are members of the BSGMS can enter patients after approval of the BELTRIMS registry protocol by local and central ethics committee and obtaining informed consent from each patient. An electronic CRF was developed, with forms for starting a treatment, patient history, adverse events and serious adverse events. 6 monthly follow-up forms contain clinical status including relapses and EDSS, as well as standard MRI data. The registry is owned and managed by the BSGMS, with support of Custodix NV.

Results: As of April 1st 2018, 1375 patients have been registered by 42 centers. 286 Patients are treated with fingolimod, 265 with dimethylfumarate, 253 with teriflunomide, 139 with natalizumab, 78 with injectable first line treatment, 42 with alemtuzumab. 45 patients are untreated while 5 received other treatments. Data cleaning is ongoing. Final results will be presented during ECTRIMS.

Conclusions: We describe here the first analysis of data from the BELTRIMS registry. Adverse events, serious adverse events and real-world efficacy will be discussed.

Disclosure

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EP1630

Prospective real world observational multi-center study in patients with relapsing-remitting multiple sclerosis treated with dimethyl fumarate in Campania, Italy

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Objective: Our observational study aimed to evaluate the efficacy and safety of DMF in a real-life setting and analyze factors related to drug response.
Design/Methods: We collected prospectively data for all patients treated with DMF in six MS centers in Campania region Southern Italy) since 2014. Univariate and multivariate analyses were performed to assess relations of baseline parameters with DMF efficacy outcomes.
Results: We collected data for 428 patients (70% female subjects, mean age 39 ±12 years). Proportion of Naïve versus pretreated with other DMTs patients was 166/262, with 90 patients switching to DMF for disease activity and 162 for safety and tolerability issues. Mean treatment exposure to DMF was 589 ±315 days. Mean ARR decreased from 0.24 during the 2 years previous DMF start to 0.09 while on DMF (p=0.001). Dropped out patients were 83 (19%) after 334±264 days : 33 out of 83 dropped for inefficacy, 32 patients dropped out for tolerability or poor compliance and 8 patients for safety issues. Baseline higher EDSS predicted the drop out for inefficacy (HR 1.380, CI 1.121, 1.698, p=0.002).
At multivariate analysis, we found that male gender (OR 0.32, CI 0.132 - 0.772, p=0.011) and older age at diagnosis (OR 0.952, CI 0.919-0.986, p=0.006) were protective factors for relapse occurrence. EDSS remained stable in 89% of patients. We divided patients switched to DMF in 2 groups: horizontal switch from another first line therapy or "de-escalation" from a second line therapy. In the first group, 57 out of 80 patients switching for disease activity to DMF, were clinically stable on oral drug, whereas 14 dropped for poor tolerability. In the second group, switching mainly for safety and tolerability issues, disease control was lower than in first group, with higher ARR and proportion of progressing patients ($p < 0.0001$, X^2 test).
Conclusions: We confirm in a real life setting a good efficacy with high persistence of patients on DMF, both for naïve patients and patients switching from other first line DMTs. Male sex and older age at diagnosis are prognostic factors for DMF efficacy, while higher EDSS is a risk factor for poor response to treatment. Safety was reassuring confirming a favorable safety profile for DMF, but tolerability can still be improved.

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· Dr. L. Lavorgna received speakers honoraria from Sanofi, Teva, Novartis, Merck, Roche, Bayer, Biogen.
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· Dr. G.T. Maniscalco has served on advisory boards and/or received travel grants and speaker honoraria from Almirall, Biogen, Merck Serono, Novartis and Teva.
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· Dr. F.Romano, C.V.Russo, A. De Rosa, M.De Angelis, S. Bonavita, C. Florio and B. Ronga have nothing to disclose.

EP1631

Clinical characteristics of relapsing-remitting multiple sclerosis patients with persistent lymphopenia with dimethyl fumarate and comparison with no lymphopenic patients

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Introduction: Dimethyl fumarate (DMF) is a treatment approved for relapsing-remitting multiple sclerosis(RRMS) DMF can be associated with a decrease in leukocyte and lymphocyte counts that might persist after treatment discontinuation.
Objectives: To make a comparison between patients that develop persistent lymphopenia(L-patients) or not develop lymphopenia(NL-patients) with DMF in order to find differential characteristics that might predict this adverse event.
Material and methods: Retrospective observational study in patients with RRMS treated with
DMF since January2014 to May2018 at a tertiary-care hospital. We compare demographic/disease characteristics and previous disease modifying treatments (DMT) in L-patients and NL-patients and analyze lymphoenia characteristics in L-patients.
Results: 13 patients (6,6%) (9women;4men) had persistent (>6months) ⩽600 lymphocites/mm3 (total sample: 195 patients) The average age in L-patients was 48,8y (SD10,72) Mean time to RRMS diagnosis in L-patients was 12,8y (SD5,34) There were no differences between average age or mean time to MS diagnosis between L-patients and NL-patients. The mean disease-modifying treatment (DMT) before DMF was 1,62 in L-patients and 1,28 in NL-patients (ns) The proportion of different previous DMT was similar in both samples. Basal lymphocyte counts were similar in both groups. In L-patients, mean time to first documented lymphopenia was 8,2m (SD5,19) and mean time to DMF discontinuation was 15,5m (SD7,5m) 12/13 of L-patients developed lymphopenia during the first year of treatment. After DMT discontinuation in L-patients, mean time to lymphocyte count normalisation was 3,5m(SD1,2m) 4 patients had lymphocyte counts fluctuations during the wash-out period(30,77%) None of the patients had relapses during the wash-out period.
Conclusions: In our sample there are no differences between age, sex, basal lymphocyte counts or previous DMT among patients that develop or not lymphopenia with DMF. The proportion of patients who developed lymphopenia was lower to figures in

clinical trials and the appearance of lymphopenia occurred in almost all patients during the first year of treatment. None of the patients had relapses during the wash-out period.

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EP1632

The potential influence of long term individualized patient coaching to optimize therapy management and address challenges in an individualized patient support program

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Background: The complex nature of Multiple Sclerosis (MS) creates a need for long term treatment. Despite initial coaching, efficient therapy handling and long term adherence is not guaranteed and adherence barriers may change over time. The objective of this retrospective cohort study was to evaluate the real-life situation for MS patients. Furthermore, the potential benefit of individual coaching is analysed.
Methods: From February and September 2014 delayed-release dimethyl fumarate (DMF) and Peginterferon beta-1a (PEG) patients were recruited to the patient support program (PSP). All patients signed a written consent form. Contents and coaching frequency were adapted according to side effects as well as challenges and patient needs. Patients were stratified pursuant to individual adherence risks at therapy start and after each year of coaching.
Results: As of March 2018, 16996 patients have been recruited. Data for 9226 and 6081 MS patients including 3036 and 2554 dropouts could be analysed for DMF and PEG, respectively. Overall, gastrointestinal issues (GI) (23.9%) followed by changes of blood counts (18%) and ongoing disease activity (ODA) (16.8%) for DMF and flu-like symptoms (FLS) (36.6%) followed by ODA (15.9%) and injection site reactions (ISR) (13.3%) for PEG were reported as the most frequent dropout reasons of the discontinuers. After one year of individualized patient coaching changes in blood counts (29%) and ODA (22%) became the main discontinuation reasons for patients on DMF; no change to the main dropout reasons for PEG, though share of FLS was reduced, were observed. Evaluation of adherence risks after one year of individualized coaching showed a shift to the lower adherence subgroups for DMF and PEG. Time to therapy discontinuation was differentiated for more intensively and less intensively coached patients. Overall, 18.4%, 25% and 27.5% of more intensively coached DMF patients stopped therapy after 12, 24 and 36 months compared to 26.1%, 33.3% and 38.1%, respectively. PEG therapy discontinuation after 24 and 36 months was reduced for more intensively coached patients by 11.2% and 8% to 30.8% and 41.8%, respectively compared to the less intensively coached group.
Conclusion: GI for DMF as well as ISR and FLS for PEG can be efficiently addressed by intensively individualized coaching and side effect mitigation strategies. Individualized coaching may be a suitable tool to reduce adherence barriers and to promote treatment satisfaction.

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EP1633

A Swedish nationwide pharmaco-epidemiological study of the long-term safety and effectiveness of teriflunomid (IMSE 4)

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Background: Teriflunomid (TFM) is an oral therapy for relapsing-remitting multiple sclerosis (RRMS), which has been included in the Swedish post-market surveillance study "Immunomodulation and Multiple Sclerosis Epidemiology 4" (IMSE 4) in order to surveille and determine the long-term safety and effectiveness in a real-world setting.
Objectives: To follow-up the long-term safety and effectiveness of TFM in a real-world setting.
Methods: MS patients are registered into the nationwide Swedish Neuro Registry (NeuroReg) in Sweden. The IMSE 4 study obtains descriptive data of adverse events (AEs), Extended Disability Status Scale (EDSS), Multiple Sclerosis Severity Scale (MSSS),

Symbol Digit Modalities Test (SDMT), Multiple Sclerosis Impact Scale (MSIS-29), European Quality of Life - Five Dimensions Test (EQ-5D) and Visual Analog Scale (VAS) from NeuroReg. Drug survival was measured using the Kaplan-Meier curve.

Results: 481 TFM-treated patients have been included in the IMSE 4 study between March 2014 and April 2018. 70 % were female and the mean age at treatment start was 45.8 years. The mean treatment duration was 20.5 months. 89 % of the patients had RRMS with 3 % missing data on MS phenotype. Most patients switched from interferon and glatimer acetat (37 %) and 14 % of the patients were treatment naïve before starting TFM. The overall one year drug survival rate was 81 % and the overall two year drug survival rate was 41 %. 168 (35 %) patients terminated their treatment at some point, of which 33 % started rituximab treatment and 22 % have no new treatment registered. The most common reasons for discontinuation were AEs (49 %) and lack of effect (40 %). 318 patients have been continuously treated with TFM for ≥12 months and mean baseline values compared to values at 12 months have been noted for EDSS (2.0 ± 1.5 to 2.2 ± 1.5, n=141); MSSS (2.6 ± 2.2 to 2.9 ± 2.3, n=126); SDMT (50.8 ± 10.5 to 50.8 ± 10.7, n=165); MSIS-29 Physiological subscale (20.2 ± 19.3 to 19.7 ± 20.0, n=181); MSIS-29 Psychological subscale (28.1 ± 22.2 to 23.7 ± 21.7, n=181); EQ-5D (0.74 ± 0.24 to 0.73 ± 0.26, n=154); and VAS (70.0 ± 20.8 to 70.8 ± 19.6, n=150).

Conclusions: NeuroReg proves to function well as a post-marketing drug surveillance platform, providing data regarding drug effectiveness and AEs. However, a longer follow-up period is needed to assess the real-world effectiveness and safety of TMF.

Disclosure

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EP1634

Early stages of disability in patients with multiple sclerosis by physician and patient-reported outcomes: a two-year study

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Background: Multiple sclerosis (MS) is a chronic disease with a variety of affected functional systems. Treatment strategies primarily aiming at improving long-term outcomes for patients with MS need to consider changes in the course of the disease from the patient's and physician's perspective.

Goals: To compare the course of different domains of the physician-based EDSS and patient-based UNDS over time.

Methods: In a multicenter study, 171 patients with relapsing-remitting multiple sclerosis (RRMS) were followed over up to two years. As part of a larger assessment, the UK (Guy´s) Neurological Disability Scale (UKNDS) and the Expanded Disability Status Scale (EDSS) were applied at baseline and every

3 months. Data were analyzed via Generalized Linear Mixed Models. Values are presented as mean ± SE.

Results: Estimates of EDSS were stable (2.5) in the study population over the course of two years. Over time, patients showed no significant change of disability in any sub domains of the UNDS and EDSS, i.e. in the areas motor function, cognition, mood, fatigue, visus, speech and swallowing, bladder and bowel, sensitivity and pain, sexuality. EDSS score remained stable but the UNDS sum score presented significant changes over time (p=.020), by age (p< .001), as well as an interaction between time and age (p=.032) and between time and gender (p=.018). Further, age, and to some extend gender, had an effect on all sub scores of the EDSS and UNDS in favor of younger patients and male patients.

Conclusions: After two years, patient-reported disability domains did not differ from physicians' EDSS assessment. Only the sum score of the UNDS was able to differentiate courses of the disease over time in a stable population at the early stage of disease.

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EP1635

Autoimmune alopecia totalis; a complication of alemtuzumab therapy in multiple sclerosis

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Introduction: Alemtuzumab, a humanised monoclonal antibody targeting CD52 that selectively depletes T- and B- lymphocytes, can be associated with secondary autoimmune conditions. Here, we describe a case of autoimmune alopecia totalis following exposure to alemtuzumab. Although alopecia is recognised in patients treated with alemtuzumab, generalised alopecia has rarely been reported in the literature. Along with an unclear mechanism, this complication understandably can cause significant distress to the MS patient.

Case: A 34-year-old woman with relapsing-remitting MS and no history of other autoimmune disease received alemtuzumab therapy after two disabling relapses and radiological evidence of disease activity whilst on treatment with glatiramer acetate. There were no initial complications, post infusion screening was uneventful and she demonstrated clinical and radiological disease stability. Two years after her second course of alemtuzumab she developed subacute onset alopecia areata progressing over several weeks to alopecia totalis. A trial of Tacrolimus 0.03% was unsuccessful but six months post onset she began to make a spontaneous, although limited recovery.

Conclusion: This case highlights the importance of counselling patients, prior to alemtuzumab therapy, on all potential complications including alopecia. The temporal relation of alopecia onset to alemtuzumab treatment in this case was in keeping with other autoimmune complications of alemtuzumab and patients should undergo active monitoring for at least 4 years after the last course. Clinicians should be aware of potential treatments for autoimmune alopecia areata and have local referral systems in place for dermatology services. The element of reversibility in hair loss would differentiate this from androgenic alopecia, which may provide some reassurance to the MS patient.

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EP1636

A milestone in multiple sclerosis treatment: what changed in the landscape of the multiple sclerosis treatment with oral medications

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Introduction: Since 2009, three new oral medications have been approved in addition to the newly approved alemtuzumab and ocrelizumab. This has dramatically changed the treatment options for peole with multiple sclerosis (pwMS). These newer oral medications (OMs) allow patients to avoid injection-related side effects and improve the ease of medication administration.
Objectives: This retrospective study was conducted to examine the patient records of Dokuz Eylul MS Clinic.
Methods: The patient records (all clinic days throughout the year) in 2010, which OMs were not available, were compared to those in 2017. Patients who applied to the clinic for routine control, and having a clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), or primary progressive MS (PPMS) were included. Patients applied to the clinic for a suspected relapse were excluded.
Results: The records including 2045 visits in 2010 were compared to 2308 visits in 2017. No significant difference was found in age and disease duration of the patients visited in 2010 and 2017. There were significantly more number of patients with SPMS (26.8% vs. 20.2%, $p< 0.001$) in 2010; however, significantly less number of patients with RRMS (59.2% vs. 71.6%, $p< 0.001$). The number of patients with the Expanded Disability Status Scale (EDSS) scores of ≤ 3 were significantly higher in 2017 (73.7 vs.65.4%, $p< 0.001$). On the other hand, the number of patients with the EDSS scores of 6-6.5 and ≥ 7 were significantly less in 2017 (8.3% vs. 13.4% and 3.1 vs. 7.9%, respectively, $p< 0.001$). Significantly more patients with SPMS, EDSS scores of ≥ 7 (wheel-chair dependent patients) came to the clinic in 2010 compared to 2017 (2.7 vs. 1.4%, $p< 0.001$).
Conclusions: The increasing availability of new treatment options for patients with inadequate treatment response have changed the MS patient profile over the years. Especially OMs improved the patients adherance to the tratment. The proportion of patients with SPMS and higher EDSS scores reduced. Thus, the number of wheelchair-dependent patients also reduced.

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Skin autoimmune problems following alemtuzumab treatment in multiple sclerosis

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Introduction: Alemtuzumab is a humanized monoclonal antibody approved for the treatment of active relapsing remitting multiple sclerosis (RRMS). Its mechanism of action involves selective binding to CD52, a cell surface antigen on B and T lymphocytes. A course of alemtuzumab, administered over 5 days or 3 days, depletes lymphocyte counts but as the drug spares precursor cells, T and B lymphocytes repopulate starting within weeks of the initial depletion. Alemtuzumab is related with dermatological adverse events, like urticaria or rash reported as Infusion Associated Reactions; but there are few cases reported about long-term dermatological disorders caused by the drug.
Objectives: To describe skin problems in patients who received alemtuzumab in patients with RRMS.
Methods: Observational and retrospective study of patients treated with alemtuzumab in Hospital Universitario Virgen Macarena (UEMAC) and University Hospital Center Zagreb since April 2009 to May 2018 that developed skin disorders after alemtuzumab.
Results: 196 patients were treated with alemtuzumab, and 9 of them (3 men, 6 women) developed skin disorders after drug. Average age was 39 years (31-50) Among these disorders were alopecia areata (2), vitiligo (2), impetigo (1), common skin warts (1), acne (2) and dermatitis (1). Median time of skin disorder since Alemtuzumab was started: 10 months (2-102). Both vitiligo appears before the first cycle (6 and 11 months). The majority of these infections were mild or moderate, and there were no cases of treatment discontinuation owing to dermatological reactions.
Conclusions: These skin lesions have a pathophysiological basis in which the immune system is involved, whether as an autoimmune, infectious or inflammatory reaction.
Few skin adverse events have been reported in RRMS patients who received Alemtuzumab. Only one case of alopecia universallis associated with the treatment was published. These auotimmune disorder is probably due to the immune reconstitution that causes prolonged alterations in the lymphocyte count, with relatively increased regulatory T-cell numbers and reduced naïve T cells.
We insist on the need to make a careful clinical observation of alemtuzumab-treated patients and refer them to a dermatologist for early care and treatment. More real-life data will be needed in patients treated with alemtuzumab to determine the actual prevalence of dermatological lesions and their relationship to the drug.

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EP1638

Real life effectiveness and safety of teriflunomide in relapsing-remiting multiple sclerosis (RRMS): a MS reference center-based observational study with two years follow-up

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Introduction: Teriflunomide, a once-daily, oral first-line disease modifying treatment (DMT), has demonstrate efficacy and safety in patients with relapsing-remitting multiple sclerosis (RRMS) through numerous clinical trials, but there is a shortage of data from real-world evidence.
Objective: To describe our experience with teriflunomide in clinical practice within the two years of follow up in terms of efficacy and safety.
Methods: Prospective, observational, noncontrolled study with 116 patients. We evaluated the clinical effectiveness (annualized relapse rate -ARR- and expanded disability status scale -EDSS-) and safety of teriflunomide in those patients who completed the two years of treament. Changes in MRI performed at year 1 after receiving teriflunomide was also evaluated. Patients with clinical activity and those who discontinued teriflunomide for any reason before completing one year of follow-up, or between the first and second year, were classified in the group of patients who completed one year and two years of follow-up, respectively.
Results: We analyzed 116 patients who switched to teriflunomide, due to adverse events (59.5%) or unefficacy (19%) to previous DMTs (86.7% injectable immunomodulators; 9.2% dimethyl fumarate; 4,1% natalizumab), or as first-line treatment (21.5%). Median age was 42 [range 21-65]. 71% women (64% < 45 years). Time of disease evolution: 46% < 4 years, 30% between 5-10 years, 24% >10 years. Mean baseline ARR vs mean ARR 1-year and 2-years: 0.49 vs 0.17 and 0.21 (ARR reduction: 65.4% and 57.2% respectively, p< 0.0001). Mean baseline EDSS vs mean EDSS 1-year and 2-years: 2.41 vs 2.16 and 2.36 respectively (p>0.05). Annual MRI showed 88% and 90% of patients without new lesions in T2 or gadolinium enhanced lesions, respectively. 98 patients completed 1-year follow-up, 75 2-years and 13 without clinical activity have not completed 2-years follow-up yet. 18 and 10 patients discontinued teriflunomide during the first year (9 ineffectiveness, 9 adverse events) and the second year (6 ineffectiveness, 4 adverse events) respectively. None of them discontinued due to hepatic disorders.
Conclusion: In our experience, teriflunomide shows a high effectiveness and a good safety profile in real-life settings in the short and medium term,which make it an outstanding therapeutic option not only for naïve and patients who switched because of lack of efficacy, but also for those who switched due to adverse effects with previous DMTs.

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EP1639

Real-world effectiveness and safety of pegylated interferon beta-1a in patients with multiple sclerosis: a multicentre retrospective study in Central Italy

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Background: Pegylated-interferon beta-1a (Peg-IFN) is a disease-modifying treatment, proven efficatious in RRMS patients in the ADVANCE phase III trial, with the advantage of low frequency administration. It is available in Italy since the last quarter of 2014.
We aimed to evaluate effectiveness, safety and prescribing patterns of Peg-IFN in a cohort of patients with RRMS.

Methods: Clinical, radiological and laboratory data of RRMS patients under Peg-IFN treatment during the years 2015-2017 were retrospectively collected in 7 centres in Central Italy, following a common database.
Results: Overall 169 patients were eligible for data analysis, 24,3% naive and 75,7% switching from other treatments (91,4% from injectable drugs). The main reason for switching to Peg-IFN was lack of tolerability in 43%, ineffectiveness in 3.1%. Mean disease duration was 8.6 ± 7.6 years, with mean EDSS of 1.3 ± 1.1. The mean follow-up period was 9,8 ± 6,7 months. MRI analysis during follow-up revealed 18,4% of patients with new/enlarging T2-lesions, 13,3% with new Gd-enhancing lesions. Flu-like syndrome was reported by 50,2%, injection-site-reactions by 17,7%, 8,3% had abnormal liver enzymes. The overall discontinuation rate was 33,1%, of which 51,8% for systemic tolerability and 17,9% for ineffectiveness. Switchers to Peg-IFN for "lack of tolerability" with previous treatment (n=73) resulted at higher risk of treatment discontinuation (p=0,038) than switchers for "patient decision/treatment frequency reduction" (n=50) and treatment-naive patients (n=41).
Conclusions: Effectiveness and tolerability of Peg-IFN appeared comparable with the class of drugs. Unlike clinical trials, our analysis showed a prevalent use of PegIFN as replacement therapy for other injectable agents, in older patients with stable disease and mild disability. Switchers to Peg-IFN for tolerability problems with previous treatment were more likely to discontinue Peg-IFN.

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- FB has served on advisory boards for Teva and Roche and has received travel grants and/or speaker honoraria from Merck Serono, Teva, Biogen, Sanofi-Genzyme and Novartis.
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EP1640

Real-world longitudinal data of peginterferon beta-1a from a Swedish national post-marketing surveillance study (IMSE 6) - efficacy and safety profile

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Background: Subcutaneous peginterferon beta-1a (PegIFN) was approved for relapsing-remitting multiple sclerosis (RRMS) in Europe 2014. Phase II and III studies have shown that PegIFN reduces relapse rate and reduces the tendency to deteriorate disabilities. However, the long-term safety is important, therefore PegINF is included in the Swedish "Immunomodulation and Multiple Sclerosis Epidemiology Study 6" (IMSE 6). Which characterizes the real-world profile of PegIFN, including efficacy, safety, tolerability and patient outcome parameters.
Objectives: To follow-up the long-term safety and effectiveness of PegIFN in a real-world setting.
Methods: Approximately 60 collaborating neurology clinics continuously recruited PegIFN patients and documented clinical and demographic data in the nationwide Swedish Neuro Registry (NeuroReg). Data were obtained from NeuroReg between June 2015 and April 2018 for the IMSE 6 study.
Results: A total of 324 patients (78% female; 88% RRMS; mean age at treatments start 43 years) were followed up to 34 months (mean 15 months) with 26% treatment naïve and 49% switched from other injectables. Mean duration from initial symptom(s) to treatment start was 114 months, and 69 months from MS diagnosis to treatment start. In total, 169 patients discontinued for various reasons (60% adverse events, 24% lack of effect) and switched mainly to rituximab (63 patients, 37%). The discontinuation rate at 12 months was 42.6%. Relapses before treatment were reduced from 207 to 130/1000 patient years during treatment. With 55% having no relapse and 9% having 1 relapse during treatment period (35% missing data). After 12 months, all clinical effectiveness measures (Extended Disability Status Scale (EDSS), Multiple Sclerosis Severity Scale (MSSS), Multiple Sclerosis Impact Scale (MSIS-29), European Quality of Life - 5-Dimension test (EQ-5D), Visual Analogue Score (VAS), and the mean Symbol Digit Modalities Test (SDMT)) remained stable. A total number of 9 adverse events (6 serious: 1 gastrointestinal disorder, 2 general disorder and administrations site, 2 skin, 1 reproductive) were reported to Swedish Medical Product Agency (MPA).

Conclusions: NeuroReg proves to function well as a post-marketing drug surveillance platform, providing data regarding drug effectiveness and AEs. This real-world study presentation from IMSE 6 shows a stable efficacy and safety profile in long-term clinical use.

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EP1641

The Multiple Sclerosis Data Alliance: better data for better decision making, a multi-stakeholder approach

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The ultimate goal of the MS Data Alliance (MSDA) is improved care for people with Multiple Sclerosis (MS). We believe a crucial step towards this goal is to invest in "better data for better decision-making". Two key priorities are formulated: 1° The implementation of a minimal data set and quality standards, approved by the European Medicine Agency (EMA), in as many MS data registries and cohorts as possible. 2° The existence of a federated IT independent data ecosystem that supports re-use and request-based pooling of data when necessary and tackles the challenges of data sharing.
Real-World Data (RWD) can provide longitudinal information on the effectiveness and tolerability of drugs, their impact on resource use, medical costs, and patient-reported outcome (PRO). This is particularly important in MS, where economic treatment benefits of long-term disability reduction are a cornerstone of drug approvals by the payer. These factors are typically not examined in RCTs themselves but modelled using RWD. A growing number of MS databases and registries have started to produce long-term outcome data from large cohorts of patients with MS treated with disease-modifying therapies in real-world settings. However, collaborative initiatives face many challenges, because access to MS registries and/or cohorts is limited and data discovery is time consuming. Data is acquired heterogeneously and differences in definitions, indexing and software platforms preclude direct integration.
Three objectives are formulated for this project proposal: 1° Facilitate community engagement and raise awareness on the value of quality RWD. We do this by launching a multi-facetted awareness and motivation campaign and by organizing large scale engagement meetings for a wide group of stakeholders; 2° Develop tools for data discovery and sharing in collaboration with experts in data sharing (e.g. ELIXIR, Observational Health Data Sciences and Informatics (OHDSI), European Medical Information Framework (EMIF), European Health Data Networks (EHDEN), Big Data for Better Outcomes (BD4BO), …). 3° Support implementation strategies and standard operating procedures for a wide international implementation of a minimal data set including PRO and MRI measures.
We believe a collaborative and synergistic approach is required to jointly tackle these challenges. We are currently in the process of finalizing the project consortium and implement our raising strategy to make this vital project happen.

Disclosure

Liesbet M. Peeters: nothing to disclose

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EP1642
Real world effectiveness of fingolimod in patients with relapsing remitting multiple sclerosis and non-response to previous treatment: a prospective analysis in Buenos Aires, Argentina

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Introduction: Growing evidence demonstrated the effectiveness of fingolimod in the real world (RW) setting, however scarce information exists from Latin America. The aim of this prospective study was to evaluate fingolimod effectiveness in non-responders to treatment patients in Buenos Aires, Argentina.
Methods: non-responders to first immunomodulating treatment who were prescribed fingolimod and at least ³18 months of follow up were included during August 2013 and June 2018. Non-response was defined as patients who experienced 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions or ≥3 new or enlarged T2 or T1 GAD+ lesions while on therapy. Three-monthly clinical evaluations and 12-monthly magnetic resonance were performed. Demographic and clinical variables were described as well as the effectiveness outcomes that included the proportion of patients free from clinical relapses, from disability progression, from new or enlarging T2 or T1 gadolinium-enhancing lesions on annual MRI and from any disease activity during the follow up.
Results: 97 patients were included: 68 % female (n =66); mean age 30 ± 10.5 years; mean disease duration 6.5 ± 3.1 years; mean EDSS 3.5 ±1, mean fingolimod use 30 ± 13 months (range 18-68 months). All patients used previous therapy (interferons n = 78; glatiramer acetate n= 12; teriflunomide n= 7). 15 patients (15.4 %) discontinued/ withdrew fingolimod (12 due to disease activity and 3 due to tolerance and personal decisions). 74 %were free from clinical relapses and 79% were free from disability progression; 65% of patients remained free from new or newly enlarging T2 lesions and 76% of patients were free from gadolinium enhancing lesions. The proportion of patients free from any disease activity was 54%.
Conclusions: We observed a high effectiveness data of fingolimod in non-response to previous treatment in a newly RW setting

Disclosure
The sudy was done without external support.

EP1643
Efficacy of alemtuzumab treatment in active RRMS - a real-life study

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Background: Alemtuzumad (Alem) is a monoclonal anti-CD52 antibody which depletes circulating lymphocytes followed by their reconstitution. Alem is currently used as a treatment for active relapsing remitting multiple sclerosis (RRMS) and administered in two courses one year apart.
Objective: We evaluated the efficacy of Alem treatment in active RRMS in real-life settings assessing treatment effects on relapse rate and disability progression.
Methods: We performed a retrospective review of 35 RRMS patients (19:16 f:m), with mean disease duration of 14.2 years, mean EDSS of 4.6 and median age of 38 years. All patients treated with Alem and had an average follow up of 24 months post infusion.
Results: The mean annualized relapse rate at 1 year prior Alem treatment was 2.06 and 1.63 at 2 years prior the Treatment. At 2 years of post-infusion follow-up, The mean annualized relapse rate was 0.54. The mean change in number of relapses within 2 years from start Treatment from 2 year prior treatment -1.09, (*P value* < .0001). The mean EDSS at the baseline was 4.57, EDSS after 2 years 4.47 mean change was -0.1. There was no significant EDSS Change from baseline (*P value* < .0.6177).
Treatment related adverse events: Total number of 13 patients (13/35) had adverse events. The adverse events profile recorded: 7 patients were diagnosed with Urinary tract infection, 4 patients were diagnosed with cutaneous Herpes-Zoster, 2 patients were diagnosed with Thyroid abnormality and 1 patient was diagnosed with Gastric Carcinoma.
Conclusion: Alem treatment given with one cycle or more reduced significantly the annualized relapse rate and prevented disability progression during two years of follow-up. Treatment-related adverse events were minor and tolerability of treatment was high.

Disclosure
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EP1644
Guillain-Barré syndrome after treatment with alemtuzumab in a patient with multiple sclerosis

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Alemtuzumab is a humanised monoclonal antibody which targets the surface molecule CD52, resulting in a rapid depletion of innate and adaptive immune cells. The major complications of therapy with alemtuzumab are infectious and autoimmune diseases.
We report a case of 25-year-old Multiple Sclerosis (MS) patient who switched to alemtuzumab due to high disease activity, after having been treated with two different disease modifying therapies.
After twelve weeks from the first five-day cycle of alemtuzumab, he developed Guillain-Barré Syndrome (GBS). The patient reported a flu-like syndrome two weeks earlier. Electrophysiological exam and cerebrospinal tap confirmed the suspect. He was treated with four cycles of plasmapheresis with a complete clinical and instrumental recovery after two months.
No cases of GBS have been described in MS patients, however few cases have been reported during treatment with alemtuzumab in Chronic Lymphocytic Leukemia. In haematologic patients however, alemtuzumab is given at different dose and following different protocols, but symptoms have an onset at CD4+ nadir.
A defined mechanism of the etiology of GBS while in treatment with alemtuzumab is not yet known. Suppression of CD4+ regulatory T cells, that normally have an inhibitory role on autoimmunity may be involved. Although antecedent infection should be considered as a probable risk factor for the development of GBS, a correlation between alemtuzumab and acute polyneuropathy cannot be excluded. Therefore, further studies are necessary to better characterise this mechanism and clinicians should be aware of this possible complication during therapy with alemtuzumab

Disclosure

Nothing to disclose.

EP1645

Spanish registry of multiple sclerosis patients on glatiramer acetate 40 mg/ml treatment: real-world results and initial results of first year follow-up

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Aim: Describe the profiles of patients undergoing treatment with glatiramer acetate (GA) 40mg/ml in Spanish real-world clinical practice. This abstract shows the initial results of first year follow-up.
Methods: This is a prospective, observational, multicenter patient registry from 50 Spanish multiple sclerosis (MS) hospital units. Relapsing MS patients on GA 40 mg/ml treatment were recruited and will be followed for a maximum of 5 years. Patients' visits were performed as per daily clinical practice.
Results: At baseline 1331 patients were evaluated (892 females, median age 43 years). Mean age at diagnosis was 35.3 years and time from diagnosis to registry recruitment was 8.5 years. Majority of patients (n=994, 74.7%) had previously been treated with other immunomodulatory/ immunosuppressive drugs before entering the study. Prior therapies included GA 20 mg/ml(58.2%), interferons(34.0%) and other drugs(2.9%).Mean EDSS before starting GA 40 mg/ml was 1.9. The annualized relapse rate (ARR) was 0.4. Mean T1 Gd+ enhancing lesions was 0.9±5.1. Mean T2 new lesions were 2.0±4.9. 1056 patients(79.3%) completed visit 1.Mean time from baseline to visit 1 was 6.2 ± 2.1 months. Mean EDSS was 1.9 ±1.7.Majority of patients (n=973, 92.1%) showed no relapses since previous visit, 75 (7.1%) had 1, 5 had 2 and 1 had 3 relapses. Mean T1 Gd+ enhancing lesions was 0.4±1.7. Mean T2 new lesions were 1.0±2.7.813 patients (61.1%) completed visit 2.Mean time from baseline to visit 2 was 11.8±2.7 months and mean EDSS 2.0 ±1.7.The vast majority of patients (n=755, 92.9 %) showed no relapses since previous visit, 38 (4.7%) had 1 relapse, and 1 had 2 relapses.ARR in the first year of participation in the registry was 0.135.Mean T1 Gd+ enhancing lesions was 0.4±1.3.Mean T2 new lesions were 1.1±3.0.To date, mean time to follow up was 8.8 months.9.2% patients have discontinued the study; the main reason was end of treatment with GA 40mg/ml, mostly due to adverse events (42.6%) and lack of response (36.5%). 2 Severe Adverse Events, considered non-related to treatment, were reported in the annual pharmacovigilance report as per April 2017. Real World Data studies provide broader information on real-world safety, additional safety information will be reported in following communications.
Conclusion: Data from visits 1 and 2 from the 1331 patients included in the Spanish registry show that patients maintain low disease activity (low relapse rate, lesion load, and mild disability scores).

Disclosure

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EP1646

Real World Evidence (RWE) on impact of age on long-term persistence to disease modifying therapies (DMTs) in relapsing-remitting multiple sclerosis (RRMS) in Australia

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Introduction: In a previous study of treatment persistence in multiple sclerosis it was demonstrated that age, in addition to other factors, was independently associated with higher rates of treatment discontinuation[1].

Objectives: We previously reported persistence in the overall MS population[2] and the current study examines the impact of age on persistence for all reimbursed DMTs for RRMS in Australia.
Methods: The Pharmaceutical Benefits Scheme (PBS) 10% sample supplied by the Department of Human Services was used in this study. Eligible patients must have received a script for a reimbursed DMT for RRMS between September 2011 and February 2016. Patients were classified into five age-groups (ages 18-30; 31-40; 41-50; 51-60; 61+) and defined as persistent if their DMT script was filled within 4 months. Persistence was derived using the Kaplan-Meier method and hazard ratios (HR) to represent the relative rate of drop-off of different age groups.
Results: A total of 1866 treatment episodes were eligible for the study. Overall the median persistence to therapy was 30 months with 68% of patients remaining on therapy for 12 months. Patients aged 18-30 had the shortest persistence (18 months) and a 44% increased risk of discontinuation when compared to the 'all ages' cohort (HR 1.44 (95%CI: 1.22-1.72) and was identified as a 'high-risk' group. For all other age-groups, when compared to Product Average, hazard ratios were between 1.08 and 0.92.
For patients aged 18-30 there was statistically significant lower persistence (median 9 months) on injectable therapy (glatiramer acetate, interferon beta-1a, interferon beta-1b) when compared to the persistent product average (median 18 months) with a hazard ratio of 1.95 (95% CI: 1.35-2.81). Patients on non-injectables (dimethyl fumarate, fingolimod, natalizumab, teriflunomide; n=188) had a median persistence of 24 months and this result was not significantly different from the product average (HR 0.81 (95% CI: 0.65-1.02). A larger sample has been requested to explore discontinuation rates of individual DMTs.
Conclusions: In this analysis of PBS sample data, patients aged 18-30 were least persistent to treatment when compared to the product average. The persistence on injectable therapy was significantly lower compared to all drugs in this high-risk group.
1. Warrender-Sparkes et al. Multiple Sclerosis Journal. 2016; 22(4): 520-532
2. Spelman et al. 7th Joint Congress of the ECTRIMS-ACTRIMS. October 25-28, 2017, P1193

Disclosure

T Spelman serves on steering committees for trials conducted by Biogen and has received honoraria and consulting fees from Biogen and Novartis
A Kornberg has served on scientific advisory boards for Novartis
M Schulz is an employer of Novartis
B Arora is an employer of Novartis
E Chung received compensation from Novartis for research and authorship of this publication
P Juneja received compensation from Novartis for research and authorship of this publication
R Walker is an employer of Novartis
S Verhaeghe is an employer of Novartis
A van der Walt has served on scientific advisory boards for Novartis, Merck and Sanofi and has received travel support from Novartis, Biogen, Merck and Teva. She has received research support from Novartis, Merck and the NHMRC Australia
H Butzkueven has served on scientific advisory boards for Biogen, Roche, Merck, Novartis, Teva and Sanofi and has received conference travel support from Novartis, Biogen and Merck. He serves on steering committees for trials conducted by Merck, Biogen and Novartis, and has received research support from Novartis, Biogen, NHMRC Australia, MS Research Australia and the UK MS Trust

EP1647

Very long term use of natalizumab is possible but carries a high burden

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Introduction: Natalizumab (NTZ) is a highly effective disease modifying treatment for relapsing-remitting multiple sclerosis (RRMS) that has been linked with an increased risk of developing Progressive Multifocal Leukoencephalpothy (PML). In most developed countries its use has since been restricted mostly to patients negative to JC virus antibodies or altogether avoided. In Brazil other highly effective therapies are not available in public healthcare, making Natalizumab an important tool to manage MS patients with active and/or aggressive disease. We report a single-center experience in very long-term use and risk management of NTZ.
Objectives: To report efficacy and safety of very long-term use of NTZ in a real-world setting using a strict surveillance protocol.
Methods: We retrospectively analysed charts from our clinic and identified patients who received NTZ for ≥ 48 infusions. We acquired data regarding clinical activity, JCV serostatus and severe infectious complications. All patients followed in our center with a high risk of PML who opt to maintain treatment with NTZ must adhere to a strict monitoring protocol consisting of routine clinical appointments every 3 months and MRI every 3-4 months, to allow for early detection of imaging changes suspect of PML.
Results: We identified 25 patients (84% female) with a median 60 infusions of NTZ (50 - 73). Nineteen (76%) patients were JCV positive, 13 of them with an AI titer ≥ 1.5 (52%). Three patients had a history of previous immunosuppressive drug use (Mitoxantrone, n=2; Cyclophosphamide, n=1), one of them negative for JCV antibodies. Post-treatment ARR was 0.07. Six patients presented 9 relapses, 3 of them related to discontinuation of treatment. Complete clinical remission was achieved by 76% of patients and there were no severe infectious complications in the entire cohort. Other side effects were rare, mild and well tolerated.
Conclusion: Most patients achieved successful control of disease activity following the start of NTZ treatment. In patients who are willing to accept a risk of PML and intensive clinical and imaging monitoring, it may be viable to continue treatment for a very long time. This strategy is, however, costly and puts a high burden in both the patient and the healthcare provider.

Disclosure

Nothing to disclose.

EP1648

Patients switching to fingolimod in daily clinical routine: 2 year interim results from the non-interventional study PANGAEA 2.0

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Background: Fingolimod (Gilenya®) was approved in 2011 as the first oral disease modifying treatment (DMT) for highly active relapsing remitting multiple sclerosis (RRMS). Since 2011, therapeutic options of baseline MS treatment especially using oral drugs for RRMS have continuously increased. As pivotal studies have been run before the availability of other oral drugs in clinical practice, data on switch from oral vs. injectable baseline treatments to fingolimod are missing.
Objectives: Here we present two year interim results of PANGAEA 2.0 including effectiveness data of patients switching from injectable (interferons and glatiramer acetate; iDMT) and oral (dimethyfumarate and teriflunomide; oDMT) baseline DMT to fingolimod.
Methods: PANGAEA 2.0 is an ongoing non-interventional study conducted in Germany documenting effectiveness, safety and patient reported outcome data of patients that switched to fingolimod between 2015 and 2018. As of January 2018, baseline data for 1802 patients were available. Interim results of approximately 200 patients, who will have completed two years of observation by July 2018, will be presented.
Results: 48.3% patients switched from iDMTs (64.9% interferons, 38.8% glatiramer acetate) and 25% patients from oDMTs (64.9% dimethylfumarate, 35.1% teriflunomide) to fingolimod within PANGAEA 2.0. 12.7% of the patients were treatment naïve. The baseline characteristics of both groups were comparable: Patients switching from iDMTs have been longer on any iDMT (4.2 ±3.9 years) than patients switching from oDMTs (1.4 ±1.1 SD). While only 32.5% of patients in the iDMT subgroup had more than 1 pre-treatment, 71.1% within the oDMT subgroup had more than 1 pretreatment. The annualized relapse rate (± 95%CI) 12 months after switch to fingolimod was reduced by 79.3% from 1.31 ±0.07 to 0.27 ±0.03 (iDMT) and by 72.4% from 1.34 ±0.09 to 0.37 ±0.05 (oDMT). Similar results were obtained for treatment naïve patients and patients switching after different treatment sequences in their disease history. The EDSS (± 95%CI) for the whole population remained stable at 2.3 ±0.37. Similar results were obtained for the subpopulations. An updated analysis focusing on patients who completed two years of observation will be presented.
Conclusion: Real world data from PANGAEA 2.0 indicate that active disease patients switching from iDMT or oDMT to fingolimod can benefit from this switch.

Disclosure

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B.Ettle and C. Cornelissen are employees of the Novartis Pharma GmbH, Nuremberg, Germany.

EP1649

Clinical protocol for the prevention of rebound phenomenon after natalizumab cessation in multiple sclerosis. A multiple sclerosis reference center experience

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Introduction: In multiple sclerosis (MS) natalizumab (NTZ) withdrawal may lead to a "rebound" of inflammatory activity defined, in several patient series, as a severe relapse and unusually high inflammatory MRI activity increase. In our MS center two different schedules with intravenously metilprednisolone (IVMP) were established to reduce the probability rise of inflammatory activity.
Objectives: To assess the clinical disease activity following cessation of natalizumab therapy.
Methods: Retrospective analysis data of patients treated with NTZ during more than 2 years that was discontinued between January 2012 and January 2017 for inefficacy or safety reasons. A new disease modifying treatment (DMT) was initiated after NTZ withdrawal through two IVMP schedules within NTZ washout period (WP): Schedule 1 (years 2012 and 2013): 3 months WP. 1, 2 and 3 IVMP grams, every month respectively. Schedule 2 (years 2014, 2015 and 2016): 2 months WP. 1 and 2 IVMP grams every month respectively. Ten days after every schedule, new DMT was initiated. Clinical and MRI evaluations were performed at 3rd, 6th, 12th and 24th months after NTZ-washout. Clinical variables and MRI activity (new/enlarged T2 and gadolinium enhancing lesions) were studied.
Results: Fifty patients discontinued NTZ in the analyzed period (68% women, mean age -years- 40.39+/-11.12, mean EDSS 3.59+/-1.74). New DMT was fingolimod in 80% of cases. At 6th month relapse or MRI activity (return to previous MS activity) was observed in 32% and 38.5% of patients respectively, "rebound" criteria (severe relapse and unusually high inflammatory MRI activity) was observed in 6% (n=3) and 8% (n=4) presented only high inflammatory MRI activity. No relapses during WP was observed. No differences of clinical and MRI activity between both schedule IVMP was observed. Return to previous

MS activity was found in younger patients and was associated with higher annualized relapse rate (ARR) during the two years after cessation of NTZ and a higher presence of MRI activity, with no differences in EDSS scores after two years of follow-up.
Conclusions: IVMP schedule 1 and 2 during NTZ washout period was well tolerated and "rebound" phenomenon was observed in only 6% of cases. In our study IVMP could have reduced the possibility of rebound since in other patient series the proportion is higher. Return to previous clinical and MRI activity at 6th month after NTZ cessation could imply a worse prognostic in the following two years.

Disclosure

L. Fuentes Rumí: Nothing to disclose.
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The other authors disclose neither conflict of interest in the elaboration of this communication. Authors have not received any funding for the elaboration of this study.

EP1650
Evolving predictors to medication adherence in patients with MS - a prospective analysis with multiple indicators

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Background: Medication adherence to is the extent to which a patient acts in accordance with the prescribed interval and dose. Little is known about the course of adherence to Disease Modifying Treatment (DMT) and its predictors in MS.
Methods:
Participants were PwMS (relapsing-remitting) treated at Carmel MS Center in Haifa, Israel: 171 at baseline (T1) and 6 months (T2) and 126 at 12 months (T3).
Design - *prospective* survey at three time points combined with *retrospective* review of health records and medication claims.
Measures - predictors were habit, medication beliefs, illness perceptions, physical disability, emotional factors and demographic characteristics. Outcome was adherence as assessed by three indicators: medication withdrawal records and two patient-reported measures - Probabilistic Medication Adherence Scale (ProMAS) and MS-TEQ. Adherence was defined as either => 80% medication claims per regiment, or => 80% self-reported medication use by MS-TEQ or being at medium-high and high categories of ProMAS.
Results: Adherence rates were: 62%, 62% 63.5% at Time1, time2 and Time3, respectively. Adherence by modalities was 57.5% vs. 65.9% for injections and oral, respectively at time1, 48.5% vs. 72.9% for injections and oral, respectively at time2 and 59.6% vs. 66.7% for injections and oral, respectively at time3. The difference was significant only at time 2 ($\chi^2(1)=9.57$, $p=0.002$) . Time2 adherence was predicted by medication perceptions of over-treatment and harm at time1 ($t(150)=2.37$, $p=0.019$ and $t(150)=2.39$, $p=0.018$ respectively) time3 adherence was predicted by habit strength at time2 ($\chi^2(1)=3.77$, $p=0.05$). Emotional states, disability and demographic characteristics were not predictive of adherence at the 3 time points (one exception: gender at time1).
Conclusions: As PwMS gain more experience with their medication, the predictors for adherence change from general perceptions to the strength of habit with the particular medication. Future interventions in medication adherence should take into consideration the different perceptions at different treatment stages.

Disclosure

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EP1651
17 - year adherence to interferon beta-1b treatment in patients with multiple sclerosis

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Introduction: The interferon beta-1b (IFNB-1b) was approved 25 year ago for the treatment of relapsing remitting MS. Researchers have shown that 13-30% of patients discontinued therapy.
Aims: This study aims to highlight adherence to long-term treatment with IFNB-1b.
Objectives: The primary outcome of this study was to assess the degree of adherence and the reasons for discontinuation of INFB-1b treatment, during 17 year follow- up.
Methods: In our observational retrospective study, we included a group of 88 relapsing remitting multiple sclerosis (RRMS) patients and 12 secondary progresive multiple sclerosis (SPMS) patients. They started IFNB-1b treatment subcutaneously at a dose of 250 μg every other day. The inclusion period took place between October 2000 and March 2001, while the follow-up ended on March 2018. The including criteria for treatment were: age between 18-56 years and EDSS score under 5,0. Our patients underwent clinical evaluation every six months, focused on the number of relapses, EDSS score, and adverse events.
Results: Mean follow up was 11 years. During this period, 62% discontinued treatment. Patients desire (lack of efficacy) was the main reason for stopping the treatment (27%). Other factors included: moving to another place (10%), adverse events (7%), reaching the EDSS score ≥ 8 (6%), reconsidering the diagnosis (5%), pregnancy (3%) and other reasons (4%).
Conclusion: Only 38% MS patients were persistent to INFB-1b treatment during 17 year exposure. Lack of efficacy (patient's

opinion) was the main reasons for stopping treatment, despite a good safety profile.

Disclosure

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Mihaela Mirela Micu has nothing to disclose
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EP1652

Comparative efficacy of natalizumab and fingolimod in multiples sclerosis in a Tunisian population

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Introduction: Natalizumab and Fingolimod are two second-line treatments that are significantly more effective than first-line treatments. Given the benefit / risk ratio of these two treatments, it seems useful to compare their effectiveness to guide the choice of treatment for patients with relapsing-remitting multiples sclerosis (RRMS).
Methods: This is a retrospective study of 80 patients followed for RRMS in the Neurology department of Habib Bourguiba Hospital in Sfax and in the Neurology department of Razi Hospital in Manouba. Comparative efficacy data between Natalizumab and Fingolimod were judged by the annualized relapse rate (ARR), Expanded Disability Status Scale score (EDSS), Multiple Sclerosis Severity Score (MSSS) and by reducing or stabilizing of lesions in brain and/or spinal magnetic resonance imaging (MRI).
Results: The mean age of patients at the beginning of second-line treatment was 34.25 ± 9.1 years [17-59]. The mean age at introduction of Natalizumab was 30.6 ± 7.4 years [17-50]. The mean age at introduction of Fingolimod was 37.4 ± 9.4 years [21 - 59]. This difference was statistically significant ($p < 0.0001$). The percentage of patients treated with Natalizumab and remaining free from relapses was comparable to that seen in patients treated with Fingolimod. We have seen a better efficacy of Natalizumab in reducing ARR compared to Fingolimod (93% vs 79%) ($p = 0.026$). The percentage of patients remaining free of EDSS progression was similar between the two molecules. An improvement in EDSS score was seen in 36% and in 11% under Natalizumab and Fingolimod respectively ($p=0.014$). The percentage of patients remaining free from radiological activity was greater in those who received Natalizumab ($p = 0.002$). The percentage of patients free of clinical and radiological activity was 60.5% and 41%, respectively, after two years of treatment with Natalizumab and Fingolimod ($p = 0.017$).
Conclusion: Natalizumab and Fingolimod showed better efficacy compared to first-line treatments. However, Natalizumab appears to have better clinical and radiological efficacy compared to Fingolimod.

Disclosure

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Delayed-release dimethyl fumarate in patients with relapsing-remitting multiple sclerosis - findings from a real-world setting in Russian Federation

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Introduction: Delayed-release dimethyl fumarate (DMF) has demonstrated a favorable benefit-risk profile in patients with relapsing-remitting multiple sclerosis (RRMS). As of January 31, 2018, >311,000 patients have chosen DMF treatment, representing >544,000 patient-years of exposure. Of these, ~6252 patients (~12,631 patient-years) were from clinical trials. There are no any published data on patient outcomes evaluation on DMF treatment in Russia.
Objective: To evaluate patients' outcomes in patients receiving DMF treatment ≥ 12 months in Russia.
Methods: Data from 96 RRMS patients treated with DMF in Moscow MS center was included in this retrospective analysis. Data starting from the first exposure to DMF are included in the analysis. The data cutoff date was April 09, 2018. The mean patient age - 37 years. 66 (69%) patients - female. Mean time since MS diagnosis - 10 years. Mean EDSS score before DMF treatment was 2.6. 94 (98%) patients were pretreated with the disease modifying therapies: 14 (14,5%) with high dose interferons beta (HDIFNβ), 2 (2%) - low dose interferons beta(LDIFNβ); 35 (36.5%) - glatiramer acetate (GA); 2(2%) - laquinimode, 41(43%) had more than one DMT previously, 2 (2%) - treatment naive. 22 of pretreated patients had 1 relapse in previous 12 months, 18 have active lesions in previous 12 months. 40 (42%) pretreated patients switched to DMF due to lack of efficacy: 11 (12%) from HDIFNβ, 2(2%) from LDIFNβ, 27(28%) from GA. 56 (58%) pretreated patients were switched to DMF due to previous treatment intolerance.

Results: 62 patients received DMF treatment ≥12 months: 54 (87%) have no relapses on DMF treatment; 60 (97%) - without disability progression, 52 (84%) have no active lesions on MRI. 85 patients, received DMF treatment ≥6 months: 12(14%) had gastrointestinal (GI) adverse events (AE), 54 (64%) had "flashing", 47 (55%) had lymphopenia, 6 (7%) had severe lymphopenia with absolute lymphocyte count (ALC)< $0.5x10^9$/L. Treatment discontinuation of 96 patients due to GI AE was in 4(4.2%), due to "flashing" in 4(4.2%), due to severe lymphopenia in 3 (3.2%), due to lack of efficacy in 2 (2.0%) patients.
Conclusions: Most of patients on DMF treatment were stable without disease activity. DMF treatment was generally good tolerated. AE spectrum was typical for DMF, treatment discontinuation rate due to AE was lower than in phase III studies.

Disclosure
Nothing to disclose

EP1654
Comparison of use oral and injection disease-modifying therapies in persons with multiple sclerosis

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Introduction: The treatment of relapsing-remitting multiple sclerosis (RRMS) has become more effective over the last decade with the advent of the recently available disease-modifying therapies (DMTs). There are several DMTs have the different effect on the course of the disease, slow down the progression of disability, reduce relapses in persons with multiple sclerosis (pwMS).
Objective: The aim of this study is to investigate the difference between disease-related variables (duration of disease, disability level, number of attacks) and clinical variables such as walking, balance and upper extremity functions of the pwMS receiving oral (fingolimod, teriflunomid, dimetil fumarat) or injection (glatiramer acetate, interferon beta-1a, interferon beta-1b) therapies. Oral treatment was often initiated in pwMS who have higher duration of disease, disability level.
Methods: In total 387 pwMS participated. Disease-related variables were evaluated by a neurologist and disability levels was determined according to Expanded Disability Status Scale(EDSS). Walking capacity were assessed with 12-Item Multiple Sclerosis Walking Scale(MSWS-12), Timed 25-Foot Walk(T25FW), Timed Up and Go Test(TUG) and the 6 Minute Walk Test(6MWT), balance were assessed with Activity-Specific Balance Confidence Scale(ABC) and One Leg Stand Test(OLST), upper extremity function was assessed with 9 Hole Peg Test(9DPT).
Results: The MSWS-12 (25.59±13.36 vs. 18.48±9.66, p< 0.001), T25FW (6.65±4.86 vs. 5.65±4.13, p=0.002), TUG (8.82±6.66 vs. 7.01±2.19, p=0.009), 9DPT (22.97±7.88 vs. 20.74±4.64, p=0.005), duration of disease (9.90±6.98 vs. 4.23±5.95, p< 0.001), number of attacks (3.79±2.51 vs. 2.01±1.35, p< 0.001) and EDSS score (2.24±2.02 vs. 1.48±1.21, p< 0.001) were significantly higher in participants receiving oral therapy. The 6MWT distance (405.86±117.29 vs. 457.89±79.94, p< 0.001), ABC score (66.05±30.78 vs. 81.35±22.25, p<0.001) and OLST time (31.97±25.25 vs. 39.28±24.03, p=0.011) were significantly higher in participants receiving injection therapy.
Conclusion: This study suggests that pwMS receiving oral therapy have lower performance and perceived skill levels in terms of walking capacity, balance ability, and upper extremity functions than pwMS receiving injection therapy. Furthermore, higher disability level, duration of disease and number of attacks were found in pwMS receiving oral medication. We concluded that these may cause the poor performance in the oral medication group.
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4. Serkan Ozakbas: nothing to disclose

Risk management for disease modifying treatments

EP1655
Serious adverse events related to Rituximab in multiple sclerosis and neuromyelitis optica spectrum disorder patients

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Introduction: Rituximab, monoclonal antibody that selectively targets CD20 positive B cells, has shown significantly lower frequency of relapses and a reduction in the total number of gadolinium enhancing (Gd+) lesions relative to placebo in phase II HERMES trial for relapsing remitting multiple sclerosis (RRMS). While Rituximab itself is currently not being further developed specifically for multiple sclerosis (MS) in the setting of newer era anti-CD20 agents, its use in the clinical setting has enjoyed an upsurge in use. It has also been adapted as one of the first line agents for treatment of neuromyelitis optica spectrum disorder (NMOSD). Data supporting the long term, real world safety of Rituximab is limited as there is no risk evaluation and mitigation strategies (REMS) program to allow for thorough investigation of serious adverse events (SAEs) to this drug in MS or NMOSD patients.
Objectives: To present three cases of SAEs related to Rituximab in treatment of RRMS and NMOSD.
Aims: To contribute to the body of literature regarding the long term use of Rituximab in MS and NMOSD patients.
Methods: Comprehensive chart review of patients identified to have SAEs related to Rituximab.
Results: The first two cases were seen after 3 years of bi-yearly infusions, with 27-year-old female patient with RRMS in case 1 developing vulvovaginal pyoderma gangrenosum and 65-year-old woman in case 2 with NMOSD who developed biopsy proven eosinophilic colitis. Case 3 involves a 28-year-old woman with

RRMS who developed serum sickness seven days after her initial Rituximab infusion marked by high fever, rash, and arthralgias which resolved with steroids.

Conclusions: These are rare side effects that have been described with Rituximab in rheumatological and oncological literature but have not previously be seen in patients with demyelinating disorders of central nervous system who in general use smaller doses of Rituximab without concomitant immunosuppression from other agents. Therefore, these side effects may be less known to neurologists utilizing this drug. As the anti-CD20 drugs become more popular in the current treatment era with more patients being exposed to these agents for longer period of time, it is prudent to continue to contribute to the body of literature related to side effects related to Rituximab in this population. Large scale thorough retrospective and prospective studies are needed to supplement the lack of safety data which currently exists.

Disclosure

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EP1656

Quality of life improves with alemtuzumab over 6 years even in patients with relapsing-remitting multiple sclerosis who developed thyroid adverse events

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Introduction: Alemtuzumab, approved in >65 countries for treatment of RRMS, has demonstrated a positive benefit-risk profile across clinical trials. In two phase 3 trials (CARE-MS I [NCT00530348]: treatment-naive; CARE-MS II [NCT00548405]: inadequate response to prior therapy), patients (pts) had significantly improved efficacy and quality-of-life (QoL) outcomes with alemtuzumab vs SC IFNB-1a over 2 years (y). Efficacy was maintained through Y4 in an extension (NCT00930553), in which 81% of pooled CARE-MS I/II pts remained on study from core study baseline until end of Y6 in the absence of continuous treatment. The safety profile of alemtuzumab is well known and includes among other the risk of autoimmune thyroid adverse events (AEs).

Aims: Examine the impact of thyroid AE occurrence on QoL outcomes over 6 y in pooled CARE-MS I/II pts.

Methods: Alemtuzumab pts received 2 treatment courses (12 mg/day; baseline 5 days; 12 months later: 3 days) in the core CARE-MS studies, with additional courses of alemtuzumab (12 mg/day; ≥12 months apart) as needed for disease activity or other disease-modifying therapies in the extension. QoL assessments: Functional Assessment of Multiple Sclerosis (FAMS); Short-Form 36-Item (SF-36) survey mental component summary (MCS) and physical component summary (PCS); EuroQol 5-dimensions (EQ-5D) visual analogue scale (VAS). Thyroid function testing (baseline and quarterly) was done per comprehensive monitoring program.

Results: Of the pooled CARE-MS I/II alemtuzumab pts (n=811), 42% had thyroid AEs over 6 years. Thyroid AE incidence peaked in Y3 (16%) and then declined. 95% (767/811) of pts had no serious thyroid AEs, and 83% of thyroid AEs occurred in the first 2 y after the last alemtuzumab course. At Y6, pts with thyroid AEs showed significant improvements from core study baseline in FAMS (least-squares mean change from baseline [95% CI], 4.0 [0.98, 6.92]; $P< 0.01$), SF-36 PCS (1.0 [0.08, 1.94]; $P< 0.05$), and EQ-5D VAS (2.1 [0.06, 4.09]; $P< 0.05$) scores; change in SF-36 MCS score was numerically improved but was not statistically significant (1.1 [-0.09, 2.35]). 80% and 78% of pts with thyroid AEs had stable or improved PCS and MCS, respectively, over 6 y. QoL improvements were also observed in pts without thyroid AEs.

Conclusion: Improvements in QoL were observed with alemtuzumab over 6 y, even in pts with thyroid AEs. These findings further support the favourable benefit-risk profile of alemtuzumab.

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EP1657
Daclizumab: side effects and efficacy in a real world setting

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Background: After European Medicines Agency (EMA) approval Daclizumab (DAC) had been available in Germany for relapsing remitting Multiple sclerosis since August 2016. We started the medication in 53 patients. Due to safety concerns, we discontinued all patients in November 2017.
Objective: An evaluation of 53 patients treated with DAC concerning side effects and efficacy.
Methods: We analysed data of 53 patients (MDOC database) regarding side effects and efficacy of Daclizumab.
Results: 53 patients (10 male, 43 female) were included, mean age 39.6 years, mean EDSS 3.2.
The most and long lasting side effects were skin reactions in nine patients, in two still severely present one year after stop, recovering after Cladribine within 4 weeks. Two autoimmune hepatitis so far showed no recovery, two elevation of liver enzymes normalized. Three inflammatory bowel disease, one iritis, one tenosynovitis, three excessive lymphnode swellings occurred and a life threatening eosinophilic meningoencephalitis, proven by brain biopsy. To our knowledge at that time no similar cases had been reported. One cholangiocellular carcinoma occurred.
All patients had MS activity before start of DAC, on therapy 13 out of 15 had MRI activity and six relapsed.
Conclusion: Compared to the SELECT and DECIDE data we observed more severe side effects than expected. There was no spontaneous recovery in autoimmune hepatitis and severe skin reactions. A life threatening meningoencephalitis made us stop DAC even before the drug was withdrawn from the market. The efficacy in our patients was less than expected: 36% with disease activity on therapy.
There is an unmet need for independent registries to collect in time real life data for safety.

Disclosure
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S. Raunegger has nothing to disclose

EP1658
Tuberculosis screening in the setting of multiple sclerosis disease modifying therapies

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Background: Disease modifying therapies (DMTs) for multiple sclerosis (MS) have diverse effects on the immune system, and several can affect the risk for certain infections such as tuberculosis (TB). Screening for TB is recommended prior to initiation of certain DMTs, but TB testing generally occurs in the setting of ongoing DMT use. Results of the serum Interferon Gamma Release Assay (IGRA) for TB screening may be affected by use of certain DMTs, but this has not been described.
Objectives: To determine the effects of different MS DMTs on serum-based TB screening via IGRA, and to evaluate the degree to which lymphopenia is related to an indeterminate test result.
Methods: We identified all patients with MS at our institution who underwent TB testing via IGRA between January 2016 and December 2017. We recorded the IGRA results, current DMT, and absolute lymphocyte count (ALC). The proportion of patients with indeterminate TB test results was compared across DMTs via Chi-squared testing. Logistic regression will be used to determine whether the odds of indeterminate testing are increased in the setting of lymphopenia.
Results: To date, we have collected overall test information on 955 patients with MS who underwent TB testing via IGRA: 96.3% (n = 920) tested negative, 1.0% (n = 10) tested positive, and 2.6% (n = 25) had indeterminate results. We have analyzed 70 of these records in detail, with collection of DMT and ALC information. 51.4% (n = 36) were on DMTs at the time of testing, including fingolimod, natalizumab, dimethyl fumarate, glatiramer acetate, and interferon beta. There was not a statistically significant difference in IGRA test results across DMT (chi-squared p-value = 0.91). However, at this time, we likely do not have a dataset sufficiently large enough to appropriately examine the association of certain DMTs or lymphopenia with an indeterminate IGRA result.
Conclusions: Overall, abnormal IGRA testing was uncommon in our MS population. Certain DMTs may affect the results and interpretation of serum TB testing via IGRA. Our small database

thus far does not demonstrate consistent patterns of indeterminate results within certain DMTs or lymphocyte counts, likely due to its small size. However, based on clinical observation of this phenomenon, we anticipate more informative data as we continue to include more patients in the study. Ongoing analysis will examine the effects of lymphopenia in more detail.

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Mary A Willis serves on the speakers bureau for Genzyme, Biogen, Novartis, and Ipsen.

EP1659

Patients' perception about risk and benefit in disease modifying therapies: an Italian multicentric survey

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Background: Patient's perception of risks and benefits associated with Disease Modifying therapies (DMTs) is relevant for the therapeutic adherence and the impact on the clinical outcome.
Goals: To investigate in a multicentric survey the response of Multiple Sclerosis (MS) DMT treated patient about the risks and benefits.
Methods: A questionnaire was submitted to 708 patients with relapsing-remitting MS. The questionnaire explored the patient's overall satisfaction with DMTs and their awareness of the potential therapy-specific associated Adverse Event (AE).
Results: 505 participants (65% females, mean age=43) completed the survey. A higher percentage of patients treated with second line (SL) DMTs, compared with patients treated with first line (FL) DMTs, declared to be overall satisfied with the therapy (64.8% vs 45.5%, χ^2=16.5, p< 0.001) and with the related improvement of the quality of life (QoL) (55.1% vs 32%, χ^2=24.6, p< 0.001). The patients of both groups were aware of the AE associated with the DMTs (90.1% vs 93%, χ^2=1.2, p=0.2). No difference was found between oral and injective DMTs experience (51.8% vs 46.7%, χ^2=0.9, p=0.3), but it is higher for infusive treatment (63.7%) respect to oral (51.8%, χ^2=3.5, p=0.06) and injective (46.7%, χ^2=8.9, p=0.003) DMTs.
10.47% of FL-DMTs and 25.9% of SL-DMTs patients might consider to interrupt the therapy to avoid AEs (χ^2=10, p< 0.001). Regarding the Progressive Multifocal Leukoencephalopathy (PML), 92.8% of Natalizumab (NTZ) patients were aware of the possibility to develop PML, compared to 47.6% of Dimetil Fumarate (DF) (χ^2=42.3, p< 0.001) and 67.3% of Fingolimod (FTY) (χ^2=16.1, p< 0.001) patients. A lower percentage of patients treated with NTZ (10%) felt higher levels of anxiety about PML, compared with FTY (15%) and DF (20%, χ^2=3.6, p=0.05).
Conclusion: Infusive therapies have the highest profile for both satisfaction and QoL, followed by oral and injective ones. The patients prefer to face the risk of AE than to interrupt the therapy and this is particular relevant for NTZ treated patients, where the higher PML risk doesn't match with a similar anxiety. The profile of this cohort of patients suggests that a lower amount of information is related to higher anxiety. This should be considered when discussing therapeutic options with patients, since all these elements can influence adherence.

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EP1660

Pharmacy-led prescribing of natalizumab in MS patients improves the quality of monitoring and overall safety

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Introduction: Regular monitoring, with MRI assessments and blood samples, of MS patients on natalizumab exerts a significant burden on specialist centres. We investigated how the introduction of a pharmacy-led prescribing service impacted on the quality of monitoring and on the safety of patients.
Methods: Among patients receiving natalizumab at Imperial College Healthcare Trust (ICHT) MS centre, we evaluated the frequency of consultant reviews and recording of EDSS scores, of JC virus (JCV) status measurements and timeliness of MRI assessments before and after the introduction of a pharmacy-led prescribing and monitoring service.
Results: At ICHT 331 patients are treated with natalizumab each month; 839 prescription charts were reviewed by a pharmacist, between December 2016 and April 2018. Treatment duration ranged from 1 month to 9 years (mean 4.5 years, 53 doses) and

EDSS at last infusion ranged from 1 to 7.5 (mean 3.9). Of the 299 patients reviewed in 2017, the most recent JCV status was negative in 40% (n=120) and positive in 60% (n=178) of patients; 28% (n=83) had low titre (≤ 1.5) and 32% (n=95) had high titre (> 1.5). The pharmacy led prescribing and monitoring service was introduced in December 2016. Following this, a higher number of patients had EDSS score recorded (74% in 2016 to 86% in 2018; p< 0.001) and JCV status assessed (98% in 2016 to 100% in 2018; p=0.13). In addition, we observed a significant reduction of the number of patients, who had an overdue MRI. An MRI was considered overdue if the interval since the last scan was more than 12 months for JCV negative, 6 months for low positive or 3 months for high positive patients.

The number of MRIs overdue fell from 16% in 2016 to 5% in 2018, p< 0.001. In the subgroup with a high JCV titre the number of patients with an overdue MRI fell from 7.6% to 1.8%, (p< 0.001) and no patients had an MRI more than 3 months late. This indicated a significant improvement in timeliness of MRI surveillance.

Conclusion: A pharmacy-led prescribing and monitoring service is feasible, frees up time for the MS clinical team and greatly helps complying with natalizumab monitoring requirements, which overall improves patients safety.

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EP1661

Effectiveness of reduced fingolimod dosage in relapsing remitting multiple sclerosis - a Portuguese cohort

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Introduction: Fingolimod is an oral daily treatment approved for Relapsing Remitting Multiple Sclerosis (RRMS). Lymphopenia or elevated liver enzymes are the main persistent side effects and the reasons to clinicians propose a reduced dose rather than discontinuation of fingolimod. However, current data on the effectiveness of less frequent dosing regimens are scarce and contradictory.

Objectives: To investigate if the fingolimod effectiveness is maintained with reduction in dosing frequency.

Methods: Unicentric, retrospective and observational study at a tertiary Multiple Sclerosis Center. Using our local clinical database (iMed® software), we identified RRMS patients taking reduced dose (nondaily) of fingolimod for at least 6 months. Propensity score-based matching was performed to select patients taking daily dose of fingolimod with comparable baseline characteristics: age, sex, disease duration, annualized relapse rate (ARR) and Expanded Disability Status Scale (EDSS).

Results: We retained 36 patients in each group (reduced dose vs. daily dose of fingolimod) after propensity score matching, with similar baseline characteristics. Lymphopenia was the main reason for switching to reduced fingolimod dose (88.9%), followed by liver function abnormalities (11.1%). Treatment with natalizumab before fingolimod was inversely associated with risk of reducing dose (OR 0.253, 95% confidence interval= 0.08-0.807, p=0.016), while age, disease duration, lymphocyte count before fingolimod, baseline EDSS and ARR were not significant predictors. Before reducing dose, patients took daily fingolimod during 18.5 ±16.01 months. One patient on reduced dose (2.8%) suspended fingolimod and 6 (16.7%) returned to the daily dose; the other patients remain in the alternative scheme for 23.07 ±8.04 months.

The clinical disease activity was similar between patients taking daily dose compared with reduced dose: mean ARR 0.4 vs. 0.3 (p=0.247); median EDSS 2.0 vs. 2.0 (p=0.687); proportion of patients with EDSS increase 9.1% vs. 16.7% (p=0.481). Fingolimod in reduced dose was overall well tolerated and was associated with an increase in the mean lymphocyte count (0.36/mm3 before reducing dose vs. 0.65/mm3 after reducing dose, p=0.009).

Conclusion: These data suggest that the effectiveness of fingolimod is maintained despite the reduction of the dose, allowing to minimize the most common adverse events. These findings warrant further confirmation, ideally with randomized clinical trials.

Disclosure

All the authors: nothing to disclose.

EP1662

Disease-modifying treatment and infectious risk in patients with multiple sclerosis - the experience of a Portuguese tertiary care hospital

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Disease-modifying therapies (DMT) for Multiple Sclerosis (MS) especially non-BRACE drugs raise concerns about infectious risk. Our aim was to analyse the result of a systematic Infectious Diseases consultation (IDC) in a cohort of MS patients about to be treated or already in treatment with non-BRACE DMT.

We collected data from clinical records of MS patients followed simultaneously in the MS Clinic and IDC (2010-2017): demographics, diagnosis, treatment, prior infections, immunizations, prophylaxis and infectious complications.
We found 104 patients (73 females) planned to begin (17 naïve) or switch (87) to a non-BRACE DMT: natalizumab (44), fingolimod (32), dimethylfumarate (16), teriflunomide (6) or rituximab (6). At first IDC, median age was 36 years (IQR 16.8), disease duration was 5.8 years (IQR 7.45) and 27 patients had already started non-BRACE DMT. In 25 (24%) patients a diagnosis of latent tuberculosis (TB) was elicited, 88% of whom were treated due to high risk of TB reactivation. We found a positive varicella-zoster virus (VZV) IgG or a history of varicella in 95 patients and a negative or borderline VZV antibodies in 7 (2 patients were not tested); 53 patients were not immune to Hepatitis B and 47 to Hepatitis A. Vaccination was recommended in all seronegative cases prior to new DMT, which could be done in 6 patients for VZV, 48 for Hepatitis B and 37 patients for Hepatitis A. Due to recurrent genital herpes infection, prophylaxis was done in 1 patient. In 2 patients, low CD4+ count prompted *Pneumocystis jirovecii* chemoprophylaxis. Anti-pneumococcal vaccines were recommended in all cases. In infectious diseases surveillance, 12 patients had urinary tract infections; 8 upper respiratory tract infections; 2 gastroenteritis and 1 tracheobronchitis, herpes-zoster, pustulosis and human papillomavirus related cervical lesion. Two patients were hospitalized due to chickenpox (1 patient already under natalizumab was not vaccinated) and CMV-EBV co-infection, both recovered.
Epidemiology in Portugal places tuberculosis as an important infection to screen, as here confirmed. We underline the high number of patients that were vaccinated which together with prophylaxis measures significantly reduced the risk of infections and allowed a more confident use of the chosen DMT. This study brings important information about the healthcare in MS, highlighting the role of IDC in the individualized observation and risk assessment in the era of enlarging number of DMT.

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EP1663

Tuberculosis screening in patients with multiple sclerosis who are candidates for natalizumab and fingolimod in a Portuguese tertiary centre

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Introduction: Moderate to high efficacy treatments for multiple sclerosis (MS) are biological or immunosuppressor drugs that increase the risk of opportunistic infections, as tuberculosis (TB).
Aims: To describe the prevalence and treatment of latent tuberculosis infection (LTBI) in MS patients who are candidates for Natalizumab or Fingolimod in a Portuguese tertiary centre.
Methods: Retrospective chart review of relapsing-remitting MS patients that received Fingolimod or Natalizumab as first second-line therapy between 2007-2018. We analysed TB screening, its results, prophylactic treatment regimens and related complications. The recommended method for screening is the interferon-gamma assay (IGRA), after exclusion of active TB. Tuberculin skin test was used simultaneously in some patients.
Results: We identified a total of 91 patients for analysis. At the time of screening our cohort had a mean age of 36.4 years (SD= 9.3) and 60 (65.9%) were women. Thirty-three (36.3%) were current or past smokers. Mean duration of disease was 8.7 years (SD= 6.9) and median EDSS was 3.5 (min=0; max=6). Only 13 patients (14.3%) were treatment-naïve and the average days of corticosteroid therapy in the previous 2 years was 5.5 (SD=4.5). Forty-four (48.4%) patients received Fingolimod and 47 (51.6%) Natalizumab. Screening with IGRA was performed in all but 7 patients. The results were as follows: 62 (68%) negative, 13 positive (14.3%) and 9 (9.9%) indeterminate. Twenty-eight patients (30.8%) received prophylactic therapy for LTBI, mostly with a 9-month course of isoniazid (23/28=82.1%). The median interval between treatment for MS and for LTBI was 2 months (min=0; max=17). Hepatotoxicity was reported in 4 patients.
Conclusions: Our results highlight the importance of tuberculosis screening in MS patients before immunosuppression. Positively screened patients should be treated for LTBI and may start therapy after 1 to 2 months. In our patients preventive regimen for LTBI was safe and well tolerated.

Disclosure

All authors have nothing to disclose.

EP1664

Genomic profiling and in vivo rat toxicity characterization of Copaxone and the Synthon European follow-on glatiramer acetate product

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Background: Copaxone (glatiramer acetate, Teva), has provided a safe effective treatment option for multiple sclerosis for 20+

years. In April 2016, a 20 mg/mL follow-on glatiramer acetate product (FoGA, Synthon) was approved in the EU. Employing high resolution physicochemical (PCC) methods, Teva Pharmaceuticals, the manufacturer of Copaxone, has reported consistent differences between Copaxone lots and Synthon FoGA lots in attributes of surface charge distribution and compositional parameters of molecular and spatial size. Also, while within Copaxone specifications for potency, average observed relative potency of Synthon EU lots was higher than mean estimated values of Copaxone lots and 2 of 6 Synthon EU lots were out-of-Copaxone specification range for cytotoxicity testing, showing higher activity and higher lot-to-lot variability.

Objective: Present analyses focus on the genomic profiling and in vivo rat local toxicity assessment conducted to determine the functional characteristics of the active substances in the Synthon FoGA lots as compared to Copaxone lots.

Methods: Three lots of Synthon EU FoGA were compared to 3 randomly selected Copaxone lots for the genomic profile assays (THP-1 cells and ex-vivo activated mouse splenocytes immunized with FoGA or Copaxone). A 13 week rat toxicity study with daily dosing was conducted.

Results: Comparisons of Copaxone vs. Synthon EU FOGA with mannitol correction showed 1802 probesets to differ at adj. $p < 0.05$ in the THP-1 model, and 510 (Copaxone immunization) and 460 (Synthon EU FoGA immunization) probesets in splenocyte model. Many of immunologically relevant expressed genes that differ between Copaxone lots and Synthon EU FoGA lots are relevant to the mechanism of action of Copaxone and exhibit concordance with previously reported PCC and biological attribute differences. In the in vivo toxicity study, the number of skin swelling and induration episodes recorded (minimal-slight severity) following subcutaneous injections of Synthon EU FoGA was higher than that recorded for Copaxone (201 vs 122, $p< 0.0001$; 95 vs 68, $p=0.0177$, respectively).

Conclusions: Consistent differences were observed in genomic profiling and functional characteristics of the active substance in the Copaxone and Synthon EU FoGA lots. Together with the PCC and biological differences previously noted, these observations raise concern for possible immunogenicity differences, particularly in (repeated) substitution settings.

Disclosure

Authors SK, JZ, JF, and BZ are employees of Immuneering Corporation which was contracted by Teva Pharmaceuticals to perform gene expression analyses. Authors NA, BT, OB, AK, JA, PL, MV, VW, SM-G, IG, SN and MRH are employees of Teva Pharmaceuticals Ltd.

EP1665

Risk of pulmonary embolism in patients with multiple sclerosis on dimethyl fumarate

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Introduction: Dimethyl Fumarate (DMF) was FDA-approved for treatment of Multiple Sclerosis (MS) in March 2013. At Ochsner Health System (OHS), we have observed an increased incidence of pulmonary embolism (PE) in patients on DMF.

Objectives: To explore whether DMF use is associated with an increased risk of PE.

Aims: To calculate the cumulative incidence of PE in MS patients taking DMF at OHS between 5/2013-5/2018, and compare it to the cumulative incidence of PE in MS patients not taking DMF at OHS System between 5/2013-5/2018.

Methods: We conducted a retrospective chart review of MS patients between the ages of 18 and 55 treated at OHS between May 2013 and May 2018. All data were collected from Ochsner's electronic health record (Epic). Within this cohort, we determined the cumulative incidence of PE in patients taking DMF and the cumulative incidence of PE in patients not on DMF.

Results: A total of 1,614 patients with MS aged 18-55 were treated at OHS between 5/2013 and 5/2018. Within this group, 424 patients were treated with DMF and 1,190 patients were not treated with DMF. There were 5 PE events (cumulative incidence 1.2%) within the DMF group, and 3 PE events (cumulative incidence 0.25%) within the no DMF group. The difference in the cumulated incidence of PE in MS patients on DMF as compared to MS patients not on DMF is statistically significant at $p = 0.03$ (Fisher exact test).

Conclusions: DMF may increase the risk of PE in patients with MS.

Disclosure

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EP1666

Recurrent autoimmune uveitis after alemtuzumab treatment for multiple sclerosis

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Introduction: Previously reported autoimmune disorders following alemtuzumab therapy include thyroiditis, glomerulonephritis, and autoimmune thrombocytopenic purpura, and have been described as mono-phasic disorders.

Objective: to describe a case of recurrent uveitis occurring in a woman affected by multiple sclerosis, occurring after alemtuzumab therapy.

Methods/**Aims:** We report for the first time a case of anterior uveitis presenting one month after the first cycle of Alemtuzumab that recurred after the second and fifth month from therapy.

Results: We describe a 39-year-old Caucasian woman affected by MS according to current criteria, whose disease course was not modified by previous treatments with beta interferon and glatiramer. In July 2017 she began Alemtuzumab according to standard treatment protocol. She underwent to standard prophylaxis with acyclovir. Three weeks after last Alemtuzumab infusion, the patient presented pain, redness and decreased visual

acuity in the right eye. Slit lamp examination identified protein Tyndall effect and the presence of keratin precipitates, compatible with the diagnosis of anterior uveitis that recovered after steroid therapy. Two similar episodes recurred 2 and 5 months later. HLAB27 antigen, ACE, PCR for viruses were all negative. A diagnosis was made of recurrent bilateral anterior uveitis that lasted in a consistent reduction of visual acuity. Peripheral blood samples study showed an increase in lymphocytic CD28+ expression, significantly higher compared to unaffected controls and also to another MS patient treated with alemtuzumab who did not show signs of autoimmune disorders. A further blood sample performed more than three months after complete stabilization of the last episode of uveitis, showed an initial decrease of CD28+ lymphocytic expression.

Conclusion: This is the first report to our knowledge, describing a new auto immune disorder which appeared indeed to relapse even after steroid therapy was administered. The sustained increase of activated CD28+ cells, which have been associated to uveitis pathogenesis, during the recovery phase from lymphocytes depletion determined by alemtuzumab, may explain the recurrence of the uveitis observed in this patient.

Disclosure

Erika Portera has nothing to disclose.

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EP1667

Prevalence of therapeutic inertia in multiple sclerosis care in Argentina: results from EDUCAR MS 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 despite evidence of disease progression. The consequences of TI include poorer patient's outcomes and diminished quality of life.

Objectives: To evaluate the prevalence of TI in Argentina

Design: 117 neurologists with expertise in MS were invited to participate in an online study. Participants answered questions regarding risk preferences,management of 10 simulated case-scenarios commonly encountered in clinical practice and complications associated with disease modifying agents. TI was defined as lack of treatment escalation when evidence of clinical and radiological activity(8 case-scenarios). 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).

Results: Of 117 invited neurologists, 90 (76.9%) completed the study. The mean age (SD)was 46.4 (10.3); 47.7% were female neurologists and 34.4% were MS specialists.Overall, 36.7% of participants acknowledged some limitations to prescribe MS drugs. There was no difference on restrictions between specialists and general neurologists (p=0.28)

TI was present in 74.4% of participants in at least one case scenario. Themean TI score (SD) was 1.7 (1.4).Specialist were less likely to exhibit TI compared to general neurologists (GN) (mean TI score: 1.10 vs 2.02; p=0.003). The analysis of individual responses (total=720) showed similar results (TI 13.7% specialists vs 25.2% in GN; p< 0.0001).

Conclusions: TI is a common phenomenon in MS care affecting 7 out of 10 neurologists. Findings are similar as in a previous report from other countries.

Disclosure

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EP1668

Fingolimod cessation and multiple sclerosis rebound syndrome: a case report and literature review

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Introduction: Many reports of MS rebound syndrome after cessation of fingolimod have emerged over the last 6 years. This complication, defined as a severe clinical and radiographic reactivation of inflammatory activity exceeding that at baseline, is yet poorly understood.

Aims: To report a case of MS rebound syndrome after fingolimod cessation and review the key features and outcomes of previously reported cases.

Methods: Case report. Systematic review in PubMed using the search terms "fingolimod" + either "rebound", "withdrawal" or "cessation".
Results: A woman whose first MS symptoms date back to age 30 was initially diagnosed with relapsing-remitting MS and treated with interferon β-1a. At age 49, she was escalated to fingolimod due to breakthrough disease, and remained clinically and radiographically stable for 5 years. The emergence of basal cell carcinoma and coincident onset of secondary progressive MS prompted discontinuation of fingolimod at age 54. Five months later, she presented subacute, severe deterioration of cognitive, cranial nerve, motor, sensory and sphincteric function with >15 gadolinium-enhancing lesions on MRI. High dose IV steroids led to nearly complete recovery. A comprehensive literature review identified a total of 45 cases (87% women) across the spectrum of disease (RRMS [80%], SPMS [13%], PPMS [7%]). At time of rebound, the median age was 36 years (range 19-60) with median duration of disease being 11 years (range 2-42). Median fingolimod treatment duration was 2.5 years (range 0.1-10) and reasons for stopping included adverse events (41%), patient decision (33%), onset of SPMS (9%) and lack of efficacy (9%). Median latency from cessation to rebound was 9 weeks (range 2-39). Lymphocyte count was back to normal in 75%. On MRI, 75% had >10 gadolinium-enhancing lesions. 30% required further-line acute treatment after high dose steroids. Recovery was partial or complete in 85%. 15% had life-threatening complications and 1 patient died.
Conclusions: MS rebound after cessation of fingolimod can occur regardless of age, whether relapsing or progressive, even after short treatment periods. It mostly follows discontinuation for reasons other than lack of efficacy. The fulminant enhancement pattern across all stages and duration of disease suggests widespread blood-brain-barrier dysfunction, which may provide key insights into MS pathophysiology. Our analysis may inform patient counselling and strategies to manage this syndrome.

Disclosure

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EP1669

"We'll test your blood for an infection that might kill you" - a qualitative study describing how risks of disease modifying treatment are communicated to people with relapsing multiple sclerosis

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Background: The number of disease modifying treatments (DMTs) for people with relapsing multiple sclerosis (pwRMS) continues to increase. Involving pwRMS in disease management decisions to start, choose between, or switch DMTS, requires provision of evidence-based information about treatments' short and long-term benefits and risks.
Goal: To identify how risks and benefits of DMTs are communicated to pwRMS making decisions about the management of their MS.
Methods: Qualitative interviews (n=30) with pwRMS and focus groups (n = 17, neurologists, MS nurses, pwRMS). Data was analysed within and across sources using thematic framework analysis.
Results: Four meta-themes were identified. 1) *Multiple decisions*: Each choice is emotionally hard and nested in multiple decisions (lifestyle changes). First treatment choices are made when DMT and RMS understanding is limited. Switching DMT is characterised by concerns about progression, and less DMT availability. 2) *Multiple uncertainties.* Decisions are made in a clinical context defined by MS heterogeneity, fluctuating unpredictability, and DMTs which do not completely reduce attacks. 3) *Multiple risks*.

Most DMTs are associated with long term risks. The probabilities and types of risks vary and are not always well quantified. Small risk of death is recalled by pwRMS as oversimplified and overemphasised whilst higher likelihood of co-morbidity (thyroid autoimmunity, hepatotoxicity) appears less likely to be emphasised in consultations. As disability evolves, DMTs previously considered "too risky" are often re-visited and then considered "worth the risk". 4) *Multiple trade-offs*. Major clinical change, such as loss of mobility, and/or significant life events (parenthood and employment), impact on trade-offs along the life course.
Conclusions: PwRMS trade off a complex set of interrelated DMT risks and benefits at multiple interrelated decision points. There is variation in how information is given and little guidance to support reasoned decision making. This project aims to improve the decision making process for pwRMS and health professionals.

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EW: Nothing to disclose

EP1670

Early onset autoimmune manifestations after alemtuzumab treatment for multiple sclerosis: a single-center cohort study

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Alemtuzumab has been demonstrated to reduce the risks of relapse and accumulation of sustained disability in MS-patients compared to β-interferon. With alemtuzumab autoimmune side-effects commonly affect the thyroid (20-30%) and usually occur during the first three after treatment. Recent data have shown that mild neutropenia is observed in 16% of MS-patients whereas severe neutropenia occurred in 0,6 %. We aimed to evaluate the serological parameters, rate, timing of the development of autoimmune manifestations after the first-year of alemtuzumab treatment for MS in our cohort study. We analyzed prospectively clinical and serological data from 16 MS-patients treated with alemtuzumab with median follow-up of 28-months. Four out of sixteen patients (25%) developed thyroid dysfunction after a mean of 11-months following the first alemtuzumab treatment. One patient developed Graves' disease with increased anti-TSI antibodies (11th-month) and another developed Hashimoto´s disease (12th-month). Hypothyroidism in the absence of antibodies was noticed in one patient (13th-month), whereas another patient showed high titers of anti-TG antibodies (6th-month) with normal levels of thyroid hormones. One patient developed generalized erythema-multiforme (2th-month) which resolved after prezolon and antihistamine treatment. Finally, 70-days after the last alemtuzumab-administration one patient displayed neutropenia (500 neutrophils/μL) in the absence of B-cells (0,6% of total lymphocytes), low values of CD4-T-cells (6,6%) and predominance of CD8-T-cells (48%) and NK-cells (47%) with large-granular lymphocytes (LGL) predominating in the blood-smear examination. Due to prolonged neutropenia (5-days) the patient was placed on low-dose corticosteroids leading to sustained remission. Autoimmunity following alemtuzumab therapy in MS appears to occur as part of an immune-reconstitution syndrome. A range of hematologic, dermatological and thyroid side-effects we observed. Patients experienced an early thyroid impairment, a phenomenon that raises the need for regular thyroid retesting every 3-months. The most intriguing feature concerns the expansion of LGL cell population in the peripheral blood of one patient that developed neutropenia.

Disclosure

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EP1671

Hepatitis B reactivation in a patient with primary progressive multiple sclerosis under ocrelizumab treatment

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Ocrelizumab is a disease-modifying therapy (DMT) belonging to the family of anti-CD20 monoclonal antibodies. This drug targets B cells expressing the CD20 receptor and has been recently approved for the treatment of primary progressive (PP) and relapsing (R) multiple sclerosis (MS). Risk of infections is increased during ocrelizumab treatment. Although Hepatitis B virus (HBV) reactivation is considered a possible event because of the evidences coming from similar DMT targeting B cells, no cases of HBV reactivation have been reported for ocrelizumab, so far. Here we describe the first case of HBV reactivation in a patient under ocrelizumab treatment. A 60-year-old Caucasian male affected by PPMS since 2012, with an expanded disability status scale of 6.5 and previously treated with azathioprine, was started on ocrelizumab in February 2018, receiving two administrations of the drug (15 days apart). Pre-ocrelizumab serologic tests showed the presence of antibodies against HBV surface and core antigens (HBsAb and HBcAb, respectively), while HBV surface and e antigens (HBsAb and HBeAg, respectively) and antibodies against HBV e antigen (HBeAb) were negative. Furthermore, pre-ocrelizumab HBV-DNA was undetectable (< 20 IU/ml) and liver enzymes were within normal ranges. Considering the status of

HBV inactive carrier, ocrelizumab treatment was started and HBV infection was monitored with monthly determination of liver enzymes and HBV-DNA, according to a pre-emptive approach. After one month the patient was asymptomatic, liver enzymes remained unchanged, while HBV-DNA became detectable (41 IU/ml). After two months HBV-DNA increased to 132 IU/ml, while liver enzymes remained within normal ranges and patient was still asymptomatic. A treatment for HBV infection with entecavir 0,5 mg once daily was started. The patient is currently under follow-up and HBV-DNA will be assessed monthly. HBV genotyping is underway for resistance mutation detection. Ocrelizumab should be re-administered in three months.
Ocrelizumab can reactivate HBV infection in PPMS patients. HBV-DNA monthly assessment is a valid method to detect pre-clinical HBV reactivation, in HBsAg negative, HBV-DNA negative and HBcAb positive subjects under ocrelizumab treatment. A pre-emptive approach could be an effective strategy for the management of patients with HBV reactivation risk. Prompt treatment with HBV specific nucleoside analogues can limit virus reactivation, avoiding ocrelizumab discontinuation.

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EP1672

A case of immune-mediated encephalitis related to daclizumab therapy

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This report will detail a case of immune-mediated encephalitis in the context of daclizumab therapy. Daclizumab is a humanised monoclonal antibody which, prior to its recent worldwide withdrawal due to safety concerns, was utilised as a disease modifying therapy in relapsing-remitting multiple sclerosis. The withdrawal of this therapy was prompted by concerns over twelve cases of serious immune-mediated adverse reactions in the central nervous system. We report an additional case, including clinical data and results of neuroimaging, CSF examination and brain biopsy

Disclosure

For all authors: Nil to declare.

Tools for detecting therapeutic response

EP1673

Brain atrophy estimation from incomplete clinically-acquired MRI scans - a validation of the MS ´Frankenstein´ approach

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Introduction: Brain atrophy is a promising marker of future disability in multiple sclerosis (MS) and is currently used as an outcome measure in clinical trials. As patients undergo frequent MRI exams, it would be beneficial if clinical scans could be exploited for research purposes. Unfortunately, scanners, protocols, and sequences vary substantially across MS centres and scan quality is adversely affected by time and cost constraints. In particular, we found that the brain is often not fully imaged, e.g. 84% of 76 randomly selected T1-weighted scans acquired on 5 scanners in 3 hospitals in the East Midlands had missing slices. This negatively impacts atrophy estimation approaches, such as SIENA. We previously proposed a SIENA-based method able to deal with missing slices (Pitiot et al. 2017). Here we report results of a preliminary validation study.
Methods: We selected 27 patients (2 CIS, 23 RRMS, 1 PPMS, 1 SPMS) from the Nottingham MS clinic who had at least two T1w scans acquired at different time points, with different protocols and brain coverages. We also simulated cases by cutting a varying number of slices from two complete T1w clinical scans from a healthy control (PSM). In all cases we created two "Frankenstein" scans by combining the potentially incomplete ones with a full scan from either the same patient or a different patient when necessary. We obtained brain atrophy maps from SIENA, visually assessed them for quality control, and estimated annual atrophy rates.
Results: For the real patients, mean age at the time of the first clinical scan was 35.24 years (±8.66) and mean scan interval was 4.78 years (±2.38). PSM scans' were acquired 7 years apart, with the number of missing slices in either or both scans ranging from 0% to 20%. SIENA was unable to process any of the original pairs of scans but could adequately handle 13 Frankenstein patient cases (50%) and all PSM cases (100%). For the patients, the average annual atrophy rate was -0.26%, and -0.19% (±0.03%) for PSM.
Conclusions: We previously proposed an approach enabling SIENA to estimate atrophy in clinical scans with missing slices. The estimated atrophy rates are in keeping with the literature for patients and very tightly grouped for the simulated cases. This suggests great promise for the analysis of abundant clinical data.
Pitiot et al. (2017). Brain atrophy estimation from incompletely acquired clinical MR scans in multiple sclerosis. Poster presented at ECTRIMS-ACTRIMS, Paris.

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EP1674

Using label-free NAD(P)H-FLIM to monitor effect of teriflunomide on NOX enzyme activation in CNS cells

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Introduction: In Multiple Sclerosis therapy an immunomodulatory effect was attributed to teriflunomide. It is known to block the *de novo*synthesis of pyrimidine in mitochondria by reversibly inhibiting the enzyme dihydroorotate-dehydrogenase (DHODH). In adult healthy mice high levels of DHODH activity were measured in the central nervous system (CNS). Besides, astrocytes and microglia - as CNS resident cell subsets - play a pivotal role during the inflammatory response once the disease has been initiated by lymphocytes and macrophages originating from the periphery in MS and EAE.
Objectives: We want to analyse whether these CNS components are affected by teriflunomide, especially the potential induction or inhibition of NOX enzymes activity in the tissue.
Methods: We recently developed a label-free analysis method (NADP(H)-FLIM) by which we can monitor cell function *invivo* to identify the cellular sources of oxidative stress in the CNS of mice. In this way, we analysed in the presented study effects of teriflunomide on NOX activation levels of CNS cells *ex vivo* in slice cultures of healthy mice (basal and after stimulation).
Results: In our *ex vivo* slice culture model, the contribution of astrocytes to oxidative stress within the tissue is equivalent to the contribution of the traditional phagocytes as microglia and macrophages after stimulation, thus reflecting the role of astrocytes as central contributors to oxidative stress in the acute and chronic phases of EAE. Interestingly we could not detect any increase or decrease of NOX enzyme activation after incubation of the tissue with teriflunomide in any analysed cell type in our *ex viv*o model.
Conclusion: We think that our results support the understanding of the direct effect of teriflunomide on astrocytes and microglia, especially regarding oxidative stress. It seems that teriflunomide is in our artificial model not directly anti-oxidative in the absence of overt inflammation. But regarding the drug safety we can also confirm that teriflunomide is not additionally inducing NOX activation in the cultured CNS tissue. A potential effect considering functional consequences of directly reducing neurodegeneration and promoting myelin preservation and repair in MS patients has to be evaluated in the future.

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EP1675

Deep learning for cell-specific high-throughput quantification of oligodendrocyte ensheathment

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Introduction: Reducing myelin injury and enhancing myelin repair are central therapeutic objectives in reversing the progression of multiple sclerosis. Despite the unique identifiable structure of myelin, elaborated by oligodendrocytes (OL), quantifying the injury and repair responses of OLs on a large-scale still poses a significant challenge to researchers. The lack of high-throughput systems capable of extracting cell-specific morphological information has impeded the screening and development of therapeutics aimed at promoting myelin protection and repair.
Objective: To establish automated quantitative approaches that eliminate the time for image acquisition and analysis while successfully matching human analytic quality in assessing OL ensheathment.
Methods: We developed our analytic systems using post-natal rat oligodendrocyte progenitors cultured in nanofiber multi-well plates. The sensitivity of the system to detect biologically relevant effects was validated by treating the cells with brain-derived neurotrophic factor and platelet-derived growth factor to enhance and reduce the number of ensheathing OLs respectively.
Results: We first generated a classic algorithmic approach that used the basic morphological characteristics of OL ensheathments to assess the myelinating potential of OLs. Next, we improved on the classic algorithmic approach by combining automated imaging with deep learning techniques. Our deep learning approach employed a convolutional neural network that followed a "UNet" architecture to learn cell-specific information. During training, the UNet was presented with images appended to single nuclei masks so that the network could learn to associate ensheathments to specific cell nuclei rather than identify ensheathments globally. Through validation on cell-specific and whole-image levels, we demonstrate that both approaches match the accuracy of human segmentations on several parameters, including length distributions and number of sheaths formed per cell. The combination of automated imaging and analysis offers a 5- and 20-fold increase in whole-well analytic speed for the UNet and classic algorithmic approaches respectively
Conclusion: By enhancing analytic speed without sacrificing analytic quality we have developed a high-throughput system capable of quantifying single-cell ensheathments. This new technology permits the detection of nuanced differences associated with myelin injury and repair.

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EP1676

White matter diffusion and myelin integrity improvement after 6 months of fingolimod treatment in relapsing-remitting multiple sclerosis

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Background: Conventional magnetic resonance imaging (cMRI) is mainly used for evaluation of lesional inflammatory activity and diffuse atrophy in diagnosis and follow-up of MS (multiple sclerosis). However, diffusion tensor imaging (DTI) can reveal microstructural alterations in the normal appearing white matter (NAWM), undetectable in conventional MRI.
Objectives: To evaluate structural brain changes, using DTI, in patients with relapsing-remitting multiple sclerosis (RRMS) during 6 months of fingolimod treatment.
Methods: 10 RRMS patients (28-53 years, 10 female, 1 male) and 15 healthy controls (HC, 21-51 years, 9 female, 6 male), were imaged with 3T Philips Achieva MRI scanner. Scanning protocol included 3D T1-weighted and T2-weighted fluid-attenuated inversion recovery sequences and DTI with 64 directions (resolution 2x2x2 mm). T2 hyperintense lesions were segmented with Lesion Segmentation Tool and extracted from WM to yield NAWM masks. The mean values of diffusion scalars, fractional anisotropy (FA), mean (MD), axial (AD) and radial (RD) diffusivities, were calculated with ExploreDTI within whole NAWM and segmented white matter WM regions (deep WM, cingulate, frontal, temporal, occipital, parietal). The extent of white matter damage was also analyzed using tract-based spatial statistics (TBSS). Voxel-wise TBSS analysis was implemented with threshold-free cluster enhancement method (TFCE), with family-wise error correction and threshold of $p < 0.05$.
Results: After 6 months of fingolimod treatment, mean FA was significantly increased ($p = 0.02$) and mean RD decreased ($p=0.04$) in cingulate WM of RRMS patients. TBSS analysis showed that 18.1% of NAWM skeleton voxels of RRMS subjects had significantly decreased FA at baseline imaging compared to HC. This number decreased to 3.7% of voxels after 6 months of fingolimod treatment, compared to HC. The extent of voxels with significantly increased RD was 17.7% and 11.1%, respectively. Meanwhile, there were no significant changes in the T2 lesion, NAWM or GM (grey matter) volumes during the 6 months.
Conclusion: The results suggest improvement in microstructural white matter integrity in RRMS patients after 6 months of fingolimod treatment with concomitantly unchanged cMRI parameters. This indicates, that DTI could be used as a sensitive imaging biomarker in longitudinal studies to evaluate treatment response in the NAWM in MS.

Disclosure

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EP1677

Evaluation of dimethylfumarate in treatment of focal DTH and MOG EAE using TSPO-PET imaging

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Introduction: Dimethylfumarate (DMF) is a therapeutic for multiple sclerosis (MS). The exact mechanism of action is still unknown, however, DMF is thought to promote Th2 polarization of T-cells.
Objectives: The objective of this study was to determine the efficacy of DMF therapy in two different types of focal EAE models.
Aims: Longitudinal positron emission tomography (PET) imaging was performed using the translocator protein (18 kDa, TSPO) -tracer [18F]GE-180 to detect the progression of neuroinflammation during therapy.
Methods: Delayed type hypersensitivity (DTH) and a myelin oligodendrocyte glycoprotein (MOG) EAE rat models were induced by peripheral activation of the immune system and by injecting antigens in a stereotaxic operation. The rats were treated orally twice daily before the lesion formation (starting on day 0 after lesion induction) either with H2O (control group $n = 4$) or with DMF (15mg/kg) diluted in 0.08% methocel and water ($n = 4$). The animals were imaged with [18F]GE-180 on days 0, 7, 14, and 33 (DTH), or on day 14, 33 or 56 (MOG), and the binding potential (BPND) was calculated.
Results: DMF reduced the BPND in the treated animals in the DTH-model when compared to the control animals at day 7 (two-tailed unpaired t-test, $p = 0.031$) and at day 33 ($p = 0.040$), but not at day 14 ($p = 0.66$). In the MOG-model the treatment showed a trend towards decreased inflammation in the treated animals at day 14 ($p = 0.088$). The analysis of histological events is still on-going.

Conclusions: DMF reduces neuroinflammation in the DTH-model after 7 and 33 days of treatment, but at day 14 it did not seem to inhibit lesion formation. In the MOG-model treatment effect was not detected at day 14 or day 33. The research leading to these results has received funding from the European Union´s Seventh Framework Programme (FP7/2007-2013) under grant agreement n° HEALTH-F2-2011-278850 (INMiND). The study was supported by BiogenIdec, GE Healthcare and the Swedish Cultural Foundation in Finland.

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EP1678

Comparative analysis of natalizumab versus fingolimod by including cortical lesions into NEDA-3 concept

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Introduction: Cortical lesions (CLs) are typical of multiple sclerosis (MS) and have been recently incorporated into the MRI diagnostic criteria for MS. Up to date no study has included CLs into the "No Evidence of Disease Activity" (NEDA) status.
Objective. We evaluated the occurrence of NEDA3+CLs in relapsing remitting MS (RRMS) patients treated with natalizumab and fingolimod.
Methods: Natalizumab or fingolimod treated RRMS patients were enrolled in a 2-year longitudinal study with clinical and MRI evaluations performed biannually and annually, respectively. MRI examination included the 3D-double inversion recovery (DIR) sequence to detect CLs. NEDA3+CLs condition was evaluated at baseline (T0) and then annually (T1 and T2).
Results: Eighty-six propensity-matched RRMS patients were included in the study. At T2, NEDA3+CLs was achieved in 72.2% of natalizumab and 11.1% of fingolimod treated patients ($p< 0.005$), as also confirmed by the survival analysis ($p< 0.005$). This difference was mainly explained by the significantly different impact of treatment on CLs accumulation, namely, 11.1% of natalizumab-treated and 61.1% of fingolimod-treated MS patients presented new CLs ($p< 0.005$). At T2, but not at T1, the occurrence of new WM lesions was lower in natalizumab- than in fingolimod-treated patients ($p< 0.05$). NEDA-3 survival analysis disclosed a trend in favour of natalizumab ($p=0.070$).
Conclusion: The inclusion of CLs in the NEDA status highlighted the higher efficacy of natalizumab compare to fingolimod in suppressing focal demyelinating lesions, especially in the cortex of MS patients.

Disclosure

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EP1679

PROMiS (a prospective, non-interventional study in US patients with relapsing-remitting multiple sclerosis treated with alemtuzumab in routine clinical practice): interim results on treatment history and satisfaction with alemtuzumab

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Introduction: In phase 3 studies, alemtuzumab significantly improved clinical, MRI, and quality-of-life outcomes vs SC IFN beta-1a over 2 years (y) in RRMS patients, and remained efficacious up to 6 y. Patient-reported outcome (PRO) measures are increasingly used to understand patients' satisfaction with MS therapies.
Aims: To report interim results on treatment history and patient-reported treatment satisfaction in patients receiving alemtuzumab in clinical practice.

Methods: PROMiS is an ongoing 1-y, real-world, prospective, non-interventional, online PRO study of adults with RRMS in the USA who had initiated alemtuzumab treatment; a 1-y follow-up study will also be performed. Patients were recruited from the MS One-to-One support program under a separate protocol requiring informed consent. Patients provided their baseline (BL) demographics, disease history, and treatment history (including most recent MS therapy and reason for discontinuation), and their level of treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication version 1.4 (TSQM; assesses Side Effects, Effectiveness, Convenience and Global Satisfaction domains; scale 0-100 in each domain; higher scores indicate greater satisfaction). This interim analysis focused on treatment satisfaction at Month (M) 7.
Results: Of the 171 patients included in the interim analysis (mean age 44.8 years; 72.5% female), 97.7% had taken another MS therapy before initiating alemtuzumab, including natalizumab (38.3%), dimethyl fumarate (22.7%), fingolimod (16.2%), glatiramer acetate (15.0%), and interferon beta (7.8%). Main reasons for discontinuing therapy included side effects, medication not working, and worsening of MS symptoms. The mean BL TSQM Effectiveness score (on previous therapy prior to start of alemtuzumab) was 52.7, increasing to 64.0 at M7 ($P< 0.0001$) after alemtuzumab initiation. The mean Side Effects score increased from 72.2 to 81.1 ($P=0.0007$), the mean Convenience score increased from 67.0 to 70.9 ($P=0.0388$), and the mean Global Satisfaction score increased from 50.0 to 68.4 ($P< 0.0001$).
Conclusion: In this interim analysis, patients reported significant improvement in treatment satisfaction across all 4 domains of the TSQM 7 months after alemtuzumab initiation, compared with their previous therapies (or no therapy). It will be important for patients to complete the full alemtuzumab regimen (2 courses) to allow accurate assessment of benefit.

Disclosure

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EP1680

Elevated neurofilament light chain levels in progressive multiple sclerosis effectively reduced by cladribine treatment

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Introduction: Evidence suggests people with progressive multiple sclerosis (pwPMS) may benefit from immunomodulatory disease modifying treatment (DMT). However, only one such treatment (ocrelizumab) has been licensed. The difficulty assessing treatment outcome in pwPMS may be an important cause for the lack of respective DMT. The concentration of neurofilaments in the cerebrospinal fluid provides a substrate of neuro-axonal damage, and both neurofilament light (NfL) and heavy chain levels have been used as outcome indices, and to guide treatment choices.
Objectives: We explored the value of NfL as a marker for treatment success in pwPMS treated with cladribine.
Methods: Here, we report our experience treating two pwPMS with subcutaneous cladribine undergoing cerebrospinal fluid (CSF) Nfl testing, alongside MRI and clinical follow-up, before and after treatment.
Results: CSF samples obtained before and after treatment revealed substantial reduction of NfL levels in both cases (from 1700pg/ml to 453pg/ml in case 1, and from >10.000pg/ml to 525pg/ml in case 2), corroborating the MRI detectable drop in disease activity.
Conclusions: The level of NfL seems to be a sensitive index of treatment success in pwPMS. Cladribine, or the oral prodrug preparation (Mavenclad®) that has recently been licensed (in Europe) for relapsing MS, may be an effective treatment option for people at an advanced stage of MS.

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EP1681

Tolerability and persistence in therapy with PEGylated-IFN: results from a multicentric observational study in northern Italy

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Objectives: PEGylated Interferon (PEG) pivotal trials in Multiple Sclerosis (MS) have shown its favourable efficacy and tolerability profile. Aim of this study is to confirm these data in a real-life setting and understand predictors of good tolerability and persistence in therapy.
Materials and methods: We invited MS centres in Lombardy to prospectively follow MS patients who started PEG in the two-year span 2015-2016, recording demographic and clinical features and laboratory tests results.
Results: 251 patients (166F) were enrolled from 9 MS centres (mean age 42.1 ± 10.6 years (y)), mean disease duration 11.2 ± 7.8 y). Mean ARR in the two y before PEG was 0.2 ± 0.2; median baseline EDSS was 1.5. 31/251 patients were treatment naïve and 94/251 started PEG switching from Interferon (IFN) once a week (IFN-1w), 109/251 switched to PEG from IFN multiple times a week (IFN-mw), while 17/251 switched from other therapies. Mean follow up was 21 ± 5.1 months. 178/251 patients reported Adverse Events (AEs): 60% (n=151) complained of flu-like syndrome (FLS) (in 46 cases leading to PEG discontinuation), and 27% of skin reactions. FLS was reported more frequently by patients switching from IFN-1w (74%), compared to patients previously treated with IFN-mw (48%), naïve (61%) or other patients (59%) (p=0.03). Other notable AE included blood test count abnormalities (2%, in 3 cases leading to discontinuation) and elevation in transaminases (3%, 3 leading to discontinuation). 94/251 patients stopped PEG: 65 for AEs, 6 for pregnancy and 23 for disease activity. 29% of the patients switching from IFN-1w stopped PEG, with respect to patients previously treated with IFN-mw (14%), naïve (6%) or other patients (41%). Predictors of non-persistence in therapy were switching to PEG from IFN-1w (HR 0.31, 95% CI: 0.06-0.86, p = 0.001), but not gender, age, disease duration, baseline EDSS or the number of previous therapies. Among patients switching to PEG from IFN-mw no increase in the relapse rate was observed.
Discussion and conclusion: Despite the limitations of an open label study, our data seem to confirm the good tolerability profile of PEG. Switching from non-PEGylated IFN to PEG does not seem to affect relapse rate. Persistence in PEG is maximized in patients whose previous IFN regime was of high frequency, suggesting that the benefit of a sharp decrease in the number of injections overwhelms PEG side effects.

Disclosure

PA received honoraria for lecturing and participation in advisory boards, and/or travel expenses for attending congresses and meetings from Merck, Biogen, Teva, Sanofi-Genzyme, Almirall, Roche and Novartis.
GM received support to travel to scientific meetings from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Sanofi-Aventis, Teva; received speaker honoraria from Biogen Idec and served on the scientific advisory board for Biogen, Genzyme and Merck Serono.
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VM received honoraria for participation in advisory boards and/or travel expenses for attending congresses and meetings from Merck, Biogen, Teva, Sanofi-Genzyme, Roche and Novartis
CB served on the scientific advisory board for Merck
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MR, AMP, ES, MLF, and LA have nothing to disclose

EP1682
Comparative efficacies of dimethyl fumarate and fingolimod in quantitative radiographic disease measures using clinical MRI

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Background: Quantitative measures of radiographic disease makers in multiple sclerosis (MS) are important in clinical trials and in clinical practice, where clinical MRI scans are difficult to standardize. DMF and FTY are oral disease-modifying agents (DMT) that are effective in reducing relapse rate in randomized placebo-controlled trials. Their comparative efficacies in quantitative radiographic outcomes are unknown.
Objective: To quantify and compare dimethyl fumarate (DMF) and fingolimod (FTY)'s effects on brain parenchymal fraction (BPF) and T2 lesion volume (T2LV) using clinical MRI scans of MS patients from a retrospective cohort.
Method: Available MRIs were collected from an existing clinical practice cohort treated with DMF and FTY. Subjects with scans at baseline, 12 month, and 24 months were selected. Scans were extracted and pre-processed. BPF and T2LV values were obtained via a previously validated automated machine-learning algorithm.

A propensity score (PS) model was built using baseline patient characteristics. PS weighting was utilized to compare BPF and T2LV values with linear regression models.
Results: Baseline BPF and T2LV were similar for DMF and FTY groups (p = 0.445, p=0.861, respectively). PS adjustment achieved good covariate balance between the two groups. At 24 months, BPF was higher by 0.004 in FTY group as compared to DMF (p = 0.020). Although FTY group has 0.324ml less T2LV as compared to DMF at 24 months, there was no statistically significant difference in T2LV between the two groups (p = 0.741).
Conclusion: In a real world setting, automated imaging techniques can successfully quantify radiographic disease measures using clinical MRI scans. Both DMF and FTY treated grups observed increases in T2LV and decreases in BPF at 24 months compared to baseline. Patients who received FTY have slightly less brain atrophy at 24 months compared to DMF group. There was no statistically significant differences in T2LV between the two groups.

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EP1683
Favorable response to disease modifying treatments in Chinese patients with relapsing multiple sclerosis - results from a prospective registry in Hong Kong

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Background: Limited data exist regarding the response to disease modifying treatments (DMTs) and their side effects in Chinese patients with relapsing multiple sclerosis (MS).
Methods: Relapsing MS patients, who were prescribed approved DMTs for MS, were identified from the prospective Chinese University of Hong Kong - Multiple Sclerosis Registry (CU-MSR). We included subjects who used DMTs for at least six months to evaluate annualized relapse rate (ARR), including subjects who were treatment-naïve or switching from first-line agents. Patients were evaluated by nurse and neurologist for all suspected relapses, and all patient-reported side effects were recorded.
Results: We identified 64 subjects who were prescribed DMTs between March 2013 to April 2018. The DMTs used were interferons (n=54, 84%) [interferon-beta-1a subcutaneous (41, 64%); interferon-beta-1a intramuscular (15, 23%); interferon-beta-1b subcutaneous (4, 6%)] and fingolimod (27, 42%). The mean age was 29.4 +/- 9.6 years; 48 (75%) were female; disease duration was 5.8 +/- 9.6 years, Expanded Disability Status Scale at drug initiation was 2.0 +/- 2.0, and duration of DMTs used was 4.6 +/- 3.5 years.
For treatment-naïve subjects, the ARR and relapse rate reduction (RRR) were: interferon (ARR 2.18 to 0.74, RRR 60.0%, p< 0.001); fingolimod (ARR 5.86 to 0.32, RRR 94.5%, p< 0.05). For subjects who switched to fingolimod as a second-line agent, the ARR was reduced from 1.82 to 0.35 (RRR 80.7%, p< 0.001).
The commonest side effects were: interferons - flu-like symptoms (42.6%), injection site reactions (33.3%), malaise (22.2%); fingolimod - liver derangement (3, 11.1%); grade 4 lymphopenia (3, 11.1%), herpes zoster infection (2, 7.4%), and significant bradycardia requiring prolonged first-dose monitoring (1, 3.7%).
Discussion: We found very favorable improvements in relapse rates and good safety profiles to interferons and fingolimod among Chinese MS patients. The higher RRR as compared with published literatures could be due to the inclusion of clinically definite MS patients with higher pre-treatment relapse rates.

Disclosure
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Symptomatic treatment

EP1684
Italian botulinum toxin network study on the management of spasticity in multiple sclerosis

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Background: Spasticity can result in gait disorders, upper-limb dysfunction and pain. Intramuscular injection of botulinum toxin (BT) has proven efficacy for spasticity in multiple sclerosis (MS) but, so far, little evidence is available on the use of BT in the clinical management of MS. We aim to describe the use of BT in MS, in relation to clinical features and concomitant treatments.
Methods: This is a retrospective observational study within 15 Italian BT network centres. Patients with MS and injected with BT were included. We collected characteristics of BT injections, MS features and concomitant treatments. Linear regression models were used to explore correlates of BT injections; different BT formulations were included as covariates in the statistical models.
Results: We included 281 MS patients (age 53.7±11.3 years; female 59%; EDSS 6.5 [2.5-9.5]). Main goals of BT injection were movement (43%), functioning (18%), pain (15%), hygiene (15%), and ease in daily assistance (9%). Patients underwent 5.8±5.7 BT injections in the past, every 4.5±3.5 months; patients with more injections in the past received higher BT dose (Coeff=11.14; 95%CI=4.77/17.51; p=0.001). Higher BT dose was associated with higher Expanded Disability Status Scale (Coeff=48.40; 95%CI=21.70/75.11; p< 0.001) and with higher Modified Ashworth Scale (Coeff=110.32; 95%CI=56.39/164.25; p< 0.001). BT was the only treatment for spasticity in 48.8% patients, whilst 51.2% patients were treated with 1.4±0.7 concomitant medications; higher BT dose was associated with more concomitant treatments, (Coeff=111.619; 95%CI=41.052/182.185; p=0.002).
Discussion: This is the largest study conducted on the use of BT in MS. BT in monotherapy can be used for spasticity-related symptoms in MS, particularly in less-spastic patients at low dose. Once disease severity increases, higher doses of BT and additional medications can be considered.

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EP1685

"I'm in a very good frame of mind": the experience of standing frame use in people with progressive multiple sclerosis

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Introduction: People with severe multiple sclerosis (MS) often find it difficult to stand independently, spending most of their day sitting down. Disabling complications resulting from immobility can be minimised if physical activity is increased.
Aims and objectives: The aim was to explore the impact of engaging in a self-managed, home-based standing programme, from the perspective of people with severe MS and their carers.
Methods: This qualitative study was embedded within a multicentred randomised controlled trial (RCT) evaluating the clinical and cost effectiveness of a home-based standing programme. We explored the experiences of 12 people with progressive MS (six female, aged 35 - 71 years) and eight carers (four female), who used an audio diary to record their thoughts and feelings about using a standing frame over 36 weeks. Recordings were transcribed verbatim and data analysed thematically. Data was triangulated with informal exit interviews from 126 persons participating in the RCT.
Results: Four themes emerged: (1) 'Feeling like the old me' encompasses the sense of normality gained from standing, and the physical, psychological and social benefits experienced; (2) 'Noticing a difference' captures the variety of changes people reported in their function as well as wide ranging symptoms such as spasms, strength, bladder and bowel function; (3) "I want to do it right" reflects the value placed on having guidance and support in establishing a standing programme that worked for them; (4) "You have a good day, you have a bad day" highlights the issues faced by people living with a progressive and fluctuating condition in implementing a self-management programme.
Conclusions: The use of a standing frame enabled people to incorporate regular standing within their lives, which was an

activity many had not achieved for some time. In addition to the objective physical benefits demonstrated from the RCT, the qualitative data highlighted wide ranging physical, psychological and social benefits. It underlined the importance of providing people with support and guidance in sustaining this over the longer term.

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EP1686

Biofeedback based home balance training can improve balance but not gait in people with multiple sclerosis

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Background: Impaired balance is common in people with multiple sclerosis (MS) and can be present even in persons with mild disability level. With increasing disability level gait and balance impairment progress and lead to increased risk of falls. In some recent studies interactive commercial video games were used for improving balance but their limitation is lack of individual training parameters settings.
The aim of this study was to evaluate the effect of balance exercise in home setting using Homebalance® system.
Methods: Participants were assessed at baseline, after 4 weeks of home training and follow up after 4 weeks. The primary outcome was the Berg Balance test and the Mini-Best test. The secondary outcome measures include Timed Up and Go test, Timed 25 foot walk test and spatio-temporal gait parameters evaluation using GAITRite instrument. Patient reported outcome include 12-item MS Walking Scale, Activities-Specific Balance Confidence Scale a Falls Efficacy Scale.
The intervention consisted of home-based balance training performed daily for 15-20 minutes for 4 weeks using Homebalance® system in standing position. First exercise session was supervised by physiotherapist who individually set exercise parameters.
Results: Total number of 23 people with relapsing-remiting MS (4 men) were enrolled to the study. Mean age was 39,3 (SD 9,6), disease duration 14,9 (SD 8,5) and EDSS 3,9 (SD 1,9). After training significance improvement was reached in Berg balance (p=0.001) and in Mini-Best test (p=0.001). This improvement did not persist at follow-up assessment after interrupting training. Gait performance measured did not reach improvement. Patient reported outcomes did not reach significant improvement.
Conclusion: Short term home balance training using Homebalance® (stabilometric platform providing audio-visual biofeedback) showed positive effect on balance but not on gait performance in people with MS. Long term study is needed to confirm this results.
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EP1687

Does cognitive training improve attention/working memory in persons with MS? A pilot study using the Cogmed Working Memory Training program

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Background: Cognitive impairment is common in persons with MS (PwMS), with estimates ranging from 40-65%. It is frequently cited as the reason for work disability and lower quality of life. Improving cognitive functioning in PwMS represents an important therapeutic target. Recent work has shown promise for cognitive rehabilitation to improve attention/working memory, defined as the ability to maintain and process/manipulate information in the mind. As attention/working memory deficits are common in MS, training this cognitive domain may improve cognition and thus lead to improved function in PwMS.
Objective: To determine whether cognitive training with Cogmed Working Memory Training (CWMT) improves attention/working memory in PwMS.
Methods: PwMS, either relapsing or progressive, aged 18-64, who demonstrated impaired attention/working memory on 2 of 3 measures (Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modality Test (SDMT), and/or Stroop Colour Word Test (Stroop)) were randomized to CWMT training for 5 weeks (5 days per week, 30-60 minutes daily) or to a no treatment group. These 3 measures served as the co-primary outcomes. Upon recruitment, other measures of mood, cognition and quality of life served as secondary outcomes. Participants were not blinded to group assignment but all assessors were blinded. Participants received follow up assessments 6 weeks and 6 months post-intervention (the no treatment group received the same assessments at equivalent time frames). Analysis of covariance was performed to compare treatment and control groups at pre and post-intervention on primary outcomes.

Results: At the time of this submission, 22 participants had completed baseline and 6-week post intervention assessments; 12 were assigned to CWMT. There was no difference between the two groups on age (CWMT (51.0) vs. no treatment (53.1) years, p=0.32), gender (CWMT (8) vs no treatment (7) females, p=0.29) or type of MS (CWMT (6) vs. no treatment (8) relapsing, p=0.53). After 6 weeks, the CWMT group showed significant improvement on the PASAT compared to the no treatment group: 28.6 ± 4.6 and 30.0 ± 3.2 at baseline, compared to 35.9 ± 3.8 and 30.8 ± 3.2 at 6 weeks, in the CWMT and no treatment groups respectively ($p < 0.001$). There was no significant improvement noted on the SDMT or Stroop.
Conclusion: This pilot study demonstrates that cognitive training with CWMT has the potential to improve attention/working memory in PwMS.

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EP1688

Implementing cognitive rehabilitation for people with multiple sclerosis: translating research into clinical practice

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Introduction: People with multiple sclerosis (PwMS) frequently report cognitive problems, which can affect function and quality of life. Although the effectiveness of cognitive rehabilitation to address these problems is evaluated in research studies, inadequate reporting of the content of the interventions may hamper clinical implementation.
Aims: To develop an evidence-based, clinician-informed checklist to guide researchers to better report cognitive rehabilitation studies in order to increase the clinical impact of research.
Objectives: To review how cognitive rehabilitation for PwMS is reported in scientific journals; to complete a detailed analysis of the actual content of the intervention delivered as part of a large-scale cognitive rehabilitation in MS (CRAMMS) trial; to reach consensus on the content of cognitive rehabilitation interventions for people with MS that should be reported in research studies.
Methods: Mixed-methods research with three phases: (1) A systematic review of descriptions of the content of cognitive interventions to document salient details and omissions in reporting; (2) A content analysis and time-sampling analysis of video recordings of an intervention delivered as part of the CRAMMS trial, focusing on the content of treatment. Findings from these two stages informed phase three; (3) A modified Delphi consensus study with healthcare professionals and researchers who work with PwMS, which ascertained the key aspects of cognitive rehabilitation that research studies should report to enable implementation in clinical practice. The outcome of this stage will be a consensus checklist.
Results: (1) 54 studies involving different types of MS and techniques to address difficulties with memory, attention and executive function were included in the review. The published results showed that important features of cognitive rehabilitation, such as intervention procedures, were not reported well. (2) The content analysis showed that all components of the CRAMMS manual were delivered as planned. The most frequent discussion topic for both therapists and patients was memory and attention coping strategies. (3) The Delphi consensus study is ongoing.
Conclusions: The development of an appropriate, clinician-informed, evidence-based checklist is vital as it will enable researchers to report important aspects of complex cognitive rehabilitation interventions which may enhance the implementation of such research in clinical practice.

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EP1689

Medical and recreational cannabis use in patients with multiple sclerosis in Denmark

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Introduction: In Denmark cannabis is illegal for recreational use and the criteria for physicians to prescribe cannabinoids for neuropathic pain and spasticity to patients with multiple sclerosis (MS) are very rigorous, why few patients are offered this treatment.
Objective: To evaluate the prevalence, benefits and side effects of medical and recreational use of cannabis among MS patients.
Design: Cross-sectional survey in Denmark.
Methods: All patients at the Danish Multiple Sclerosis Center (DMSC), Copenhagen University Hospital, were sent an anonymous web-based questionnaire. The 38-items questionnaire included questions about sociodemographic and lifestyle factors, disability status, pain, spasticity and medical or recreational cannabis use.
Results: Questionnaires were completed by 1411/3606 (39.1%) and included 1338 (94.8%) patients with MS. Forty-nine percent had used cannabis at least once and of these 78% used cannabis in form of hashish or hash oil. Cannabis was used on a daily basis by 9.4% (133/1411). Only 10% of the cannabis users received prescribed cannabis-based medicine. The primary reason for cannabis use was to alleviate MS symptoms such as pain (73 %),

spasticity (62%) and sleep disturbances (59%). Reasons for recreational use included pleasure (42%) and party (29%). The most common side effects were drowsiness (37%), feeling quiet/subdued (28%) and balance problems (16%). Three percent had hallucinations when using cannabis. Almost half (45%) of the non-cannabis users would use cannabis to alleviate MS symptoms if the drug were legalized.

Conclusion: MS patients primarily used cannabis to alleviate MS symptoms such as pain, spasticity and sleep disturbances. Only 10 % of the cannabis users received prescribed cannabis-based medicine, which indicates that cannabis is often used without supervision by a physician and that illegal use is common. Furthermore, around half of the non-cannabis users would use cannabis to alleviate MS symptoms if the drug were legalized.

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F. Sellebjerg: Has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, EMD Serono, Merck, Novartis, Roche, Sanofi Genzyme and Teva.

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EP1690

A prospective observational registry of repository corticotropin injection for the treatment of multiple sclerosis relapse: baseline characteristics and updated interim results

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Background: Despite recent advances in multiple sclerosis (MS) treatments, patients continue to experience relapses. Effective treatment of MS relapses is highly important to minimise acute disability and potential residual deficits.

Objectives: To characterise patients receiving repository corticotropin injection (RCI) for treatment of acute MS relapse and describe treatment patterns, MS relapse recovery, and safety outcomes. The primary outcome measure was change in MS Impact Scale (MSIS-29v1) score from baseline (BL) through Month 2.

Methods: Patients whose MS relapse was treated with RCI were clinically evaluated and assessed with the MSIS-29v1, Expanded Disability Status Scale (EDSS), and Clinical Global Impression of Improvement scales. Health outcome assessments were also conducted.

Results: As of March 24, 2018, 120 patients had entered the study from multiple sites; presented results are from 98 patients in the intent-to-treat population. Mean age was 47.5 years; 88.8% of patients were female, and 86.7% were Caucasian. At BL, mean MSIS-29v1 physical subscale score (scaled to 100) was 56.3, and mean EDSS score was 4.0. The average time since diagnosis of MS was 10.6 years; 53.1% of patients had experienced a relapse within the last 2 years, and 61.2% had a history of insufficient treatment response, intolerance, or intravenous access problems associated with highdose corticosteroids. Diseasemodifying therapies (DMTs) most often used concomitantly with RCI were dimethyl fumarate (21.4%), natalizumab (16.3%), teriflunomide (12.2%), ocrelizumab (9.2%), glatiramer acetate (8.2%), fingolimod (7.1%), and interferon beta-1a (6.1%). Mean MSIS-29 physical subscale scores significantly improved from BL by 6.8 at Month 2 and by 11.0 at Month 6. There were 86 adverse events (AEs); 15 were serious AEs (SAEs), and 1 patient had an SAE (atrial fibrillation and dyspnoea) deemed related to RCI treatment by the investigator, resulting in study discontinuation and early termination.

Conclusions: This ongoing study is assessing current practices relating to RCI and its impact on clinical outcome assessments after acute MS relapse. BL data suggest that patients receiving RCI tend to be older, have longer MS duration, and use more contemporary DMTs than patients in prior relapse recovery studies. Despite this, interim results suggest clinically meaningful improvements in MSIS-29v1 scores and support the efficacy and tolerability of RCI as a treatment for MS relapse.

Disclosure

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EP1691

Work out training, coordination training and an active control condition improved subjective sleep, fatigue and symptoms of depression and anxiety among female patients with multiple sclerosis (MS)

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Background: There is increasing evidence that regular physical activity improves dimensions of quality of life among patients with Multiple Sclerosis (MS). To illustrate, symptoms of depression, fatigue and paresthesia improved after aquatic exercise and yoga, compared to a control condition. However, no data are available as regards further types of intervention and as regards their impact on sleep and anxiety and cognitive performance. The aim of the present study was accordingly, to investigate, if coordinative exercising, workout and an active control condition (handcrafting) improved symptoms of depression, fatigue, paresthesia and sleep among female patients with MS and under stable medication treatment.
Methods: A total of 56 female patients (mean age: M = 34.5 years) took part in the study, who were randomly assigned either to the workout group, the coordinative group, or to the active control condition (handcrafting, leisure time activities). The intervention lasted eight weeks, for three sessions per week. At baseline, four weeks later and eight weeks later (end of the study) participants completed a series of self-rating questionnaire focusing on depression, fatigue, paresthesia, intolerance of uncertainty, and sleep quality. Further, a brief cognitive testing was performed at baseline and at the end of the study.
Results: Depression, paresthesia, fatigue, intolerance towards uncertainty, and sleep quality improved over time. Cognitive performance improved. No group differences were observed, though, descriptively, coordinative exercising showed highest improvements.
Conclusions: To the best of our knowledge, this is the first study to show that also among patients with MS exercising impacted positively on sleep, intolerance of uncertainty and cognitive performance. Further, depression, paresthesia and fatigue improved. Last, improvements were also observed in the active control condition, suggesting that in interventions of exercising, the dimension of the social setting should not be underestimated.

Disclosure
nothing to disclose

EP1692
Intrathecal phenol is a forgotten treatment option for severe lower limb spasticity in advanced multiple sclerosis

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Introduction: Spasticity is a common symptom affecting people with multiple sclerosis (MS) and has a significant impact on quality of life. Treatment options include oral medications, botulinum toxin and intrathecal baclofen however these interventions may be ineffective or not suitable for people with advanced MS and severe lower limb (LL) spasticity.
Intrathecal phenol treatment (ITP) is an effective option in such people, but due to its destructive nature has not gained widespread use.
Objective: To review safety and efficacy of ITP in people with advanced MS and severe LL spasticity.
Methods: Data were collected prospectively from patients admitted for consideration of ITP between 2006 and 2018. Baseline demographics, spasticity assessment including Ashworth Scale for 12 muscle groups, Penn spasm frequency scale, passive range of motion (PM), numerical rating scales (NRS) and goals of treatment were collected. Prior to ITP a trial with intrathecal bupivicane was performed to confirm potential efficacy.
Results: 49 patients (mean age 51.5yrs,30 females) were admitted. Intrathecal bupivacaine was administered in 46 patients. 45 subjects proceeded to ITP (39 bilateral, 6 unilateral); 2 patients did not proceed due to side effects of the bupivacaine trial and predicted failure to achieve goals. 2 patients neither underwent the trial nor ITP due to concerns regarding side effects or absence of severe spasticity. 1 patient proceeded directly to ITP as the potential risks of the trial outweighed the benefits.
Following ITP, there was a significant reduction in Ashworth scores (mean -14.64;$p< 0.001$), Penn scores (mean -2.92;$p< 0.001$), NRS for pain, comfort and spasticity($p< 0.001$) and significant increases in PM at 5 LL joints ($p< 0.01$). Goals focussed on: ease of positioning (n=34), improved comfort (n=28), skin integrity (n=12), ease of personal care (n=33), pain (n=11), seating (n=17) and reduction of oral medications (n=23). All goals were achieved except 3 patients who did not achieve seating goal due to LL contractures.
ITP was well tolerated: adverse events included hypotension with intrathecal bupivicaine(n=9), myocardial infarction preventing treatment with ITP(n=1), infection(n=2), nausea(n=1).
16(35%) patients required repeat ITP after a mean interval of 11.4 months as spasticity and spasms returned.
Discussion: ITP is a highly effective option for severe LL spasticity, spasms and pain in appropriately selected patients with advanced MS.

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EP1693

Evaluation of the cognitive benefits of intrathecal baclofen pump implantation in subjects with intractable MS related spasticity

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Introduction: Spasticity is a common symptom in Multiple Sclerosis. Anecdotally patients report improved concentration/ cognitive performance when switching to intrathecal baclofen (ITB).
Aim: To explore whether subjects who proceed with ITB pump implantation and reduce oral anti-spasticity agents will improved on measures of cognitive function.
Methods: Thirty subjects admitted for trial of ITB via lumbar puncture and pump implantation. Measures performed pre ITB trial and at 3 months: Ashworth, Penn spasm scale, VAS: pain, stiffness, spasm, EDSS and medications. Neuropsychological tests: Sustained Attention to Response Test, Symbol Digit Modalities Test, California Verbal Learning Test-2nd Edition, WAIS-III Digit Span, VOSP Incomplete Letters and Position Discrimination subtests, Delis-Kaplan Executive Function System tests. Hospital Anxiety and Depression scale and Fatigue Severity Scale.
Paired t test for within subject change and effect sizes (Cohen's d) were calculated. Subgroup analysis of those on ≥2 or ≤ 1 spasticity medications at baseline. Re-analysis excluding 2 non-MS patients.
Results: 29 subjects completed per protocol. Mean age 46 years [30 - 56], disease duration 15 years [6 - 23], RRMS = 3, SPMS = 17 and PPMS=7. 24 were on multiple spasticity medications. Ashworth, Penn, VAS scores significantly improved with ITB. Mean ITB dose at 3 months was 144.5 mcg/day, 19 discontinued all other treatments. There was no deterioration on any cognitive or mood measure. An improvement of moderate effect size was found in Backwards Digit Span (d=0.45, p=0.038) and HADS - anxiety (d=0.47, p=0.018). FSS score decreased (d=0.52, p=0.014). This effect increased excluding 2 non-MS subjects, effect size d=0.59, p=0.008. Small improvement in SDMT score (d=0.26) and SART response time (d=0.25) were nonsignificant. Performance on other measures did not change.
A trend for improvement in depression scores was noted, (d=0.36, p=0.067).
Effect sizes were larger in subgroup on ≥2 oral spasticity medications at baseline, compared to the group on ≤1 medication (SDMT, d=0.46 vs d=0.02; Backwards digit span 0.47 vs 0.37; HADS-anxiety 0.50 vs 0.39; HADS-depression d=0.45 vs 0.20 and FSS, d=0.57 vs 0.42).
Conclusions: Switching to ITB resulted in improved spasticity scores and improvement on some measures of fatigue, anxiety, auditory attention/verbal working memory. Improvement of speed of processing was noted in those withdrawing higher doses of oral medication.

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EP1694

THC/CBD oromucosal spray in patients with multiple sclerosis bladder dysfunction: a pilot prospective study

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Background: Among symptoms with great impact on pwMS (people with Multiple Sclerosis), spasticity and urinary disturbances play a relevant role. Beyond the effect on spasticity, Cannabis has been associated with improvement in sphincteric disturbances. To our knowledge, few studies have been conducted to evaluate the effect of tetrahydrocannabinol-cannabidiol (THC/CBD) on urinary disturbances by instrumental methods.
Objectives: To assess the effect of THC/CBD (Sativex) oromucosal spray on urodynamic parameters evaluated in pwMS.
Materials and methods: This is an ongoing longitudinal study with three time-points (before the beginning of Sativex treatment (T0), after one (T1), and six (T2) months. A spasticity assessment by numerical rating scale (NRS) and VAS scales for spasms, tremors and pain, the MS Quality of Life-54 questionnaire were performed at each time-point. Patients also underwent urinary diary and urodynamic assessment: amelioration in urodynamic test will be defined by the reduction in the amplitude of the maximal detrusorial contraction (P-det) of at least 20 cmH2O and by the increase of the baseline bladder filling capacity (MaxCC) of at least one third of the value at baseline.
Results: Fourteen pwMS were enrolled in the study. All the participants performed T0 and T1 evaluation, and six of them also completed T2 evaluation. All the sample referred voiding dysfunction at T0; 50% of the sample reported improvements in urinary urgency at T1 and 75% of sample at T2. From T0 to T1, P-det value decreased in 9/14 patients (64%), and of 20 centimetres or more in three patients (27%). MaxCC increased in 10/14 patients (70%) and at least one third in five patients (38.5%). P-det value

decreased in all the sample at T2, but only one showed a decrease of 20 cm or more. MaxCC increased in 2/6 patients, but none of them showed an increase of one third of the initial value. The overall NRS score improved from 7.4 ± 1.3 (T0) to 5.3 ± 2.0 (T1) and to 5.2 ± 2.6 (T2).

Discussion and conclusion: Through the analysis of this preliminary data, Sativex seems to have an appreciable effect in ameliorating subjective perception of urinary urgency and objective urodynamic parameters, though the improvement in P-det and in MaxCC in our sample was weakly significant. An in-depth statistical analysis, also with the data received from the patients still in treatment, could highlight the effect of the Sativex in improving voiding dysfunction in pwMS.

Disclosure

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Brambilla L. received honoraria for speaking from Novartis and for traveling from Sanofi-Genzyme and Roche; acted as an Advisory Board member of Sanofi-Genzyme; she is involved as principal investigator in clinical trials for Roche.

Confalonieri P. acted as an Advisory Board member of Biogen and Novartis; received funding for traveling from Biogen, Merck, Teva, Novartis; received honoraria for speaking or writing from Biogen and Novartis. He received support for research project by Novartis and Merk and is involved as principal investigator or co-investigator in clinical trials for Teva, Novartis, Biogen and Merk.

Studer V. received honoraria for traveling from Merck; she is involved as principal investigator in clinical trials for Novartis and Biogen.

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Mercurio S., Tonietti S and Politi P. have nothing to disclose

EP1696

A survey of cannabis-based product use in multiple sclerosis patients at the University of British Columbia Hospital

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Background: Cannabis-based products (CBP) are used both recreationally and for symptomatic management in multiple sclerosis (MS). We set out to investigate the current spectrum of CBP use at the University of British Columbia (UBC) MS clinic through a patient survey.

Methods: The study was approved by the UBC Clinical Research Ethics Board. All patients attending the UBC MS clinic from January 2018 to March 2018 were invited to participate. The survey included: patient demographics (gender, age, and employment status), self-reported MS-specific data (subtype, disease duration, previous and current disease modifying therapies, symptomatic medications), and CBP use (formulation, frequency, perceived benefits/side-effects).

Results: Of 600 surveys distributed, 259 were returned and completed. Responders were 75% female, and the most common age range was 45-55 years. Those with a diagnosis other than MS were excluded (n=14). CBP use was daily for 15% (n=37), weekly for 4% (n=11), monthly for 3% (n=7), rarely for 16% (n=40), and 61% never used (n=150). The CBP users (daily, weekly or monthly) represented 22% and were predominantly relapsing-remitting disease subtype (62%). CBP use included: oral (n=43), smoked/vaporized (n=42), topical (n=14) and mucosal (n=5). Reasons for initiation of CBP were: pain (n=39, 71%), sleep (n=39, 71%), mood (n=24, 44%), spasticity (n=22, 40%), tremor (n=11, 20%), bladder dysfunction (n=5, 9%), and other (n=8, 15%). Of the CBP users, 95% responded that CBP led to symptomatic improvement. Many of these individuals (35%) had not tried other symptomatic medications. CBP usage was discussed with a neurologist in 52% of cases, and 18% of users had the CBP authorized by a physician.

Conclusions: 55 of the 245 survey respondents (22%) who attend the UBC MS clinic use CBP. Responder bias may cause overestimation of CBP use. The most frequent formulations were oral and smoked. Pain and sleep were the most common symptoms being treated and perception of CBP benefit was high. Many of these patients have not tried other symptomatic medications.

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EP1697

Acute aphasia responsive to tissue plasminogen activator in an 8-week pregnant multiple sclerosis patient after discontinuation of fingolimod

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Introduction: Tumefactive multiple sclerosis (TMS) is characterized by demyelinating lesions that are greater than 2 cm in diameter with associated peri-lesional edema, which radiographically resembles a mass lesion and rarely mimics an acute ischemic stroke.
Objective:To present a case of intravenous tissue plasminogen activator (IV tPA) being used as treatment for an acute MS exacerbation
Results: A 33-year-old woman with a history of TMS presented with sudden onset of aphasia and right sided facial droop while 8 weeks pregnant. Prior to pregnancy, she was stable on fingolimod which had been discontinued 16 weeks prior to presentation. CT head showed no hemorrhage or mass effect in the corresponding left frontal area. As she was within 3 hours of symptom onset, she was given IV tPA. Over the next 8 hours, her expressive aphasia improved to only mild word finding difficulty. This profound improvement, however, did not persist on re-assessment the following morning. MRI brain showed a 2 cm ovoid T2-hyperintense lesion in the left corona radiata with associated restricted diffusion consistent with acute demyelination. She was then treated with 5 days of IV methylprednisolone with partial improvement in aphasia noted 3 weeks later.
Discussion: Stroke and MS differ in their etiology but previous studies have shown impaired fibrinolysis in MS. Moreover, the role of the plasminogen activator system has been implicated in neuroinflammation for both diseases. tPA is a serine protease approved for acute ischemic stroke but it has also been investigated for its effect in MS. Endogenous tPA is released from endothelium and astroglia and acts on the blood brain barrier (BBB) and other neuroinflammatory cells. tPA protects oligodendrocytes from apoptosis and facilitates the migration of oligodendrocyte progenitor cells (OPCs) across the BBB in the experimental autoimmune encephalomyelitis (EAE) model. While the tPA-plasmin cascade can promote neurodegeneration via excitotoxin-induced neuronal death, in inflammatory conditions with BBB disruption, it can play a protective role by removing fibrin, which exacerbates axonal injury. Therefore, tPA, by promoting fibrinolysis has the potential to decrease axonal damage in MS.
Conclusion: This is the first reported case of tPA being given to a pregnant woman who presented with a MS relapse resulting in a transient, but profound, reversal of symptoms.Further research is needed to consider whether tPA is a potential "rescue" option for acute MS relapse.

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EP1698

Efficacy and discontinuation of nabiximols in patients with multiple sclerosis: a real-life study

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Introduction: Over the last decade, clinical experience with nabiximols in managing MS-related spasticity is growing steadily. The efficacy and safety of nabiximols in clinical trials is well established however real life observational studies are still lacking. The aim of this study is to evaluate in a real life context the self-reported efficacy and reasons for discontinuation of treatment with nabiximols in patients with MS (PwMS) followed at the Italian MS Society Rehabilitation Centre, Genoa, Italy.
Methods: 224 PwMS were recruited consecutively among those followed for rehabilitative treatment in a five months period from 1 January 2018 to 1 March 2018. PwMS were asked to compile a self-reported questionnaire on: the use of nabiximols (currently or in the past), self-perceived satisfaction and perceived efficacy on five domains (movement control, fatigue, pain, urinary symptoms and other symptoms), side effects, reasons for discontinuation, therapy duration, day dosage.
Results: Out of 224 PwMS, 146 were females, 78 males, mean EDSS 5.9 $\pm$ 1.8; mean age 58.3 $\pm$ 11.2; 76 pwMS (33.9% of the total sample) were treated with nabiximols; 37 PwMS (48.7%) were still using it, 39 (51.3%) subjects were discontinuing the drug for different reasons. The 37 subjects that were still assuming nabiximols reported: 81.1% a self-perceived improvement, 13.5% were uncertainty and 5.4% no improvements. Subjects that showed an improvement reported a one-domain improvement in 46.7% of cases, two domains improvement in 30% of cases, three domains in 13.3% of cases and four domains improvement in 10% of cases. Domains that were perceived as more impacted by the drug were: movement control 35.7%; pain 21.4%; fatigue 19.6%; bladder control 12.5%; other symptoms 10.7%. Reasons for discontinuation were: drug not effective for 14 subjects (35.9%); side effects for 25 subjects (64.1%).
Conclusions: This real-world study confirms nabiximols efficacy in the treatment of MS-related symptoms and, therefore, on relevant functional domains such as movement control, fatigue, pain and urinary function. The discontinuation percentage is in line with other studies published in literature showing that it is necessary to improve response-to-drug predictors' algorithms in order to avoid the cost of long term uneffective treatments.

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Valeria Bergamaschi, Giovanna Konrad, Mario Alberto Battaglia, Giampaolo Brichetto: nothing to disclose

EP1699

The impact of treating obstructive sleep apnoea syndrome on cognitive function in people with multiple sclerosis

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Introduction: Evidence suggests a relationship between obstructive sleep apnoea (OSA) and worsened cognitive performance in people with Multiple Sclerosis (pwMS). Fatigue is common, affecting up to 87% of pwMS. Sleep disturbance is an important factor contributing to fatigue in MS, and sleep disorders including OSA are more prevalent in MS, than the general population.
Study Aim: To investigate the effect of OSA management in pwMS on cognition using the Brief International Cognitive Assessment in MS (BICAMS); consisting of the Symbol Digit Modality Test (SDMT), California Verbal Learning Test (CVLT-2) and Brief Visuospatial Memory Test (BVMT-R), as well as 3-second Paced Auditory Serial Addition Test (PASAT-3).
Methods: 23 pwMS, aged 25-59, who reported significant fatigue were recruited from the MS outpatient clinic for overnight polysomnography and cognitive assessment between 01/03/2017 and 31/03/2018. Participants completed initial cognitive assessment with BICAMS and PASAT-3 on the day of polysomnography. Participants with OSA repeated cognitive tests after positional therapy or continuous positive airway pressure (C-PAP) were established. A cohort of participants with normal polysomnography also repeated cognitive testing for comparison.
Results: 6 of 23 participants (26%) received a diagnosis of OSA. 2 were mild (apnoea hypopnoea index [AHI] 5-15), and 4 moderate OSA (AHI 15-30). Self-reported fatigue did not predict the presence of OSA and no correlation was seen between initial cognitive results and presence of OSA. 5 participants with OSA underwent treatment, 3 with sleep position therapy belts and 2 with C-PAP. The treatment arm underwent repeat cognitive testing, mean 7 months following initial cognitive exam. 9 patients with normal polysomnography not receiving treatment also repeated cognitive tests, mean 4 months after initial assessment.There was a significant improvement in verbal memory measured by the CVLT-2 in the treatment arm ($p=0.03$). Improvement was seen in all cognitive domains in the treatment arm, but no other reached significance. There was no improvement seen in any cognitive domain in the control arm, except a non-significant increase in SDMT measuring information processing speed.
Conclusion: Treatment of OSA significantly improved verbal memory in this cohort. Results should be interpreted with caution, with low patient numbers in this pilot study, however they indicate that a more detailed investigation is warranted.

Disclosure

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EP1700

The effect of pilates exercise on balance, postural instability, functional capacity and quality of life in multiple sclerosis patients

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Background: Balance disorders and postural instability are among the most resistant problems of patients with MS(pwMS) which effect the daily living.
Aim: The aim of this study was to evaluate the effects of pilates exercise on balance, postural instability, functional capacity, quality of life and depression in patients with MS.
Methods: 16 of the 22 outpatient MS patients who fully completed the modified pilates exercise program were included. The mean age of the 16 patients (12 female) was 50,08 years (range 39-62), and the mean Expanded Disability Status Scale(EDSS) score was 3.6 (range 1-5.5). PwMS underwent 12-week (24 training session, two times a week) modified clinical pilates training designed to improve their ability to integrate multisensory inputs and challenge postural control. Breathing exercise, neutral spinal alignment, stretching and basic principles of pilates was informed in the first session. Exercises were performed with different positions (supine, prone, side lying, sitting and upright position) and with using different equipments (chair, pilates ball,latex band and light weights). Exercises and repetitions were progressed at each session according to individual´s abilities. They were all assessed with objective balance tests (Romberg Test, Tandem Romberg Test, Five Times Sit-to- Stand Test, Timed Up and Go Test), functional capacity (Six Minute Walking Test), quality of life (MSQol-54),the 12-item multiple sclerosis walking scale (MSWS-12) and depression (Beck Depression Inventory) scales. Measurements were repeated after exercise training.
Results: At the end of the 12-week period, significant improvement was noted in all objective and subjective balance parameters ($p< 0.05$-$p< 0.001$) .Modified pilates exercise program had also significant positive effect on functional capacity and quality of life in our MS patients ($p< 0.05$)

Conclusion: In this study, we showed that modified clinical pilates exercises that specifically addresses postural stability and central integration improve balance, functional capacity , quality of life of MS patients. Studies comparing this exercise approach to conventional physical therapy sessions are warranted.

Disclosure

Nothing to disclose

EP1701

Intrathecal baclofen should be considered in ambulatory people with multiple sclerosis related spasticity: an observational study

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Introduction: Spasticity is a frequent and disabling symptom in people with Multiple Sclerosis. Intrathecal baclofen (ITB) is effective but rarely used in ambulant people with MS.
Objectives: To evaluate impact on ambulation of ITB in a cohort of people with MS-related spasticity.
Methods: A single centre prospective observational cohort study was performed between 2009 - 2018. Subjects were admitted for ITB trial and subsequent pump implantation. Data of ambulatory patients were collected at baseline, after intrathecal baclofen bolus via LP (4 - 8 hours monitored) and at 3 months and annually after pump implant. Data included: baseline demographics, EDSS, spasticity scores (Ashworth), spasm score (Penn), 10m timed walk (10MTW), mobility aids, other spasticity treatment, ITB dose. Data was analysed with paired t-tests, one way ANOVA and linear regression using SPSS v22.
Results: 31 people were included, 20 female, 11 male, mean age 59 years [26-69]. All EDSS 6.0 - 7.0. 19 were taking oral anti-spasticity drugs and 9 on disease modifying drugs. Improvement on Ashworth (mean pre 1.34, post 0.72, $p< 0.01$) and Penn (mean pre 3.14, post 1.08, $p< 0.01$). Baseline 10MTw mean 69.9s [20-186] and trial 67.3s [24-211] ($p=0.8$). 21 people (68%) proceeded with pump implantation and ten (32%) did not. Lower limb MRC power was higher in those who proceeded with pump: mean 3.16 (1.7-5.0) vs 2.54 (1.4-3.7) ($p = 0.017$). There was no statistically significant difference in 10mTW from baseline measurement up to 1 year as determined by one-way ANOVA ($F(3,24) = 1.7$, $p = 0.19$). At review, 17 patients (80%) were ambulatory (mean follow up 3.14 years, [range 1 - 8]). Two people have remained ambulatory with bilateral aid for 8 years (EDSS pre pump 6.5 and 7). 2 people were unable to mobilise at 1 year. 16 people (76%) discontinued all other spasticity treatments post-pump. A linear regression was performed to predict 10mTw at 3 months from baseline EDSS score. Baseline EDSS significantly predicted 10mtW following dose stabilisation at 3 months ($p = 0.015$).
Conclusions: In this cohort we have shown that ITB can preserve ambulation whilst effectively treating spasticity in a carefully selected cohort. Baseline EDSS is a predictor of 10mTw following dose stabilisation. A small number may experience prolonged improvement in mobility.

Disclosure

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EP1702

Substantial improvement of walking after fampridine introduction indicates improvement of meaningful and self-chosen activities of daily living in patients with multiple sclerosis

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Background: Fampridine is used to improve walking in patients with multiple sclerosis (PwMS). It has been shown to improve other measures such as manual functions and balance. Little is known about its effect on patients selected activities of daily living (ADL). We assessed the effect of fampridine on patients' self-perception on performance in everyday living using The Canadian occupational Performance Measure (COPM).
Methods: We included 102 patients suggested to start fampridine treatment by their treating physicians. The 10MWT was performed along with COPM before and after the initial 14 days fampridine trial. We defined responders on all the tests if at least 20% improvement was recorded between the two measures. Chi-square test was used to evaluate the distribution of responders and non-responders on COPM in relation to responders on 10MWT and gender. Additionally we correlated changes in 10MWT and COPM with the age and EDSS.
Results: In total, 100 PwMS (70 females, 30 males, mean age 51±11 years and EDSS 5.6±1) completed the study. The mean initial 10MWT time was 25.1±42.7, compared to 18.3±37.8 at reassessment (response rate of 78.4%). The average initial COPM-P (performance) score was 4.6 ± 1.5 compared to 6.1± 1.8 at reassessment (39.2% response rate). The average initial COPM-S (satisfaction) score was 6.1± 1.8 with the score of 6.5±1.9 at reassessment (44.1% response rate).
Males were more likely to respond on 10MWT ($p=0.02$). No differences were observed in responsiveness on COPM between the genders. We observed negative correlation between the patients' age and improvement on 10MWT ($p=0.026$). Correlations for COPM were not significant. EDSS score did not correlate with 10MWT nor COPM improvements. Patients who responded on 10MWT were more likely to respond also on COPM-P ($p=0.01$)

and COPM-S (p=0.01). The improvements in COPM-P and COPM-S correlated well with the improvements in gait speed (p=0.002 and p=0.006).
Conclusions: Younger patients and males might benefit more from fampridine treatment in terms of gait regardless of the EDSS score. In certain patients with substantial improvement on 10MWT after initial 14 days fampridine trial improvement of meaningful and self-chosen ADL can also be expected.

Disclosure
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Uroš Rot: Nothing to disclose
Alenka Horvat Ledinek: Nothing to disclose

EP1703
Virtual reality training to improve upper limb motor function in multiple sclerosis: a feasibility study protocol

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Introduction: Virtual reality (VR) represents a motivational and effective remote treatment with unique tracking and monitoring capabilities for targeted neurorehabilitation, including people with MS (PwMS). VR was reported to improve the range of motion and muscle strength in PwMS with upper limb function deficits.
Objective: Evaluate the safety and feasibility of training with the innovative VR Oculus-rift device in PwMS.
Methods: A prospective feasibility study will enroll 30 PwMS with weakness in upper extremity muscles defined by the British Medical Research Council (BMRC) grade 4 in two muscle groups or BMRC grade 3 in one muscle group. Patients with visual, cognitive and/or hearing impairments will be excluded. The VR Oculus built-in head-tracking device is easily applied and enables users to explore, navigate, and move within real-size virtual environments. For the present study patients will practice two games that require arm and shoulder movements in various directions, including reaching forward toward moving targets. The strong and weak upper limbs will be trained separately. The VR session will be divided into four training rehearsals consisting of a 4-min active phase followed by a 1-min rest break, the total session will last 30 minutes. Following the training session each participant will complete a questionnaire covering aspects of quality of the training and fatigability. Additionally, the physiotherapist in charge of the training session will complete a report assessing exercise performance, compensation movements, fatigability and safety of the training. Feasibility to perform the VR accurately and any intervention-related adverse events will be recorded.
Conclusion: Assessment of VR training in PwMS in this feasibility study will help to design further targeted VR practicing to improve upper limb dysfunction in MS. Stage II will focus on implementing this intervention approach into a home-based environment.

Disclosure
All authors declare nothing to disclosure

Others

EP1704
The influence of multiple sclerosis therapies on headache

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We aimed to study the prevalence and characteristics of headache in patients with multiple sclerosis (MS) and to clarify the relationship between headache and MS therapies.Of the total population of 754 MS patients recruited in our center, 515(68%) reported headaches. Based on headache characteristics on evaluation, 20-(27%) were diagnosed with migraine. One hundred and three patients(17%) gave a history of tension-type headache(TTH) and 198(26.3%) patients described to have medication-overuse-headache(MOH). There were 12(1.6%) patients with unclassified headache. Three- hundred and fourteen(61%) female and 201(39%) men reported headache. During our study 558 MS patients(74%) were treated with interferon beta therapy/ glatiramer acetate (DMD). 115 patients(15.3%) received fingolimod.48 MS patients (6.4%) were treated with teriflunamide, and 33 MS patients(4.4%) received natalizumab. There was no no statistical difference between DMD or NTZ use and all headache types. However, a statistically significant higher incidence of TTH was found in fingolimod-treated patients.Also, there was a higher incidence of MOH in teriflunamide-treated patients when compared to the patients who have other headaches.There was a significant association between migraine and the age of onset of MS treatments, however this significant relation was not observed in the age of onset of other agents.The mean age of onset of headaches was 27.4 years. When all headache groups were compared, the age of onset of headache was the earliest in the patients with migraine. As regards the possible relationships between duration of the history of medication use and headaches, the incidence of migraine was higher in all headache patients In all headache groups, the mean value of the headache onset after treatment started was 1.63 years. In migraine patients, the duration of medication use until the headache onset was the longest when compared to other headache groups. It is interesting to note that the consultation rates for headaches in our MS patients were not rare. Four-hundred and fifty nine patients(89%) had consulted a physician about their headaches. Approximately 154 patients(78%)

with MOH were seen by physicians due to headache complaints. For migraine patients(52%), the physician consultancy tended to be higher, while this rate was less among TTH(46%) sufferers. The results of this study indicate a possible relationship may exist between headache and MS treatments.

Disclosure

nothing to disclose

EP1705

Physicians' gender differences in risk perception and therapeutic inertia in multiple sclerosis care

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Introduction: Therapeutic inertia (TI) is a common phenomenon in multiple sclerosis (MS) care defined as lack of treatment escalation despite evidence of disease progression. The perception of risk is one of the identified factors associated with TI. Limited information is available regarding physicians' gender differences in risk perception and TI in MS care.
Objectives: To evaluate gender differences in the perception of risk and TI among neurologists managing MS patients.
Design: We completed a face-to-face cross-sectional study including 50 neurologists with expertise in MS care from Spain and Chile. Participants answered questions regarding the management of 20 simulated case-scenarios in commonly encountered in clinical practice. Participants were also exposed to experiments to assess aversion to risk and ambiguity (unknown probability of an event). TI was measured as lack of treatment initiation or intensification when evidence of disease progression (e.g. clinical relapses and radiological activity). A multivariable analysis was conducted to determine whether gender is an independent predictor of TI with adjustment for covariates.
Results: Of 50 participants, the mean age was 40±11 years. There were no significant differences in baseline characteristics by gender. Male neurologists exhibited more aversion to ambiguity (76% vs 60%; $p< 0.001$). There were 800 total responses for the assessment therapeutic decisions. TI was most commonly observed in female neurologists compared to male neurologists [28.5% (115/400) vs. 21.3% (85/400); p=0.018). The multivariable analysis adjusted to risk perception revealed that the likelihood of TI was more common among female neurologists (OR 5.60; 95%CI 1.02-30.6).
Conclusions: In our studied cohort of neurologists caring for MS patients, TI was more common among female neurologists. Further studies are needed to confirm our findings and to determine the potential causes.

Disclosure

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EP1706

Early experience with ocrelizumab: patient characteristics from a large insurance claims database

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Introduction: OCR is the only disease-modifying therapy (DMT) approved for both relapsing and primary progressive forms of multiple sclerosis (MS). Limited information is available on patients initiating OCR in the real world.
Objective: To characterize patients initiating ocrelizumab (OCR) in a real-world setting.
Methods: This study used Pharmetrics Plus, a large US insurance claims database, to identify patients initiating OCR ("initiators") between April and December 2017. Patients using OCR were identified if they had either: 1) miscellaneous J codes or temporary OCR code C9399 with CPT codes indicating infusion (IV) procedures, and an MS diagnosis or previous MS DMT history, or, 2) OCR NDC code. Patients were included if they had at least 2 IVs 12 to 18 days apart, without other DMTs within 6 months of initiation. At least 12 months continuous enrollment prior to OCR initiation was required. Demographic and clinical characteristics, including DMT use prior to OCR, Charlson Comorbidity Index (CCI), MS-related symptoms, and relapse rate were reported for the year prior to OCR initiation and stratified by prior use of DMT and initiation quarter.
Results: A total of 838 OCR initiators were identified, representing 21.9% of all MS patients who initiated a DMT during the same period. The mean (SD) age for OCR initiators was 49.2 (11.0) years, CCI score was 0.39 (0.84), 63.2% were female, and the most frequent MS symptoms reported were fatigue (33.8%) and neurogenic bladder (13.6%). Approximately 33.4% of OCR initiators had a relapse in the year prior, with a pre-index annual relapse rate of 0.52. 34.7% of initiators had no DMT use in the prior year ("untreated"). Among OCR initiators switching from another DMT ("switchers"), 46.4%, 19.6%, and 34.0% switched from oral, injectable, and other IV DMTs, respectively. From Q2 to Q4 2017, the % of untreated OCR initiators increased from 30.4% to 41.3%, and the % of switchers previously treated with injectables increased from 15.2% to 29.5%. The mean CCI decreased from 0.45 to 0.33.
Conclusions: To our knowledge, this is the first real-world study documenting the characteristics of OCR early adopters. As real-world data on OCR mature, comparative-effectiveness research will examine real-world outcomes and should address the changing characteristics of OCR initiators over time.

Disclosure

Sponsored by Genentech, Inc. N.J. Engmann is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd; E. Yang is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd; L. Julian is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd; W.S. Yeh is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd; J. Whiteley is an employee of Genentech, Inc., and a shareholder of F. Hoffmann-La Roche Ltd.

EP1707

Closing the gaps for MS treatment adherence at low middle income countries. Egypt case

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Objectives: When Prevalence of multiple sclerosis in a high population country like Egypt was found to be 1.41%, from all neurological disorders the challenges on government &society will increase due to scarcity of resources and priority issues Although interferon beta (IFNβ) have been shown to reduce the risk for disease progression for MS therefor Treatment adherence is essential for enhancement patients outcomes.
The objective of this research is closing the gaps for treatment adherence policy to enhance patient's outcomes and efficient utilization of resources.
Methods: Developing patent support program (PSP) for MS patients this program includes (training injection - patient counseling from clinical pharmacist - follow up visits based medical file for the patients - fixed telephone number for any inquiries about the disease from the patients was created)
Time horizon for the assessment of the program was 12 months SF36 questioner was used for evaluating impact of the program on quality of life. Direct medical and in direct medical costs was calculated for evaluation of utilization of health care resources. Data from aged (18 -60) for 1 year was analyzed.
Results: With 200 number of patients (mean age: 33, 66.7 % female) after 12 months cost of treatment per patient was reduced with percentage (50%) the annual relapse rate was reduced by 65 % Total medical cost of relapse was discounted by(50 %)
Conclusion: Creating an effective patent support program (PSP) focusing on reducing patent's adherence may enhance outcomes for MS patients and efficient resources utilization.

Disclosure

i have no conflict of intrest

EP1708

Locked-in-syndrome in a patient with tumefactive multiple sclerosis

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A locked-in syndrome seems to be extremely rare in multiple sclerosis (MS). We are aware of only 3 previously reported patients who all died. This paper adds another patient finally treated with rituximab, who survived and remained stable up to now, i.e. for more than 12 years.
A previously healthy 32-year old woman noted diplopia and ataxia of gait. Magnetic resonance imaging (MRI) documented 5 periventricular T_2-hyperintense lesions without gadolinium-enhancement. MRI of the spinal cord was normal. Cerebrospinal fluid analysis revealed 8 leucocytes/µl and abnormal oligoclonal IgG-bands. She completely recovered with high dose steroids. This was diagnosed as a first demyelinating event in the central nervous system consistent with MS with dissemination in space but isolated in time. She did not receive a disease-modifying therapy.
Four months later, she noted horizontal diplopia and a progressive left-sided hemiparesis. She had bilateral internuclear ophthalmoplegia and a left-sided hemiparesis (movements against resistance). MRI documented a large space-occupying gadolinium-enhancing lesion in the pons (right side > left side). This was diagnosed as the 2nd bout of a now definite MS:
She was treated with 1 mg methylprednisolone/d for 5 successive days. Her condition, however, deteriorated and she received a 2nd course of high dose steroids which was also ineffective. A subsequent plasma exchange (4 cycles with 3 litres) was ineffective, too. After that she was treated with cylcophosphamide (750 mg for 2 successive days) accompanied by intravenous immunoglobulins (0,4 g/kg for 5 successive days). Her condition, however, deteriorated to a locked-in-syndrome with quadriplegia, anarthria and aphagia, and loss of all horizontal eye movements but preserved vertical eye movements, which were used to communicate with the conscious patients. She also suffered painful tonic seizures of her limbs and her face. During one of these fits she bit her tongue, which swelled massively leading to respiratory problems requiring intubation.
Finally, we started treatment with rituximab (3 cycles with 800 mg/d every 2 weeks followed by 375 mg/kg every year). She slowly improved within the following 2½ years and reached an EDSS of 3.5. Rituximab treatment continues up to now, i.e. for more than 12 years, and there is no evidence of disease activity, i. e. she neither suffered another bout nor developed any new MRI-lesion. She lives an independent life.

Disclosure

Nothing to disclose

EP1709

Self-esteem partially mediates the relationship between quality of life and depression in multiple sclerosis patients

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Background: Multiple sclerosis (MS) is associated with mood problems which negatively impact health-related quality of life (HRQoL), however these mood problems cannot be solely attributed to health-related variables. Protective psychological factors

such as self-esteem may mediate the relationship between mood problems and HRQoL in MS.
Objective: To investigate the associations between HRQoL, self-esteem, and depression in MS patients.
Method: This study had a descriptive and cross-sectional design. Eighty one patients with definite MS who were receiving follow-up care at the Dokuz Eylul University between November and April 2016 accepted to participate in the study. Data were collected using the Turkish version of the MS International Quality of Life Questionnaire, Rosenberg Self-Esteem Scale, and Hospital Anxiety and Depression Scale. Multiple linear regression analysis and Sobel test for mediation were conducted.
Results: Among the participants, 76.5% were female, 55.6% had a Bachelor's degree or higher, 67.9% were married, and 81.5% were using disease modifying drugs. Expanded Disability Status Scale (EDSS) scores ranged between 0 and 6.5, with a mean of 1.43. Mean disease duration was 7.25. Results of the regression analysis showed that EDSS (β -.31), self-esteem (β .26), and depression (β -.30) significantly predicted HRQoL, while anxiety did not significantly contribute to the model, which explained 41% of variance in HRQoL. A Sobel test was then ran and it was found that self-esteem partially mediated the relationship between depression and HRQoL.
Conclusions: MS patients often report poorer self-esteem and mood compared to the general population. Protective factors such as self-esteem should be addressed in psychological therapies in order to increase HRQoL in MS, since self-esteem partially mediated the relationship between depression and HRQoL. Psychological therapies have the potential to reduce health costs and increase psychosocial adaptation to the disease. From a holistic perspective, complementary psychotherapies should become more widespread in the management of MS. It can be posited that the medical treatment of depression in MS patients is crucial, but not sufficient. Findings of the study indicated that psychological interventions aimed at increasing self-esteem in MS patients would help improving HRQoL.

Disclosure

Gedik Z and İdiman E declare no conflicts of interests for this work.

EP1710

Online medical education improves knowledge of immune mechanisms in the treatment of MS among neurologists

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Introduction: Disease modifying therapies (DMTs) for the treatment of multiple sclerosis (MS) continue to evolve, with established and emerging therapies differing in how they modulate the immune system. Although neurologists are generally aware of the efficacy and safety of DMTs, they often lack substantive knowledge of the mechanistic basis for their treatment effects. An online educational activity was developed with the goal of improving neurologists' knowledge of the effect of MS-relevant DMTs on immune function.
Methods: An online educational intervention was developed in the form of a 30-minute video lecture with synchronized slides. Educational effectiveness was assessed with a repeated pairs pre-/post- assessment study design in which each individual served as his/her own control. Responses to 3 knowledge-based and 1 self-efficacy questions were analyzed. A chi-square test assessed changes from pre- to post-assessment. Cramer's V was used to calculate the effect size of online education. Data from the assessment were collected between March 22, 2018 and April 16, 2018.
Results: A comparison of responses from pre- to post-assessment questions demonstrated a considerable educational effect (n=153; V=0.17; P< .01). Participation in this educational intervention showed improvements in the following areas (P< .05): identification of therapies that function by immune reconstitution and the consequences of using DMTs that utilize short-term vs continuous immune suppression. There was a positive but not significant change in learners who correctly identified the patient type most likely to benefit from immune reconstitution therapy. Activity participation resulted in 20% of participants noting an increase in confidence in identifying patients with MS who are candidates for immune reconstitution therapy.
Conclusion: This study demonstrated the success of a targeted online, video lecture on improving neurologists' knowledge of modulation of the immune system by DMTs for MS. Additional education is needed to further address the impact of DMT use on immune function.

Disclosure

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EP1711

A global nurse-focused Delphi approach to management of gastrointestinal tolerability of dimethyl fumarate

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Background: Dimethyl fumarate (DMF) has demonstrated a positive benefit-risk profile in relapsing-remitting multiple sclerosis (RRMS) in clinical trials and real-world analyses. For some patients, DMF may be associated with gastrointestinal (GI) side effects that contribute to treatment discontinuation. MS nurses are well positioned to provide insight into best practices for managing these events.
Objective: Engage MS nurses to identify effective management approaches for mitigating GI side effects of DMF using Delphi consensus methodology.
Methods: A steering committee of MS nurses developed 2 sequential surveys to identify treatment practices for managing GI side effects associated with DMF. The first survey was sent to MS nurses in 7 countries (Canada, France, Germany, Italy, Spain, the UK, and the USA). Findings will be clarified and elaborated upon in a second, ongoing survey.
Results: The first survey was completed by 239 nurses. A majority (82%) have >6 years of experience treating people with MS and 92% are actively involved in patient education and support for MS treatments. Respondents estimate that concern for possible GI side effects always or almost always impacts treatment choice for 42% of patients and 38% of providers. A majority of respondents agree that education about GI side effects before treatment initiation (96%) and during the first 3 months (95%) of treatment contributes to adherence. A majority of respondents (96%) follow the dose titration schedule recommended in the label when initiating DMF. For 86% of respondents, recommending patients take DMF with food is always or almost always standard protocol, but the majority (60%) do not specify a particular type of food. Most respondents recommend pharmacologic (74%) and/or nonpharmacologic (56%) treatments for patients with GI symptoms. Descriptions of most frequently recommended food groups and pharmacologic and nonpharmacologic treatments will be presented.
Conclusion: Based on the results from this first ever survey of DMF GI management practices among MS nurses, patient education on possible GI side effects is critical to improving patient adherence. In addition, most nurses follow the label recommendation for dose titration, advise patients to take DMF with food, and recommend symptomatic therapy for patients who experience GI side effects.

Disclosure

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M Edwards: Employed by Biogen
C Minor: Employed by Biogen

EP1712

Is the primary use of generic (non-propietary) disease modifying therapies (DMTs) associated with therapeutic inertia in multiple sclerosis care?

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Introduction: The use of generic (non-proprietary)compared to brand-name drugs is becoming popular in the management of multiple sclerosis (MS). Generics for MS are not necessarily less expensive than brand-name drugs, while generic companies have more flexible compliance regulations. Argentina is one of the leading countries with higher availability of generic agents (n=16; interferon, glatiramer, dimethyl-fumarate, teriflunomide, fingolimod).
Objectives: To determine the prevalence of therapeutic inertia (TI) between primary users of generics vs. brand agents in the management of MS in Argentina.
Design: We conducted an online study comprising 117 neurologists with expertise in MS. Participants answered questions regarding their clinical practice,most commonly used disease modifying agents, and therapeutic choices of 10 simulated case-scenarios. TI was defined as the lack of treatment initiation or escalation when evidence of clinical and radiological activity(8 case-scenarios, 720 individual responses). We created the brand-name/generic score (BGS)according to the top 5 frequent use of brand-name (n=9) vs. generic (n=16) drugs for MS, where scores lower than 1 indicates higher use of generics and scores >1 indicated higher use of brand agents. Candidate predictors of TI included demographic data, MS specialist vs. general neurologist, practice setting, years of practice, volume of MS patients, risk preferences, and the BGS.
Results: Overall,90 participants completed the study (completion rate 76.9%). TI was observed in 153 (21.3%) of participants' responses.The mean BGS score (SD)was 2.75 (2.1).Overall,46 (51.1%) participants had a BGS equal to or lower than 1. The most common generic drugs used include interferon B1 b (Blastoferon® Biosidus), and Fingolimod (Bago and Raffo).The evaluation of individual responses revealed that lower BGS scores was associated with higher TI (mean BGS 2.44 for TI vs. 2.84 for no TI;

p=0.04). The multivariable analysis revealed that for every point increase in the BGS, there was areduction in TI (OR 0.64; 95%CI 0.44-0.94); equivalent toa 56% (1/OR)significant increased in TI for primary generic-name users.
Conclusions: TI is a common phenomenon affecting one in five clinical situations. The primary use of generic-name drugswas associated with a 56% increase in the likelihood of TI.Further studies are needed to understand the underlying causes of this phenomenon.

Disclosure

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EP1713
Pilates exercise has positive effect on balance but not on gait performance in people with mild multiple sclerosis

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Background: Balance and gait impairment are common in people with multiple sclerosis (MS). This disabling deficit can be present even in people with mild neurological disability. People with MS are encouraged to perform some regular physical activity for improving fitness and muscle strength. Pilates is popular exercise system focusing upon controlled movement, activation of core muscles and breathing. The aim of the study was compare effect of short-term pilates exercise on balance and gait performance in group of people with mild MS.
Methods: Participants received 10 weeks of training sessions of Pilates exercise (supervised by physiotherapist), control group has no change of lifestyle regimen. Balance was evaluated using Berg Balance Scale, MiniBest test, Timed Up and Go test, Single leg stance and Step test on baseline and after completing of training. Gait performance was assessed using Timed 25 Foot Walk test, The 2 minute walk test and by GAITRite instrument.
Results: Thirty-three participants completed the study: 21 people in pilates group (21 women, mean age 38,5 y, mean disease duration 6 y, mean EDSS 2,5) and 11 people in control group (1 men, mean age 43 y, mean disease duration 9 y, mean EDSS 2,9). After completing 10 weeks of pilates exercise participant significantly improved in balance (MiniBest test p=0.025, TUG p=0.041) and walking endurance (the 2 minute walk test p=0.002). Gait performance in normal walk measured by GAITRite was improved in both groups.
Conclusion: Pilates could be offered as possible exercise to people with mild MS to improve balance. However for treatment serious balance deficit individual physiotherapy should be prescribed.
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Disclosure

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EP1714
1 year-healthy outcomes in RRMS patients treated with teriflunomied and dimethyl fumarate

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Introduction: There is little evidence regarding the real impact in satisfaction and quality of life (QoL) with new oral immunomodulatory therapies (OIT) for relapsing-remitting multiple sclerosis (RRMS).
Objective: assessment of health outcomes in patients treated with OIT (teriflunomide [TE] or dimethyl fumarate [DMF]) in a real world setting.
Patients and methods: Clinical features, QoL (MusiQoL and EuroQoL) and treatmetn saatisfaction (TSQM) were evaluated in RRMS patients treated with TE or DMF for at least 1 year.
Results: 81 patients started 88 OIT (43DMF; 45TE). 79% women; Mean age 42.22 years (SD 8.05), mean disease duration 100.64 months (SD 66.08), mean baseline EDSS 1.79 points (SD 1.87), number of relapses 1year prior: 0.75 (SD 0.87). 18 patients (22.5%) were naïve, 65 (73.5%) received at least one DMT. The main reason for change were side effects (52.3%), followed by innefficiency (19.3%) and safety (4.5%).
EQ-VAS-EuroQoL baseline (mean points±SD): 70.3±19.8, (67.9 ± 20.3 DMF; 72.3 ± 19.0 TE). The worst-rated dimmension were: anxiety / depression (31.3%), pain (25.0%) and difficulty in carrying out daily activities (12.5%) .
MusiQoL baseline (mean points; SD): 70.1 ± 14.8 (69.9 ± 15.0 for DMF vs 70.3 ± 14.9 for TE)
EQ-VAS_year 1: 68.3 ± 20.3 points, (DMF 70.3 ± 18.3 points vs TE 66.6 ± 22.11).

Mean MusiQoL_year 1: 67.9 ± 15.5 points (70.2 ± 16.7 for DMF vs. 66.1 ± 14.5 for TE)
TSQM at baseline: efficacy (62.6 ± 23.9 points), side effects (50.4 ± 24.1 points) convenience (57.4 ± 24.9 points) and overall satisfaction (62.3 ± 23.3 points) .
TSQM at year 1: efficacy (66.4 ± 23.9 points), side effects (67.7 ± 23.3 points) convenience (82.7 ± 19.1 points) and overall satisfaction (73.6 ± 17.9 points) . DMF vs TE: efficacy (69.3 ± 19.2 vs 63.6 ± 28.0), side effects (70.1 ± 22.3 vs 64.8 ± 26.7), convenience (77.5 ± 18. 6 vs 88.2 ± 18.6). The TSQM dimensions improved during treatment with TE compared to previous TI, ($p < 0.05$).
Conclusions: QoL seems to be mantained after one year with OIT. However, patients on OIT present increased satisfaction compared to previous IT, maybe due to a better tolerance and greater convenience in the administration. Patients on DMF have greater satisfaction in terms of efficacy and side effectscompared to TE but to a decreased convenience.

Disclosure

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Elena Alvarez Merck, Biogen, Genzyme, Novartis.
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Marta Aguado-Valcarcel Merck, Sanofi-Genzyme, Biogen
Guadalupe Piñeiro-Corrales Merck, Sanofi-Genzyme, Biogen, Roche
Hadriana has no potential conflicts of interests
Cesar Sanchez has no potential conflicts of interests

EP1715

TeleSEP: development of platform to regional tele-expertise in multiple sclerosis

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Background: These last years, evolution of diagnosis criteria and development of disease modified treatment have complicated medical care of Multiple Sclerosis (MS) patients and require collaboration between neurologist and MS expert center. Telemedecine emerged as an adequate system to effective optimize care for MS patients in the whole of Normandy.
Objective: Equality of access for all MS patient to a medical expertise by development of TeleSEP, a specific platform of MS tele-expertise
Method: First step: creation of téléSEP plateform in partnership with expert neurologist and GCS normand'e-santé (Regional grouping of support for the deployment of e-health) for designer and project manager, with prior approval of health regional agency, a public funding organization. Secondly, implementation of teleSEP in all neurologist, private or hospital, with accordance with IT services. Final step: user training. All MS patient electronic record included an interfacing sheet, an informative sheet, EDMUS graph and upload MRI. Traceability is provided by final report written by expert neurologist within 3 days of the meeting.
Result: Twelve teleSEP took place with 107 discussed MS cases (mean: 8.23+/-4.13 per teleSEP). Total participants of meetings were significantly increased with an average of 21.15+/-9.07, with 12.17 present (+/-5.65) and 10.75 connected (+/-4.14). Participants are neurologists but also residents. Characteristics of patients were: 72% of female, mean age: 44.90 years (+/- 12.45), mean EDSS: 3.17 +/- 2.28 [0-8], mean disease duration: 118.02 months (+/- 112.02) and relapsing-remitting form for half of them. There were two main queries about diagnosis and/or treatment respectively in 51% and 84% of cases. Global satisfaction score assigned by users is 4.51/5 with download time of data less than 30 minutes. Another important points are save valuable time and costs due to absence of travel for neurologist or patient to expert center, with less pollution. Recommandations of teleSEP were applied in 97% of cases.
Conclusion: TeleSEP allows equality of access for all patient to a medical expertise regardless of location and neurologist in terms of diagnosis and treatment with global improvement of care to the region. It's practical tool with global satisfaction, professional training and applicable to other diseases.

Disclosure

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EP1716

Is itIt's possible to continue a really effective therapy in a patient with a severe hypersensitivity drug reaction? The importance of desensitization procedures in the monoclonal antibodies era

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Background: Alemtuzumab(ALEM) is a highly effective monoclonal anti-CD52 antibody approved for patients with active multiple sclerosis(MS). The most common ALEM's adverse events(AE) are infusion reactions(IRs). Three out of 100 IRs are severe and contraindicate treatment prosecution with the traditional schedule.
Methods: a case report
Results: a 45-year-old female, diagnosed with MS in 1998, was treated with several therapies, but only had a complete response to natalizumab. However, natalizumab had been discontinued for a high progressive multifocal leucoencephalopathy risk. After last treatment failure with fingolimod, she was started on ALEM

without any AE and with an optimal clinical and neuroradiological response. However, one year later, while she was receiving her second infusion, she suddenly developed severe hypotension, cough, dysphagia and diffuse urticaria/angioedema. She was then treated with intravenous corticosteroids, antihistamines and fluids. Four months later, 1:1000 intradermal tests with ALEM were strongly positive at 20' reading. We have carried out other intradermal tests in 5 MS patients treated with alem in order to ruled out a hypersensitivity to other molecules. All tests results negative. A diagnosis of IgE-mediated anaphylaxis to ALEM was then confirmed. Since no other effective alternatives were available to treat her MS, ALEM was infused following Castells' desensitization protocol. No mild or severe AE were observed. The treatment was effective with regard to disease activity and quality of life improvement.

Conclusions: This is the first case of ALEM-desensitization in a MS patient. This procedure allowed a safe administration of the only effective treatment for this highly active patient, despite her previous severe IR to the drug. Desensitization is a crucial procedure to induce temporary drug tolerance, when no effective alternatives are available.

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M.R Yacoub: nothing to disclose

EP1717

High-dose biotin in progressive multiple sclerosis : a prospective study of 86 patients in routine clinical practice

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Introduction: Biotin is a cofactor for four essential carboxylases, and may thus support myelin repair and protect against axonal degeneration. A recent controlled trial has established that high-dose biotin supplementation has a stabilizing effect on progression of multiple sclerosis (MS).

Objectives: To analyze the impact of high-dose biotin in routine clinical practice on disability progression, annualized relapse rate, quality of life and tolerance in progressive MS patients.

Methods: Progressive MS patients who started high-dose biotin in Nantes hospital from june 29, 2016 to march 14, 2017 were included. Patients were examined at the start of biotin, 6 months and 12 months after the beginning of the treatment. Expanded Disability Status Scale (EDSS), relapses, walking test (T25W), symbol digit modalities test (SDMT), clinical global impression (CGI) scale, safety and quality of life were collected.

Results: We included 86 Progressive MS patients. Forty-two patients had primary progressive MS and forty-four had secondary progressive MS. At baseline, patients were 52,74±0,96 yrs-old. Mean EDSS score was 5,91±0,13 and mean disease duration was 15,02±0,90 yrs.

Thirteen patients stopped biotin before 12 months.

At 12 months, EDSS score was 6,02±1,18 (vs 5,91±1,17 at baseline, p=0,58). We observed a significant increase of the T25W at 12 months (29,16±4,38 at 12 months vs 25,68±3,24, $p < 0,01$, paired t test).

Twelve patients (13,9%) presented an improvement of their disability (defined as a decrease of >=0,5 point or >=1 point in EDSS (if baseline score was 6-7 or 4,5-5,5, respectively) or a >=20% decrease in T25W time). Six of them had concomitant disease-modifying drug therapy (DMD).

Annualized relapse rate was 0,07±0,03 in the previous year and 0,04±0,02 at one year (NS). There were no significant differences for SDMT and EQ5D. Only the subscore of EQ5D about pain and discomfort improved significantly (1,89±0,06 vs 2,10±0,05, $p < 0,01$, paired t test). 45,2% of patients reported CGI= 4, 31,5% CGI< 4, 23,3% CGI>4 at 12 months. Fourteen patients reported adverse events

Conclusions: In this real-life study, 13,9% of patients improved their disability (compared to 12,3% in the controlled study). However, half of these patients had a concomitant DMD. No significant improvement of the EDSS score and T25W were observed after one year of treatment. A Phase III study is actually warranted to conclude on the efficacy of high-dose biotin.

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EP1718

Treatment of spasticity in patients with multiple sclerosis by using method of electrical stimulation according to Jantsch - a pilot study

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Background: Spasticity is a serious symptom common in many patients with multiple sclerosis (MS). The electrical stimulation

(ES) according to Jantsch was created with a primary aim to reduce spasticity, however its impact has been neither proved nor disproved by any studies. The aim of this study was to figure out if this type of ES can reduce the spasticity of triceps surae muscle (mTS) and whether decrease of spasticity of mTS can influence the speed of walk.

Methods: Fifteen probands (mean age 51.2 ±10.32 years with duration of MS 17.21 ± 6.48 years) participated in this pilot controlled study were divided in two groups - first (STIM) group (8 participants) underwent the application of ES, and the second (NONSTIM) group (7 participants) was without ES. Treatment duration was 8 days, 10 minutes per day during inpatient treatment and all participants had the same conventional physiotherapy. Spasticity was measured using by Tardieu Scale, and speed of walk was measured by using 10 metres Walk test (10MWT) and Time Up and Go test (TUG). On the end of the therapy the participants filled the subjective questionnare which was created for them. The intragroup difference was evaluated using ANOVA for repetitive measures with Fisher´s post-hoc test ($p \leq 0.05$).

Results: Our data showed that ES according to Jantsch had an immediate influence on the reduction of the spasticity of treated muscle (difference of measuring angle of catch STIM/NONSTIM was 9.86 degrees, $p<0.05$) and ES increased the active range of movement of the antagonists (difference between STIM/NONSTIM was 10.40 degrees, $p<0.05$). Furthermore, this effect had lasted throughout the whole period of treatment and it had the increasing tendency. The increase of speed of walk by using the ES was not proved ($p<0.05$). From subjective point of view all participants evaluated the ES positively.

Conclusion: ES according to Jantsh decreases the spasticity of triceps surae muscle, but does not have the influence on speed of walk measured by 10 metres Walk Test and TUG test.

Disclosure

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EP1719

MS in the 21st Century mapping study identifying the global educational offerings for multiple sclerosis patients

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Background: The MS in the 21st Century initiative, formed in 2011 and led by a Steering Group (SG) of international multiple sclerosis (MS) specialists and patient advocates, focusses on developing programmes to improve the education of and communication between healthcare professionals (HCPs) and people with MS (PwMS). Throughout 2016-2017, the SG conducted a mapping exercise to capture the existing educational offerings for PwMS across Europe and Canada (Phase 1) and USA, Asia-Pacific, South America and Middle East regions (Phase 3).

Aim: To report, for the first time, global findings of a comprehensive mapping exercise to identify the scope, diversity and number of online educational materials for PwMS produced by 1,309 stakeholders from 53 countries.

Method: Quantitative desk research (internet-based) was conducted and resources mapped against a set of standardised parameters. Research was conducted across multiple stakeholders including patient groups, pharmaceutical companies and public health providers. Resources were categorised by topic and format including, websites, information sheets and social media.

Results: Across the 53 countries mapped, a total of 13,324 different educational resources were identified. The majority of the resources were produced by 'patient groups' (48.4%) followed by 'specialist MS clinics' (18.9%). The most common topic covered by the resources was 'treatment' (25.3%) and the least covered topic was 'information for families' (1.5%). 'Patient groups' produced 73.0% of resources on 'information for families' but only 37.0% of resources on 'treatment'. Within the topic of 'treatment', 29.3% of resources by 'social media' stakeholders were about alternative treatment (i.e. holistic treatment etc.) a greater proportion than for any other stakeholder type. 'Public health providers' produced 23.8% of the resources about clinical trials despite only producing 2.8% of the total resources.

Conclusion: This research shows the breadth and depth of current educational materials available online for PwMS around the world. While the majority of these materials are accessed through 'patient group' or 'MS clinic' websites; within specific topics, sub-topics, and formats there is a large amount of variation in the relative contribution of different stakeholders. Therefore, when looking at patient education it is important to consider not just what resources are currently available but also which stakeholders are producing them.

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Diego Centonze has been an advisory board member for: Bayer, Schering, Merck Serono, Teva , Biogen Idec, GW Pharmaceuticals, Almirall, Sanofi Genzyme, Novartis. He has received honoraria for speaking or consultation fees from: Almirall, Bayer, Schering AG, Biogen Idec, Sanofi Genzyme, GW Pharmaceuticals, Merck Serono, Novartis, Sanofi Aventis, Teva. He is an external expert consultant for the European Medicines Agency (EMA), and the principal investigator in clinical trials for: Bayer, Schering AG, Biogen Idec, Novartis, Merck Serono, Sanofi Aventis, Teva, Roche.

Gavin Giovannoni is a steering committee member for: AbbVie (Daclizumab trials), Biogen Idec (BG12 and Daclizumab trials). He has received honoraria for speaking at Physicians summit Canbex. He is a clinical advisor regarding the development of VSN16. He has received consultancy fees for advisory board meeting for GW Pharmaceuticals, and speaking at launch of Sativex in Norway.
Elisabetta Verdun Di Cantogno is an employee of Merck KGaA.
MS in the 21st Century Steering Group members: Peter Rieckmann, Diego Centonze, Gavin Giovannoni, Celia-Oreja-Guevara, Jurg Kesselring, Dawn Langdon, Sarah A Morrow, Sven Schippling, Heidi Thompson, Patrick Vermersch, Birgit Bauer, Jocelyne Nouvet-Gire, Maria Paz Giambastiani, Maija Pontaga, Stanca Potra, Jane Shanahan, Pieter van Galen and David Yeandle

EP1720

Wind of change: an Italian initiative to promote water sports in people with multiple sclerosis

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Introduction: It is well known that physical activity is inversely associated with symptoms severity and stimulates neuroprotection in MS. Nonetheless, people with MS (PwMS) are less physically active than non-diseased persons, especially due to the low level of perceived self-efficacy preventing them from experiencing a large number of physical activities.
Objectives: In the context of an awareness program, promoted by the Italian Multiple Sclerosis Foundation in collaboration with the University of Genoa, to favor physical activity and participation in MS, we addressed the impact of the practice of water sports (sailing, windsurfing, Stand-Up-Paddle surf), believed too challenging by PwMS.
Aims: To evaluate the effects of a 5-days water sports training on upper limb, balance and walking performances and to reduce barriers in facing up to physical activities considered too difficult by PwMS.
Methods: The participation to the event "*Wind of Change*" held in Isola d'Elba (Tuscany) in May 2018 was obtained by recruiting participants through https://www.europewithoutbarriers.eu/. PwMS with minimal disability were admitted to the event. Descriptive measures were collected through validated patient-reported outcome for fatigue (MFIS), walking (MSWS-12) and upper limb (AMSQ) functions. Instrumental tests to assess upper limb (9hpt, grip and pinch), balance and walking (25FWT at self-paced and maximal speed, 2MWT, TUG) abilities were administered before and after the event.
Results: 17 PwMS (14 females) were selected for the event. They were from around Italy and none of them previously experienced the proposed water sports. No minor events, relapses, and/or neurological worsening were reported in the last three months. They were relapsing-remitting, mean age was 29.5 (±3.5) years, MFIS was 19.28 (±14.68), MSWS-12 was 16.71 (±6.04), AMSQ was 33.94 (±7.43). Participants showed a significant improvement in right 9hpt (pre 16.9s, post 15.9s, $p< 0.01$); left 9hpt (pre 17.9s, post 16.6, $p< 0.005$); 25FWT self-paced (pre 5.32s, post 4.61s, $p< 0.005$); 25FWT fast (pre 3.81s, post 3.63s, $p< 0.02$); 2MWT (pre 175.01m, post 192.44m, $p< 0.01$); TUG (pre 6.46s, post 6.15, $p=0.03$); No significant improvement were found in grip and pinch. Participants reported improved self-efficacy due to the water activities proposed during the event.
Conclusions: A 5-days water sports program seems to have a positive effect on upper limb, balance and walking and perceived self-efficacy in PwMS.

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EP1721

Is placebo effect getting bigger in randomized controlled trials of multiple sclerosis?

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Introduction: Randomized controlled trials (RCTs) are the principal source of evidence for the treatment guidelines of multiple sclerosis (MS). Generally, placebo or an active comparator are used as the control in these trials. Intuitively, no effect on the disease course in the placebo arm is expected in addition to the regression to the mean bias.
Aim: In this study, we aimed to compare the magnitude of the regression to the mean bias in the placebo-treated patients over the years.
Methods: We included all phase II and III RCTs on relapsing remitting MS. We collected data including gender ratio, disease duration, annualized relapse rates, number of relapses, and Expanded Disability Status Scale (EDSS) scores of the placebo-treated patients. We divided the RCTs into two groups according to the studies' publication dates (Group I: studies before 2010, Group II: studies after 2010).
Results: Baseline demographic characteristics of the patients did not differ regarding gender ratio and disease duration between group I and II. However, there was a significant reduction in the ARR in the placebo-treated patients between the groups (Group I: 1.0±0.3 vs. group: II 0.5±0.2; $p< 0.001$). We also observed a significant increase in the relative reduction of ARR (Group I: 42.1±19.9 vs. group II: 51.0 ± 12.8; $p=0.017$), although the mean EDSS score before study entry was significantly higher in group II (Group I: 2.3±0.3 vs. group II: 2.6±0.3; $p=0.026$).
Discussion: Our study suggests the presence of an increased regression to the mean bias of the placebo-treated groups in recent

studies, despite the fact that patients with higher EDSS scores were being recruited over the years. This finding should be taken into consideration in the design of future RCTs.

Disclosure

Nothing to disclose for all authors.

EP1722

Making science digestible: the development of educational activities for children with a parent with MS, and the need to better engage families

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Introduction: Multiple sclerosis (MS) onset is commonly in early adulthood; many people with MS (PwMS) have young families. The majority of health resources for children of PwMS are printed materials produced by MS charities which provide information but do not facilitate interaction. The number of young people who have a parent with MS is unknown, and they gain support from young caregiver networks rather than MS-specific charities. Communicating with these young people through social media is limited, as they may not access accounts relevant to MS. As a result, developing strategies to educate children in families affected by MS and potentially reduce the risk of MS in these children is limited by recruitment and engagement difficulties.
Methods: the Digesting Science project developed educational kits to be delivered as an event for children with a parent with MS. It aims to engage children in science and communicate health information. The project was developed by a multidisciplinary team at Queen Mary University of London (QMUL), including MS researchers, clinicians, MS Nurse specialists, a drama teacher, designers and families affected by MS. It builds on play as an integral part of the learning experience; and is delivered by facilitators via a comprehensive manual - a scientific background is not required.
Results: Since 2013, there have been 58 Digesting Science events; 42 since January 2016 using the new portable kits. In total 315 parents/relatives have attended, with 411 children. 8 further events are planned in the next 3 months. Events have been facilitated by MS nurses, MS therapy centres, young carers centres and others. The portable kits allow events to be facilitated internationally; they are currently being translated into French, German, Spanish, Turkish, Arabic and Hebrew. We are currently working on how to support and continue to engage families that have taken part.
Conclusions: This structured, safe, informal educational event allows specific topics that might not easily be raised in an unsupported family context to be addressed and discussed openly (e.g. continence issues). The activities engage people who would not normally discuss MS research to engage and ask questions relevant to them, and it has identified an urgent need to develop resources and support for families affected by MS. Importantly, the project can act as a method to communicate new advances in MS research, and engage families in preventative trials in the future.

Disclosure

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EP1723

Young MS in Italy: attitude towards present and expectations for the future

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Background: The increased knowledge on disease and ameliorated diagnostic criteria have anticipated the diagnosis of MS very early after the onset, when a person is quite young. The diagnosis of MS might worry young people in a period of life characterized by important choices about careers, family and future in general.
Goals: Our aim is to comparison the vision of young people with and without MS in terms of life prospects, inclusion and social participation, access to education and work, health needs and responses. In addition, we compared the present results with the one obtained in 2005 in a similar study.
Methods: We interviewed 613 young adults (18-40 years) with MS (PwMS) and 1.003 young adults without MS (PwoMS) living in Italy. The composition of the two groups reflects those of the reference universe, so in the sample of PwMS, women represents the 78.5%. Both samples receive the same structured questionnaire, with an added section on the disease for PwMS. The PwoMS received a telephone interview whereas the group with MS participated to a Computer Assisted Web Interviewing survey open to all users of the site of Italian patient association, or to a direct interview, always conducted by the association.
Results: About happiness, 1 young in 2 claims to be quite happy, 1 in 4 not very happy, over 1 in 8 very happy, 1 in 20 not happy at all, with few differences in the two groups. The comparison with the survey of 2005 highlights a significant decrease in the number of young self-defined happy (very happy from 15.6% to 9.9% and quite happy from 65.5% to 56.1%), while among the PwMS there are very limited variations.Analyzing the declared health status, most of young declare good or excellent health conditions (67.1% define their status as good and 22.7% as excellent, while 9.5%

declare a mediocre condition and 0.7% not good). Data on PwMS are similar to PwoMS, although the conditions declare by PwMS are clearly less positive, and a lower percent between the youngest considers its level of health excellent. The comparison between 2005 highlights an improvement in the health conditions perceived in young people especially in those with MS.
Conclusion: The improvement of perceived health in PwMS is another proof of the progress of MS treatments in the last 15 years, which led to a perception of a clear improvement in the health status declared by PwMS, which moreover appears transversal to all the conditions of disability.

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EP1724

Attendance to ECTRIMS: does it impact on therapeutic decisions in multiple sclerosis care?

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Introduction: Making therapeutic decisions in multiple sclerosis (MS) is becoming increasingly difficult due to a more complicated risk-benefit spectrum of new agents.
Medical conferences may play an important role in the ongoing education of healthcare professionals. However, limited information is available on the impact of annual ECTRIMS Congress on the management of patients with MS.
Objective: To assess the influence of attendance to the last ECTRIMS Congress on therapeutic decisions and management errors by applying principles from behavioral economics.
Methods: A web-based, cross-sectional study was conducted comprising neurologists with expertise in MS care throughout Spain. Participants answered questions regarding the management of 20 case-scenarios commonly encountered in clinical practice and completed 3 surveys and 4 experimental paradigms based on behavioral economics. We assessed treatment escalation when therapeutic goals were unmet (e.g. progressive cognitive decline, disease progression). Management errors (ME) were tested with tolerability and safety scenarios (e.g. management of gastrointestinal events, lymphopenia, or elevated liver enzymes). Multivariable analysis was adjusted for age, level of expertise, practice setting and patient volume, and reported as OR; 95%CI.
Results: Ninety-six participants completed the study. Mean age was 39.5 ± 8.5 years; 53% were female. Two-thirds primarily focused their practice on MS care (n = 64; 66.7%). Mean years in practice was 14, commonly assessing 20 ± 15 MS patients per week. Fifty-six (58.3%) attended to the latest ECTRIMS. Lack of treatment escalation was detected in at least one case-scenario in 68.8% of participants. One third of neurologists made at least one ME, whereas 18.8% made two ME out of three case-scenarios. Attendance to ECTRIMS was associated with an increase likelihood of treatment escalation in presence of progressive cognitive decline (OR 2.44; 95% CI 1.06-5.82) and lower number of management errors (OR 0.26; 95%CI 0.07-0.98).
Conclusions: Attending to ECTRIMS Congress was associated with a positive impact on the medical management of patients with MS irrespective of participant's demography, level of expertise, and practice setting.

Disclosure

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EP1725

Fulminant multifocal relapse in a fingolimod-treated patient

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Introduction: Unexpected magnetic resonance imaging (MRI) activity, with an unusually high number of gadolinium-enhancing lesions, and severe clinical rebound of disease is observed in multiple sclerosis (MS) patients, 8-24 weeks after fingolimod withdrawal. Here we describe a case of a patient who, after several years under fingolimod, presented MRI characteristics of a severe « rebound syndrome », while being adherent to treatment.
Case summary: We report the case of a 41 year-old female with relapsing-remitting MS (disease duration = 20 years), initially treated with subcutaneous interferon beta-1a during 13 years, who was subsequently switched to fingolimod due to its oral intake and the lack of control of disease activity (five relapses between 1997 and 2008, EDSS score = 1). Both clinical and radiological stability was achieved under fingolimod during six years. However, a routine MRI depicted more than 30 gadolinium enhancing lesions together with an abnormal neurological exam (EDSS = 3; back to 1 after intravenous methyprednisolone). Patient was paucisymptomatic : chief complaints included dizziness and instability. Adherence to recommended treatment was irreproachable, supported by a grade III lymphopenia. Serologic and cerebral spinal fluid (CSF) testing for infectious diseases were negative, as well

as bacterial and fungus cultures. AQP4 and MOG antibodies were unremarkable. No tumoral cells were found in the CSF. Given the unusual radiological presentation, and to exclude lymphoma or infections, a brain biopsy of the right frontal lesion was performed, showing evidence of active inflammation and demyelination as seen in MS.

Conclusion: although a large body of evidence confirms important inflammatory activity occuring after fingolimod withdrawal, only few publications reported this kind of radiological progression during adequate treatment intake, generally ressembling more to pseudotumoral relapses than multifocal widespread relapse as seen here. We hypothesize that, in certain patients, fingolimod might entail SP1Rs downregulation, thus increasing CNS inflammation risk. Further studies must be carried out to confirm this hypothesis.

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EP1726

Demographic and clinical characteristics of patients treated with ocrelizumab in the United States

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Introduction: Ocrelizumab (OCR) is the first disease-modifying therapy (DMT) to treat relapsing (RMS) and primary progressive (PPMS) forms of multiple sclerosis and is approved in the United States and European Union. Real-world evidence on OCR treatment is limited in the literature.

Objective: To describe demographics, clinical characteristics and treatment patterns of patients with MS who initiated OCR treatment in the first year of approval.

Methods: This study used data from the Adelphi Multiple Sclerosis Disease Specific Programme (DSP), a cross-sectional survey collecting data from neurologists and patients with MS with a broad geographical spread across the United States between March and May 2018. Data were analyzed from a population of patients currently receiving OCR, with a target of 300 OCR patients by late 2018. Demographic and clinical characteristics, including Expanded Disability Status Scale (EDSS) and DMT history, were reported by the physician.

Results: Among the 75 patients currently using OCR, 36% had relapsing-remitting MS (RRMS) and 64% had PPMS. The mean (SD) age was 46.8 (9.0) years, and the mean (SD) time since MS diagnosis was 5.6 (4.9) years. At the time of switching to OCR, the majority of patients had moderate (55%) to severe (12%) compared with low (28%) disease activity, and a mean (SD) EDSS score of 4.1 (1.7) points. No previous DMT use was reported in 23% of OCR patients. Among patients who switched to OCR, 57% switched from platform therapies (interferons or glatiramer acetate), 31% from orals (teriflunomide, fingolimod, dimethyl fumarate or cladribine) and 11% from another infusion product (daclizumab, mitoxantrone, natalizumab or alemtuzumab). Reasons (multiple options) for switching from previous DMT to OCR included patient compliance (32%), efficacy (63%), side effects/safety (43%) and reasons relating to insurance (9%).

Conclusions: To our knowledge, this is one of the first real-world studies describing the demographic, disease and treatment characteristics of real-world ocrelizumab users. Data collection is ongoing, and we expect to present results from the complete sample at the time of the 2018 ECTRIMS meeting.

Disclosure

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EP1727

Effect of pregnancy and exclusive breastfeeding on the rate of relapses and degree of disability in two years after pregnancy in patients with multiple sclerosis

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Introduction: Pregnancy and lactation are important issues for women with multiple sclerosis(MS). The purpose of this study was to investigate the effect of pregnancy and exclusive breastfeeding on the rate of relapses and degree of disability in two years after pregnancy in patients with relapsing remitting multiple sclerosis(RRMS).

Materials and methods: 30 RRMS pregnant women who had exclusive breastfeeding for 4 months were compared with 67 non-pregnant women with RRMS as controls from 2012 to 2017. Each patient was examined every three months for 33 months.

Findings: In the first group, patients were examined at the beginning of pregnancy, and then every three months to 24 months after delivery. Expaned disability status scale (EDSS) in the third trimester of pregnancy, third to ninth month after delivery, the last 6 months of study and collectively at the end of the study were significantly lower than the control group ($p < 05$). Also, EDSS in the second and third trimesters of pregnancy was significantly

decreased compared to the initial EDSS ($p < .05$). The mean number of relapses in the second and third trimesters of pregnancy, the third to sixth month after delivery, and the total number of relapses were significantly lower than the control group.
Conclusion: Exclusive breastfeeding after pregnancy can have a positive effect on reducing relapse rate and disability, and this effect will continue until the 24th month after childbirth.

Disclosure

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EP1728

Fuelling patient engagement in health: perceptions and utilisation of patient self-monitoring

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Introduction: Multiple sclerosis (MS) is characterised by extreme symptom variation and adverse manifestation of physical and cognitive disabilities resulting from demyelination of the central nervous system. While MS is treated pharmacologically, the complexity of the disease requires patients to be proactive in self-management of complications.
Objective: Assess physician and patient perceptions of MS patients' utilisation of self-monitoring techniques.
Methods: Patient self-monitoring data was collected from three sources and descriptive analyses were done separately. Healthcare Practitioner (HCP) Perceptual Questionnaire; collected de-identified HCP perceptions from 10/2017-12/2017; Dynamic patient record forms [PRF]; HCPs collected de-identified data from relapsing-remitting MS (RRMS) patients initiating or switching treatment at the time of consultation (1/2018 -3/2018). Lastly, the Ipsos MS syndicated Patient Community gathered qualitative patient perceptions via an online platform in the 4EU (UK/Germany/ Italy/Spain) and US from 2/2018 - 3/2018.
Results: HCPs' perception of patients' use of connected health devices in management of MS was low, with less than one-third of HCPs (27.7%, n=242) in 5EU and the US (20.2% n=109) demonstrating awareness. From a scale of 1= not at all knowledgeable to 7=very knowledgeable HCPs recorded an average of 3.8 in the 5EU and 3.7 in the US, resp. in their knowledgeability to recommend an appropriate eHealth device. PRF data indicated that for 72.7% (n=1515) and 62.5% (n=517) 5EU and US resp. of RRMS patients, HCPs were not aware of patients using eHealth devices to track health parameters such as heart rate, activity and sleep patterns. When data from the Patient Community was examined, 88% of patients in the 4EU and US (n=97) chose to self-monitor; the top three most frequently mentioned being weight, sleep and number of steps walked per day. Additionally, 84% and 47% of patients were willing to share self-monitoring data with their neurologist and MS nurse, resp.
Conclusions: Self-monitoring is a patient-led initiative, rarely suggested by HCPs who have both low awareness and comfort in their knowledgeability to recommend an eHealth device. This choice to self-monitor, despite limited HCP engagement reflects patient perceptions of self-monitoring as a self-determined responsibility. This demonstrates the acceptance and opportunity for utilisation of self-monitoring to improve disease management among MS patients.

Disclosure

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EP1729

Idiopathic thrombocytopenic purpura (ITP) during Fingolimod treatment in relapsing remitting multiple sclerosis

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Introduction: To present a case of idiopathic thrombocytopenic purpura (ITP) following treatment with Fingolimod.
Case History: A 26-years old woman diagnosed with relapsing-remitting multiple sclerosis(RRMS) in 2010, was initially treated with IFN beta-1a (Avonex) for 2 years and then Betaferon for 3 years respectively. Due to a new attack on Betaferon, the treatment switched to Fingolimod. She was then free of clinical and MRI activity for 2.5 years. At this time, we noticed a sudden drop in patient´s platelet count to 23000, whereas she had no symptoms of spontaneous bleeding, ecchymosis, petechia or purpura. Fingolimod was stopped and she was admitted to the hospital. The results of next day platelet count were 16000 and 9000 respectively and other blood tests, ultrasound investigations and bone marrow biopsy revealed normal findings. Consequently, with the diagnosis of ITP, IV immunoglobulin and dexamethasone started for her on the basis of hematologist advice. Daily blood tests revealed an increase in platelet count to 44000 in the second day of therapy. After 6 days admission in the hospital, she was discharged home with a platelet count of 116000, with prescription of Prednisolone, 50 mg once daily .The patient remained without treatment until 2 months, that she had a severe relapse, so she underwent pulse therapy for one day. Owing to ITP induced by Fingolimod and re-occurrence of relapses, it was decided to start Rituximab and she received the first dose during hospitalization. She has had a stable course of disease with no relapses and no changes in blood test results after 4 months of Rituximab initiation.
Conclusions: Co-existence or induction of other immune mediated disorders in MS patients has been reported previously. To the best of our knowledge, this is the first reported case of ITP in a Fingolimod-treated individual. This case highlights the potential risk associated with long-term immunosuppression which could lead to induction of a new autoimmune disorder. Further studies are required to determine if this is a co-incidence, an induction, or a random finding.

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EP1730

Digging up a new approach in the management of multiple sclerosis: Helminth therapy from the patients' perspective

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Background: Due to the chronic nature of MS, alternative therapeutic approaches are on the rise. Helminth Therapy (i.e. inoculation with helminthic parasites) is an approach that many view as very alternative, but with promising underlying scientific evidence for immunological involvement. With many alternative therapies, public utilization of the therapy often occurs prior to evidence acquired from clinical trials. Therefore, experiential knowledge becomes an important source of information.
Aim: The aim of this study was to explore the opinion of people with MS regarding helminth therapy and its use in the management of MS.
Methods: Interpretative description, an applied qualitative research approach, was used in this study. The data sources were online forums including blogs and discussion boards. Multiple investigators identified, extracted and analyzed the data. Preliminary codes were established using whole data immersion, inductive thematic analysis and triangulation.
Results: Four main themes were generated: 1) the experience of living with MS; 2) influential factors in contemplating Helminth Therapy; 3) logistical decisions to be made, and 4) concerns. The difficulty of living with an incurable condition, a dissatisfaction with current therapy in improving symptoms that impact their quality of life (QoL) and a shift to alternative therapy seeking was evident in theme 1. Theme 2 highlights social influences, perceived scientific evidence, expectations and hope. Following contemplation, logistics such as where to access the worms, type of worm, administration method, monitoring uptake and cost were evident. Theme 4 involved concerns such as side effects, long-term complications and social stigma of Helminth therapy.
Conclusion: Overall, there was a general consensus that conventional therapies were not providing meaningful improvement for people living with MS. When seeking alternative therapies, a paucity of available scientific evidence promotes the use of internet resources for information. However, blogs and other social media forums can contain biased opinions, including those that may not be scientifically supported. Therefore, although Helminth Therapy has not yet proven beneficial in clinical trials of people lining with MS and is not currently a recommended therapy, it is important to recognize that online media forums convey messages of efficacy and improved QoL, which can influence the decision for people with MS to obtain this therapy.

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EP1731

A comparison of the effects of yoga and clinical pilates exercise on mobility, respiratory muscle strength and cognition in persons with multiple sclerosis

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Exercise is the important non-pharmacological method to improve motor functions, respiratory functions and well-being in persons with multiple sclerosis (MS, pwMS). It has been known that exercise can improve cognitive functions as well. Therefore, the purpose was to investigate effects of yoga and Clinical Pilates exercises on mobility, respiratory muscle strength, cognition, and compare the effects of two popular exercise methods in pwMS.
Twenty-nine pwMS (age, 43±8.86; disease duration, 12.91±6.71; EDSS, 2.38±1.6) were randomized into 2 groups: Clinical Pilates group (n=16) and yoga group (n=13). Participants received the program once a week for 8 weeks. The primary outcomes were Timed Up and Go (TUG) test, TUG cognitive. Timed-25 Foot Walk (T25FW), maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP), Brief International Cognitive Assessment for MS (BICAMS) which includes Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II) and Brief Visuospatial Memory Test-Revised (BVMT-R). Secondary outcomes were International Questionnaire Investigating Quality Of Life in Multiple Sclerosis (MuSiQoL), Activities-specific Balance Confidence (ABC) Scale, Multiple Sclerosis Walking Scale-12 (MSWS-12).
After 8-week exercise training, there were no significant differences between Clinical Pilates and yoga program in inspiratory and expiratory muscle strength, MSWS-12 and CVLT-II ($p>0.05$). However, there were significant differences in favor of the Clinical Pilates program in T25FW, TUG, TUG-cognitive, MuSiQoL, ABC, SDMT and BVMT-R ($p< 0.05$). Attendance ratio was %79 in yoga group and 93% in Clinical Pilates group.
This study demonstrated that Clinical Pilates and yoga training can improve respiratory muscle strength and walking ability from the patients´ perspective ($p< 0.05$). Pilates training was more effective to improve mobility, cognition, quality of life and balance confidence, compared to yoga training. Although both intervention programs appear to be enjoyable and well tolerated, the attendance rate was lower in the yoga group.

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EP1732

EDSS score, age, disease type and inaccessibility impact on oral health and prosthodontic rehabilitation in multiple sclerosis patients of a Hellenic cohort

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Background: Multiple Sclerosis(MS) patients with high scores of Expanded Disability Status Scale(EDSS), appear more susceptive to oral infectious diseases, due to their ineffective oral hygiene and inaccessibility to dental services. Untreated dental pathologies, caries or periodontitis lead to tooth loss and patients have to undergo extensive prosthodontics rehabilitation to restore their chewing efficacy.
Objectives: This study aims to evaluate the oral and dental status of MS patients in Greece and appraise their prostodontic restorations and to associate them with the EDSS score, Disease Type, Age and accessibility deteriorations to dental services.
Methods: 157 MS patients under regular follow-up at the Outpatient Demyelinating Diseases Clinic of the Aeginition Hospital, at the 1st Department of Neurology, of NKUA participated in the study. The mean age of the sample was 43.33±12.7, 63,1% female, 56,4% married, 48,4% of Tertiary Education and Mean Healthy Lifestyle Score 6.1±1.9. Median EDSS was 3.0, mean age at disease onset 32.5±10.84, mean disease duration in months 129,18±107,13, RRMS 67.7%. They consented to answer a questionnaire on their health and OHS, accessibility to dental services and QoL, and to receive a dental examination. DMFT(Decayed-Missing-Filled Teeth) scores measured the OHS.
Results: DMFT scores were significantly related to: age, disease type, age at disease onset and EDSS scale. Only four patients had dental implants. and four patients had received dental treatment at home. Highest scores of EDSS were associated with more missing teeth and untreated need of prosthetic restoration, while there was a great number of combined fixed and removable prosthesis among them. Denture wearers were comfortable cleaning them extra-orally and speaking, but lacked chewing attribution and aesthetics, whereas patients restored with fixed partial dentures were satisfied in all fields. 75,8% of the patients attended their dentist regularly and only 24,2% of them mentioned a reason of inaccessibility. Inaccessibility correlated significantly with age, EDSS and disease type.
Conclusion: MS patients of high EDSS scores and disease duration have more missing and less restored teeth, due to inaccessibility of dental services. Treating patients at home could improve their oral health status considering that MS is a disease of periodical mobility deterioration, preventing tooth loss and help patients avoid complicated restorative procedures.

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EP1733

The main factors that influence the family life of patients with multiple sclerosis

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Background and aims: MS is a chronic, progressive, disabling and incurable disease that manifests frequently in young adults. The family life can be affected by the sum of disabilities, psychological and sexual problems, and last but not least the limitations that are imposed by the immunological therapy. This study evaluates the point of view of patients with multiple sclerosis (MS) regarding family life within the disease and the impact that the diagnosis had on it.
Methods: Our prospective study was conducted on the basis of a questionnaire of 20 questions in the period January -May 2018 on a sample of 496 patients, of fertile age, diagnosed with MS and following immunomodulatory therapy at the Neurology Clinic of Colentina Hospital, Bucharest.
Results: Our lot consisted of 496 patients of which 260 were females, 236 are under interferon treatment, 120 - glatiramer acetate, 40 - natalizumab and 100 - teriflunomide. In the women lot: 75% deny changes in their family life due to MS. 80% of those have the EDSS score < 3 points. The main elements that influence family life (from the women's point of view) are: gait disturbances (31%), sphincterian impairment (28%), depression or anxiety (20%), sexual impairment (11%) and family planning issues (10%). The male lot: 20% say their family life was affected by the disease. 90% of those have the EDSS score> 3 points. The divorce rate is 25% in the young lot (< 35 years) in spite of a low EDSS score. The main factors that lead to this decrease in the quality of life are: gait disturbances (40%), sphincterian disorders and sexual dynamic impairment (38%), depression (20%).
Conclusions: As to be expected, there is a good correlation between the EDSS score and the impact the disease has on family life. MS has a significant impact on families, influencing their wellbeing and quality of life, often creating psychological stress in each family member as well as on family functioning in generally.

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EP1734

Hepatitis B post-vaccination immunogenicity in multiple sclerosis patients undergoing immunomodulators

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Introduction: The use of drugs that modify the immune system by patients with multiple sclerosis (MS) is rapidly increasing and so is the risk of getting infections, some of them severe. The hepatitis B vaccine (HB) induces protective concentrations of HB surface antibodies (anti-HBs) in more than 90·% of healthy adults under the age of 40. MS patients risk losing these protective titers when treated with immunomodulators.
Objective: To study whether patients undergoing immunomodulator treatment for MS maintain the protective titers of anti-HBs equal to or greater than 10 mIU/ml.
Method: A unicentric, national, cross-sectional and retrospective observational study. Inclusion criteria: patients with RRMS>18 years with positive vaccine response to HB and at least 6 months of treatment with natalizumab (NTZ), alemtuzumab (ALM), fingolimod (FIN), teriflunomide or dimethyl fumarate (DMF) after vaccination. Main variable: percentage of patients who maintain positive vaccine response after at least 6 months after the start of treatment. Secondary variables: demographic and clinical considerations of the vaccine schedule and MS drugs. Statistical analysis: descriptive. The study was approved by the hospital ethics committee and all patients signed the informed consent.
Results: Fifteen patients were included: 73% women, average age 36 +/- 7.8 years; time since diagnosis: 4 years (1-15 years); EDSS at the inclusion: 2.7 +/- 1.5. Treatment at the inclusion: DMF 46.7%, ALM 20%, FIN 20%, NTZ 13.3%. Previous treatments had been used in 40% of patients, requiring an average of 2 treatments (1-7 treatments). 53% had been previously vaccinated and the anti-HBs titers were positive before starting treatment. The other 47% had anti-HBs titers below 10 mIU/ml and they required vaccination, receiving at least 1 dose before starting treatment.
All patients maintained anti-HBs titers of >=10mIU/ml after an average of 10 months (6-37 months) of immunomodulator treatment.
Conclusions: MS patients maintain sero-conversion levels after HB vaccination in spite of immunomodulator treatment.

Disclosure

Authors have not conflict of interest and have not received funding for this study.

EP1735

Methylprednisolone concentration in milk and serum during and shortly after IV pulse therapy in patients with MS

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Background: High-dose IV methylprednisolone is the first-line treatment for acute relapses. Women with multiple sclerosis (MS) experience an increased risk of relapse during the postpartum period. Previously we have demonstrated that little amounts of methylprednisolone transfer into breast milk 2 hours after end of infusion. There is only limited data into the levels of concentration in breast milk and blood during and shortly after IV pulse methylprednisolone therapy.
Objectives: The study aimed to determine the transfer of methylprednisolone into human milk and serum during and shortly after infusion in breastfeeding MS patients.
Methods: IV methylprednisolone pulse therapy was given to 12 lactating MS patients. Breast milk and blood samples were obtained just before infusion, 30 minutes into infusion, straight after infusion and 1 hour thereafter.
Methylprednisolone concentrations were quantified by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS)
Results: MS patients aged (25.6 ± 6.1), weight in kg (71.4 ± 6.4), duration of MS in years (3.88 ± 2.2), and an EDSS (1.5 ± 0.8). Infants aged (months) (7.66 ± 4.0) and weighed (kg) (7.8 ± 2.6).
The methylprednisolone concentrations in milk were below detection limits just before infusion. Concentrations at 30 minutes into infusion were 2.9 μg/ml in milk and 6.1 μg/ml in serum. Maximum levels measured straight after infusion were 3.2 μg/ml in milk and 8.35 μg/ml in serum. Blood and milk concentration levels started to drop 1 hour after infusion.
Conclusion: Relatively small methylprednisolone concentration levels were transferred into breast milk during infusion. Results demonstrate that the relative infant dose (RID) of the weight-adjusted maternal dose was lower than the generally accepted RID of 10%. Nevertheless, infant exposure should be taken into account during and shortly after the infusion and mothers are recommended to wait 2 to 4 hours to breastfeed to further limit infant exposure.

Disclosure

Authors has nothing to disclose.

EP1736

Effects of methyl prednisolone on the proliferation and maturation of oligodentrocytes. ***In vitro*** **study**

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Background: In the desmyelinating diseases the remyelination its a target. During attacks in the Multiple Sclerosis, methyl-prednisolone is the treatment of first choice, and there is controversy

about the effect of prednisolone on generation of OPC and remyelination.
Objectives: To analyze if methylprednisolone affects the expression of oligodendroglial maturation and proliferation markers in vitro
Methods: Mouse neurospheres and HOG line cells were cultured for 3, 5, 7, 10 and 15 days in the presence of different doses of methyl prednisolone (0.5, 2, 5, 10, 30 and 50 μM), we analyzed the clonal capacity, and expression by immunocytochemical of caspase 3 (as a marker of death), Ki67 (Cell proliferation) and different stages of oligodendroglial maturation (NG2, Olig2, Oligodendrocytes, CNPase and MBP / PLP).
Results: Methyl prednisolone affects the proliferation and differentiation of oligodendrocytes significantly at all times and under all doses analyzed. In addition to a higher concentration of methylprednisolone shows greater cytotoxicity and affects the expression of oligodendroglial markers.
Conclusions: Our results suggest that methyl prednisolone affects the proliferation, differentiation and maturation of oligodendrocytes. Therefore, its use as a first-choice treatment in multiple sclerosis can have a negative connotation if remyelination is target.
Key words: Neurospheres, oligodendrocytes, remyelination, Corticoids, Methyl prednisolone, Multiple Sclerosis

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EP1737

Real-world effectiveness of TYSABRI® (natalizumab) treatment in patients with relapsing remitting multiple sclerosis in Argentina and Chile

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Background: Multiple sclerosis (MS) is the leading cause of neurological disability in young adults and affects approximately 2.5 million people worldwide. The prevalence of MS is 16-21 per 100,000 in Argentina and 14 per 100,000 in Chile. Previous studies have demonstrated the effectiveness of natalizumab in clinical trials and real-world settings. However, the effectiveness of natalizumab in relapsing-remitting (RRMS) patients from Argentina and Chile has not been studied.
Objective: To characterize the real-world effectiveness of natalizumab in patients with RRMS in Argentina and Chile.
Methods: A retrospective chart review was performed by neurologists at each site. Data were analysed for changes in annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) score, the proportion of patients free from relapses, and disability worsening and improvement. Demographic and outcome variables were summarized. ARR was analysed using a repeated measure negative binomial regression model.
Results: Analyses included 117 patients. At baseline (BL), mean ARR was 1.97 (standard deviation [SD]: 1.21; 95% confidence interval [CI]: 1.75-2.20). ARR was significantly reduced at 1 year (mean: 0.06; SD: 0.24; 95% CI: 0.02-0.11) and 2 years (mean: 0.09; SD: 0.35; 95% CI: 0.02-0.16) of treatment. The proportion of patients (95% CI) free of relapses was significantly lower at 1 and 2 years than at baseline (BL: 7.69% (3.56-14.10); 1 year: 93.91% (87.86-97.52); 2 years: 92.93% (85.97-97.11). From BL, EDSS scores were reduced by a mean (95% CI) of 0.71 (0.46-0.96) at 1 year and 0.73 (0.43-1.03) at 2 years. The proportion of patients (95% CI) without disability worsening was 82.9% (74.8-89.2) at 1 year and 67.5% (58.2-75.9) at 2 years; the proportion with disability improvement was 44.4% at 1 year and 39.3% at 2 years. In the year prior to enrolment, 83 hospitalisations were recorded. During follow-up on treatment, recorded hospitalisations reduced significantly to 1 and 3 in follow up years 1 and 2 respectively ($P< 0.01$).
Conclusions: Consistent with previous clinical trials and real-world studies, natalizumab effectively reduced disease activity for patients with RRMS in Argentina and Chile as evidenced by decreased ARR and EDSS scores compared with baseline. Treatment with natalizumab also decreased the number of hospitalisations compared with the pre-treatment period.

Disclosure

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EP1738

Multiple sclerosis prognosis - our experience in Colentina Clinical Hospital

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Background and aims: Multiple sclerosis is a progressive disabling disease and the life expectancy is with 5-7 years lower than the normal population, mostly due to the complications or other comorbidities. It is estimated that the long term prognosis is better in the recurrent-relapsing (RR) form than in the secondary ones (SP) due to the fact that they have a better response to immunomodulatory therapy which is what our study is meant to evaluate.
Methods: We have conducted an ambispective observational study based on 450 patients with MS and following immunomodulatory therapy in the Neurology Department of Colentina Clinical Hospital, Bucharest, over a period of 2 years.
Results: Our lot consisted of 450 patients (280 RR and 170 SP) all of them undergoing immunomodulatory therapy (235 interferon, 84 glatiramer acetate, 76 teriflunomide and 55 natalizumab therapy), with EDSS< 3p. 14% of them had other comorbidities before entering the program. By the end of the first year, 10% of the RR lot reached an EDSS=3.5p and 15.2% of the SP. By the end of the second year 8% of the RR patients had an EDDS>4 and 12.9% of the SP. There have been 8 deaths (3 RR, 5 SP), 7 due to comorbidities (5 cardio-vascular events, 2 cases of cancer) and 1 EDSS=10 (SP). The mean of time in which they reached and EDSS=3.5 was 8 months for the RR patients, 6.4 months for SP patients that respected the indicated treatments and 5 months for those who decided to interrupt the therapy in the RR lot, respectively 4 months for SP. The patients who at the end of the 2 year period didn't have an EDSS< 3 reported having a balanced diet, exercising regularly and treating every new episode with corticoids.
Conclusions: There are many factors that influence the life expectancy of MS patients, including the age of onset, the progression rate and the treatment, but the dizability imposed by this pathology isn't necesarly a death cause. There is a sensible difference between the way that RR and SP patients respond to treatment, in favour of the first lot.

Disclosure

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