Poster Session 2

Diagnosis and differential diagnosis

P799

Multiple sclerosis mimickers on initial presentation: frequency, type and predictors

B.I. Yamout[1], S.J. Khoury[1], N. Ayyoubi[1], M. Fakhreddine[1], H. Doumiati[1], S.F. Ahmed[2], H. Tamim[3], J.Y. Al-Hashel[2], R. Behbehani[4], R. Alroughani[5]

[1]Neurology, American University of Beirut Medical Center, Beirut, Lebanon, [2]Neurology, Ibn Sina Hospital, Kuwait, Kuwait, [3]Clinical Research Institute, American University of Beirut Medical Center, Beirut, Lebanon, [4]Ophtalmology, Ibn Sina Hospital, [5]Neurology, Amiri Hospital, Kuwait, Kuwait

Objectives: The McDonald criteria emphasize the importance of excluding other diseases or mimickers before a final diagnosis is made. The aim of this study is to explore the frequency, type, and predictors of MS mimickers among cases referred to two specialized MS centers in the Middle East with a recent diagnosis of MS.
Methods: This is a retrospective review of a prospectively followed cohort of MS patients at 2 University specialized MS centers in Lebanon and Kuwait. We included all patients presenting for the first time to the MS Centers in Lebanon between 2012 and 2015 and in Kuwait between 2015 and March 2016. The final diagnosis was recorded and demographic, clinical, laboratory, electrophysiological and radiological variables were collected. Cases of CIS highly suggestive of MS (n=19) were lumped with MS patients for the purpose of this analysis.
Results: 554 patients were included in this study of which 431 were referred for diagnostic confirmation of MS. Of those 431 patients, the final diagnosis of MS was confirmed in 300 (69.6%) patients, while 116 (26.9%) turned out to have an alternative diagnosis and 15 fulfilled the criteria for radiologically isolated syndrome (RIS). Of 179 patients referred for a clinical suspicion of MS, 94 (52.5%) had MS, 81(45.3%) an alternative diagnosis and 2 (1.1%) RIS. Of 37 patients referred for radiological suspicion of MS, 3(8.1%) had MS, 22 (59.5%) an alternative diagnosis and 12 (32.4%) RIS. The most common alternative diagnoses were psychogenic (16.3%), non-specific MRI white matter lesions (14.7%), NMO (9.5%), migraine (8.6%) and systemic autoimmune disorders (8.6%). The strongest predictors of an alternative diagnosis were: older age, cognitive presenting symptoms, isolated MRI findings, MRI findings not fulfilling 2010 McDonald criteria for dissemination in time or space, absence of oligoclonal bands in the CSF, normal neurological examination ($P < 0.0001$), and normal visual evoked potentials ($P=0.002$). A detailed multivariate analysis of the predictors will be presented.
Conclusions: Our study shows that 30% of patients referred to a specialized MS center end up with a different diagnosis. The most common mimickers of MS in the Middle East are not different from what has been described in the West. Neurological signs and symptoms, age, and laboratory and radiological findings can help with the differential diagnosis.

Disclosure

Authors have nothing to disclose in reference to this work

P800

Periventricular lesions and multiple sclerosis diagnostic criteria in people with clinically isolated syndromes

W.J. Brownlee[1], K.M. Miszkiel[2], D.R. Altmann[3], D.H. Miller[1,4], O. Ciccarelli[1,4]

[1]Queen Square MS Centre, UCL Institute of Neurology, [2]Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, [3]Medical Statistics Unit, London School of Hygiene and Tropical Medicine, [4]NIHR University College London Hospitals Biomedical Research Centre,, London, United Kingdom

Background: The MAGNIMS group have recently proposed modified dissemination in space (DIS) criteria for a diagnosis of multiple sclerosis (MS) in patients with clinically isolated syndromes (CIS). These recommendations include an increase in the number of periventricular (PV) lesions required for DIS from ≥ 1 to ≥ 3 with the aim of improving the specificity of MRI criteria for diagnosing MS, particularly in light of other proposed changes such as inclusion of symptomatic lesions in DIS.
Objectives: To investigate the performance of ≥ 1, ≥ 2 and ≥ 3 PV lesions in DIS criteria for the diagnosis of clinically-definite MS (CDMS).
Methods: We studied 151 CIS patients (mean age 32.4 years, 102 [68%] female, 124 [82%] optic neuritis) from a prospectively recruited cohort who had MRI (brain + spinal cord) at presentation and 3 months later (brain only). The patients were followed up for the development of CDMS. We retrospectively applied the McDonald 2010 DIS requiring ≥ 1 PV lesion and modified DIS criteria requiring ≥ 2 or ≥ 3 PV lesions. In the subgroup of patients presenting with brainstem, spinal cord and hemispheric syndromes (n=27) we applied the same criteria with inclusion of lesions in the symptomatic region in DIS. We investigated the performance of DIS criteria with varying numbers of PV lesions, alone and in combination with dissemination in time (DIT) criteria for the development of CDMS.
Results: Over a mean follow-up period of 15.1years, 91 (60%) patients developed CDMS. The McDonald 2010 DIS criteria requiring ≥ 1 PV lesion had a higher sensitivity than modified DIS criteria requiring ≥ 2 or ≥ 3 PV lesions (81/74/70% respectively), but were less specific (72/75/77%). In combination with DIT, the respective sensitivities were 64/57/55% and the specificities were the same (78%). The results were similar when the symptomatic lesion was included in DIS; ≥ 1 PV lesion had the highest sensitivity and the same specificity as ≥ 2 or ≥ 3 PV lesions
Conclusion: Increasing the number of PV lesions required for DIS may reduce the sensitivity of MRI criteria for a diagnosis of MS in patients with CIS. Although there was a modest increase in

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specificity with DIS criteria requiring ⩾2 or ⩾3 PV lesions this was not maintained when DIS was combined with DIT criteria. Future studies should investigate varying PV lesion number in combination with other proposed changes to DIS criteria and in a larger cohort of patients with brainstem/spinal cord syndromes.

Disclosure

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Dr Altmann has nothing to disclose.
KA Miszkiel has nothing to disclose.
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Prof Ciccarelli is an Associate Editor of Neurology and serves as a consultant for GE Healthcare, Novartis, Roche, Biogen, Genzyme and Teva.

P801

Individual prediction of clinically definite MS in patients presenting with clinically isolated syndrome using machine learning

V. Wottschel[1,2], D.C. Alexander[3], D.T. Chard[2], C. Enzinger[4], M. Filippi[5], J.L. Frederiksen[6], C. Gasperini[7], A. Giorgio[8], M. Rocca[5], A. Rovira[9], N. De Stefano[8], M. Tintore[9], D.H. Miller[2], O. Ciccarelli[2]
[1]Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands, [2]Queen Square MS Centre, [3]University College London, London, United Kingdom, [4]Medical University of Graz, Graz, Austria, [5]Vita-Salute San Raffaele University, Milan, Italy, [6]Rigshospitalet-Glostrup and University of Copenhagen, Copenhagen, Denmark, [7]San Camillo-Forlanini Hospital, Rome, [8]University of Siena, Siena, Italy, [9]Hospital Vall d'Hebron, Barcelona, Spain

Introduction: A shorter interval between onset of clinically isolated syndrome (CIS) and a second relapse (onset of clinically definite MS (CDMS)) is associated with faster disease progression and therefore is of interest. We have previously shown that machine learning classification can provide an individualised prediction of early conversion to CDMS from subjects´ baseline MRI characteristics. However, it is unknown whether the contribution to the prediction comes from regional or more global MRI measures.
Aim: We aim to identify the global and regional MRI parameters and clinical measures that predict conversion to CDMS within 1 and 3 years.
Methods: 296 CIS patients studied within 3 months from onset in three MAGNIMS centres (London, Barcelona and Siena) were included in this study. Structural MRI, white matter (WM) lesion masks, and demographic and clinical information at baseline and at 1- and 3-year follow-up (FU) were collected. 66/296 patients (22.3%) converted to CDMS at 1-year FU and 107/248 (43.1%) at 3 years. The available clinical and MRI measures were grouped as follows:

1. global measures (age, gender, EDSS, CIS type, WM lesion load and count, grey matter (GM) and WM volume, brain volume),
2. lobar measures (mean MRI intensities, lesion count and load, mean cortical thickness (CT), mean GM and WM density, region-of-interest (ROI) volume of each lobe),
3. regional measures (same as in 2. but calculated in 142 ROIs).

These groups were used as inputs to random forests, which provide a likelihood of conversion for each patient as a result.

Classification performance was measured using area under curve (AUC), which is calculated from sensitivity and specificity at varying cut-off thresholds for the likelihood.

The numbers of CIS and CDMS patients were balanced to avoid bias. This was repeated 1000 times with 10-fold cross-validation to allow for generalisation.
Results: Lobar MRI measures performed best at predicting CDMS with an AUC of 62% (range 47-76%) and p=0.005 at 1 year, and an AUC of 61% (41-75%) with p=0.023 at 3 years. They are followed by regional MRI measures with AUCs ~58% at both FUs but p-values just above 0.05. Global measures had AUCs ~54% and p>0.05.
Conclusion: Random forests can be used to predict conversion to CDMS at 1- and 3-year FU using lobar features. Very small regions or global MRI measures seem to reduce accuracy due to redundancies and noise. Future work will focus on particularly predictive brain regions.

Disclosure

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M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory boards for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer´s Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).
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A. Rovira serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, has received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, OLEA Medical, Stendhal, Novartis and Biogen Idec, and has research agreements with Siemens AG.

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O. Ciccarelli is an Associate Editor of Neurology and serves as a consultant for GE Healthcare, Novartis, Roche, Biogen, Genzyme and Teva.

P802

Optic nerve MRI in patients with first-ever optic neuritis

J. Yang[1], B.-N. Yoon[2], Y.-H. Hong[3]
[1]Department of Neurology, Gil Medical Centre, Gachon University, [2]Department of Neurology, Inha University Hospital, Incheon, [3]Department of Neurology, Seoul National University Hospital, Seoul, Republic of Korea

Background and goals: Recently, several characteristics of optic nerve MRI suggesting NMOSD in patients without AQP4-IgG or with unknown AQP4-IgG status were reported by the international consensus group. In this study, we aimed to evaluate the optic nerve MRI pattern in patients with first-ever optic neuritis.
Methods: Patients with first-ever optic neuritis were included who visited in Seoul National University Hospital and Seoul National University Boramae Hospital from March 2008 to May 2015. As those institutes are tertiary and referral hospital, we enrolled patients when they were examined and treated in other hospital and soon after referred with medical records. We analyzed data of optic nerve MRI, brain MRI, and ophthalmic examinations.
Results: Total 92 patients´ data were analyzed. Numbers of female were 62 (67.4%) and bilateral eye involvements were 19 (20.7%). Mean age of onset was 41.8 year-old. Mean time of follow-up was 24.3 months. Results of AQP4-IgG test were available in 66 patients and were positive in 14 (15.2%). Number of patients diagnosed with NMOSD with AQP4-IgG was 11 (12.0%), without AQP4-IgG was 3 (3.3%), and NMO by 2006 criteria was 5 (5.4%). Optic nerve MRI patterns known to be specific in NMOSD were not significantly seen in patients with NMOSD/NMO or not different according AQP4-IgG status: lesion extending over > 1/2 optic nerve length, involving optic chiasm or posterior segment.
Conclusion: Optic nerve MRI were not characteristic in patients with NMOSD/NMO. Diagnosis of NMOSD in Korea seems to be dependent highly in AQP4-IgG status rather than optic nerve MRI.

Disclosure

Nothing to disclose

P803

Subclinical disease processes detected by fullfield and multifocal visual evoked potentials in NMO spectrum disorders

M. Ringelstein, H.-P. Hartung, P. Albrecht, O. Aktas, on behalf of the Neuromyelitis optica study group (NEMOS)
Heinrich Heine University, Medical Faculty, Düsseldorf, Germany

Background: Neuromyelitis optica spectrum disorders (NMOSD) are characterized by the presence of Aquaporin-4 antibodies, longitudinally extensive transverse myelitis and severe optic neuritis (ON). Visual evoked potentials (VEP) provide objective and reproducible measures to assess the conductive functioning of the pre-chiasmal visual pathway. Our previous cross-sectional fullfield VEP (ffVEP) study in 61 NMOSD patients primarily revealed demyelination of the visual pathway in eyes with a history of ON as well as subclinical disease processes in some eyes without a preceding ON. Multifocal VEP (mfVEP) can simultaneously detect stimulus responses from multiple regions of the visual field, significantly adding precision and sensitivity for the detection of visual deficits.
Methods: We retrospectively analyzed approximately 300 longitudinally assessed ffVEPs of 100 NMOSD patients from 20 centers of the nationwide German NMO network NEMOS. Moreover, in a single center approach we prospectively investigated mfVEP of 17 NMOSD patients in comparison to healthy controls.
Results: Preliminary fullfield and multifocal VEP data show primarily demyelinating processes or lost stimulus responses in the early phase after ON in NMOSD patients. Stimulation reoccur in some NMOSD eyes after ON, suggesting a resolution of conduction blocks and/or axonal regeneration. Moreover, delayed P100 responses in eyes without a previous history of ON suggest a subclinical inflammatory involvement of the optic nerves or subclinical trans-chiasmatic spreading of inflammation in NMOSD eyes. Detailed results of our studies will be presented at the ECTRIMS meeting.
Conclusion: VEPs provide objective and reproducible hints for degenerative and regenerative mechanisms in NMOSD eyes with previous ON as well as subclinical disease processes in those eyes without preceding inflammatory attacks to the optic nerves. Hence, VEP may be considered as reliable biomarker in the light of emerging neuroprotective therapies.

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PA received research grants from Novartis, Biogen Idec, Teva, Merz Pharmaceuticals and travel/accommodations/meeting expenses by Novartis, Teva, Biogen Idec, Merz Pharmaceuticals, Ipsen, Esai and Glaxo Smith Kline.
OA received grants by the German Research Foundation (DFG), Eugène Devic European Network (EU-FP7), German Ministry for

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P804

Assessment of 2015 neuromyelitis optica criteria in rouen university hospital

L. Fechtenbaum[1], R. Marignier[2], R. Lefaucheur[1], F. Le Goff[1], J. Gueudry[3], D. Maltête[1], B. Bourre[1]
[1]Neurology, Rouen University Hospital, Rouen, [2]Neurology, Bron Neurological University, Lyon, [3]Ophthalmology, Rouen University Hospital, Rouen, France

Aims of the study: To assess impact of the 2015 criteria for neuromyelitis optica spectrum disorder (NMOSD) diagnosis and the delay to obtain it. To evaluate indications and efficiency of serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) assessment. To describe seronegative patients features.
Methods: We performed a monocentric retrospective study. We included all patients tested for AQP4-IgG in Rouen university hospital between the 17th january 2011 and the 20th june 2014. All samples were analysed in Lyon Hospital. Clinical, biological, radiological features, final diagnosis and the delay to obtain it, were analysed.
Results: 101 patients were included. The new NMOSD criteria facilitated the diagnosis for 8 patients (42%) including 4 seropositive patients with monofocal symptoms (21%). Diagnosis delay from the first examination was significantly shorter with the new criteria (18,7 months) than with the 2006 one´s (39,3 months) (p=0,02). In our study, seropositive and seronegative patients did not differ significantly regarding the clinical, biological and imaging features.
Conclusion: The new NMOSD diagnosis criteria facilitate earlier and more accurate diagnosis. The AQP4-IgG allows NMOSD diagnosis whereas the symptoms are monofocal.

Disclosure

nothing to disclose

P805

Frequency of AQP4-Ab in NMO and NMO-spectrum disorders

T. Simaniv, A. Vorobyeva, M. Zakharova
Research Center of Neurology, Moscow, Russian Federation

Background: Antibodies to aquaporin-4 (AQP4-Ab) constitute a sensitive and highly specific serum marker of neuromyelitis optica (NMO). AQP4-Ab also could be detected in patients with NMO-spectrum disorders. NMO-spectrum disorders group includes longitudinally extensive myelitis (LETM), optic neuritis (ON), and cases of NMO, ON, LETM associated with connective-tissue diseases.
Objectives: The aim of our research was to estimate frequency and syndrome specificity of AQP4-Ab in russian group patients that clinically correspond with NMO, ON, LETM and NMO-spectrum disorders.
Methods and patients: For this purpose, serum samples from 49 neurological patients with NMO, ON, LETM were analyzed. Also comparison groups of 16 patients with connective tissue disorders and 79 patients with classical multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) were included. We used cell-based assay for the detection of AQP4-Ab (Euroimmun).
Results: AQP4-Ab was detectable in 19/22 (87%) patients with NMO, 2/16 (12,5%) patients with LETM, 1/11 (9%) patients with ON and 8/16 (50%) patients with connective tissue disorders. In cases of MS and ADEM the marker was not detected. All AQP4-Ab positive patients with connective-tissue diseases had signs (clinical and MRI) of nervous system involvement. In AQP4-Ab negative cases of connective-tissue diseases patients had not any confirmed nervous system lesions.
Conclusion: Our results confirm high specificity of AQP4-Ab as a marker of NMO and nervous system involvement in cases of connective-tissue diseases. Quite low rate of positive patients in ON and LETM have to be more investigated: more cases will be analyzed and prospective research is necessary.

Disclosure

The authors have nothing to disclose

P806

MRI evaluation of the "central vein sign" in brain white matter lesions of multiple sclerosis and systemic autoimmune diseases

L. Vuolo[1], G. Emmi[2], G. Carlucci[3], A. Repice[4], E. Magnani[3], G. Spagni[5], D. Prisco[6], E. Silvestri[2], A. Barilaro[4], P. Sati[7], D. Reich[8], L. Massacesi[3]
[1]Dept of Biomedical Sciences, University of Florence, [2]Dept. Internal Medicine, Careggi University Hospital, [3]Dept. Neurosciences, University of Florence, [4]Dept. Neurology 2, Careggi University Hospital, [5]Dept. Neurosciences, Univerity of Florence, [6]Dept. of Clinical and Experimental Medicine, University of Florence, Florence, Italy, [7]NINDS, Translational Neuroradiology Unit, National Institutes of Health, [8]NINDS, Translational Neuroradiology Unit, National Institute of Health, Bethesda, MD, United States

Background: Specificity of the MRI diagnostic criteria for MS could be improved by the visualization of white matter (WM) lesions centered by a venule ("the central vein sign"), one of the most specific pathological characteristics of MS. MRI can detect the "central vein sign", allowing discrimination of the demyelinating from the ischemic lesions, due to arteriolar chronic micro-angiopathy or to migraine (Mistry et al.; Solomon et al.; 2015). However this biomarker have never been analyzed in WM lesions due to inflammatory/autoimmune small vessel pathologies, conditions often characterized by an MS-like clinical courses. In this study frequency of perivenular lesions (PVL) was evaluated in systemic autoimmune diseases with brain lesions with inflammatory micro-angiopathies (SAD) and compared with MS,
Methods: Inclusion criteria: definite MS or SADs. Each patient received one brain MRI, including volumetric T2*-EPI and FLAIR sequences after gadolinium injection. White matter lesion number and site was evaluated. The lesions were considered perivenular if intralesional hypointense signal was completely surrounded by hyperintense signal in at least 2 perpendicular planes.
Results: Forty-four patients, 27 relapsing remitting MS and 17 SADs, were enrolled. The SADs included Behcet syndrome (BS),

systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). Most of the SADs fulfilled thr MS MRI criteria for dissemination in space. The median PVL frequency/patient was 90% (range= 68-100%) and 15% (range= 0-50%) in the MS and in the SAD group respectively ($p < 0.0001$; Mann-Whitney test). PVL frequency/patient < 50% significantly segregated with SAD ($p < 0.001$, Fisher exact test), resulting in 100% accuracy for this cohort. In SAD patients, BS showed the highest frequency of PVL (median/patient: 40%, range= 16-50).
Conclusion: The frequency of PVL was higher in MS than in SADs, including those fulfilling MS MRI criteria for dissemination in space, indicating that this marker can improve differential diagnosis between inflammatory demyelinating lesions due to MS and chronic ischemic lesions due to inflammatory small vessel diseases.

Disclosure

The author haven´t conflicts of interest related to this topic to declare

P807
Central nervous system demyelination associated to Zika virus outbreaks
O.J.M. Nascimento[1], A.C. Andorinho[1], P. Passos[1], C. Bittar[1], J.G. Dib[1], A. Matta[1], C. Hygino[2], C. Pupe[1], I. Rocha[1]
[1]Federal Fluminense University, Niterói, [2]CDPI/Hospital das Américas, Rio de Janeiro, Brazil

Introduction: Arbovirosis are a constant threat in tropical countries, such as Brazil. Since 2015, the country has been dwelling with two new viral epidemics: Chikungunya (CHKV) and Zika virus (ZIKV). Associated to that, several neurological manifestations possibly connected to viral emergence have been reported.
Objective: Report three cases of central demyelination after suggestive arbovirus infection.
Methods: Medical charts review.
Results:
Case 1) 51 yo. man acute fever and rash in Dec 2015, which was followed 11 days after by paraparesis, that evolved into tetraparesis. Two weeks later, he developed dysarthria, dysphonia, blurred vision and somnolence. MRI T2/FLAIR exhibited hypersignal in the intern capsule, thalami, brain stem, cerebellar peduncle, as well as in the spinal cord (C2-C7). CSF analysis showed no cells and slight increase in proteins. Antibody to Aquaporin 4 was negative. Acute disseminated encephalomyelitis (ADEM) was suspected.
Case 2) 33 yo. man presented tetraparesis, urinary incontinence and somnolence 10 days after fever, non-purulent conjunctivitis and rash. Brain MRI showed T2/FLAIR hypersignal in the posterior thalamo-capsular regions, extending to cerebral peduncles. CSF analysis disclosed 155 cells/mm³ (83% monocytes) and protein level of 78 mg/dL. Since the second day of internship, patient became dependent on mechanical ventilation and further deteriorated with diffuse but transitory cerebral edema. E*lectroneuromyography* indicated acute motor axonal neuropathy. Bickerstaff encephalitis diagnosis was suggested.
Case 3) 48 yo. woman was admitted with acute agitation and disorientation preceded by with fever and rash 10 days before. MRI revealed T2/FLAIR hypersignal in cerebellar peduncles and in D3/D4 levels of her spinal cord. CSF analysis showed 15 cells/mm³ (100% of monocytes) and protein level of 71 mg/dL. Acute encephalomyelitis was suspected. In all cases, CSF and serum PCR was negative for ZIKV, but serologies positive for ZIKV in the blood.
Conclusion: The current arboviruses outbreaks in Brazil might be leading to an increased incidence of cases with CNS demyelination.

Disclosure

Nothing to disclose

MS variants

P808
Asymptomatic acute NMOSD-typical brain lesions at an acute attack of optic neuritis or myelitis
S.-H. Kim[1], J.-W. Hyun[1], I.H. Jeong[1], W. Kim[2], S.-Y. Huh[3], H.J. Kim[1]
[1]Neurology, Institute and Hospital of National Cancer Center, Goyangsi, [2]Neurology, The Catholic University of Korea College of Medicine, Seoul, [3]Neurology, Kosin University College of Medicine, Busan, Republic of Korea

Background: Asymptomatic neuromyelitis optica spectrum disorder (NMOSD)-typical brain lesions on magnetic resonance imaging (MRI) may occur simultaneously with an acute attack of optic neuritis or myelitis. In fact, when a patient has severe motor and sensory deficits or visual disturbance due to myelitis or optic neuritis, deciding whether the accompanying brain lesions are symptomatic is often difficult. However, asymptomatic NMOSD-typical brain abnormality has not been considered in the recently revised 2015 criteria for NMOSD.
Objective: To investigate the frequency of asymptomatic acute brain MRI abnormalities accompanying optic neuritis or myelitis in NMOSD patients with aquaporin-4 IgG (AQP-IgG).
Method: We retrospectively evaluated the 749 brain MRI scans in 210 NMOSD patients with AQP-IgG. Among them, 329 MRI scans were performed during acute attacks of myelitis or optic neuritis without significant brain symptoms.
Results: We found accompanying acute asymptomatic NMOSD-typical brain lesions during 44 (14%) of 319 acute attacks of myelitis or optic neuritis in 41 patients. When we considered asymptomatic NMOSD-typical brain abnormalities as evidence for disseminated in space (DIS), assuming AQP4-IgG status to be unknown, the median time to diagnosis using the International Panel for NMO Diagnosis criteria was shortened from 16 months to 6 months ($p < 0.001$). The most common asymptomatic brain abnormalities were edematous corpus callosal lesions (n=19) followed by corticospinal tract lesions in the internal capsule and/or cerebral peduncle (n=14), periependymal surfaces of the fourth ventricle (n=13), periependymal cerebral lesions (n=13), large deep white matter lesions (n=12), and hypothalamic lesions (n=1). No patients showed asymptomatic acute area postrema lesions. Forty (19%) patients had recurrent myelitis or recurrent optic neuritis with a median 5 years of disease duration and six (15%) revealed asymptomatic NMOSD-typical brain abnormalities on MRI.
Conclusion: Asymptomatic NMOSD-typical brain lesions during an acute attack of optic neuritis or myelitis are not rare and might be also used as evidence for DIS, although further studies regarding the specificity of NMOSD-typical brain abnormalities on MRI is required. Identifying these asymptomatic brain lesions may

help facilitate earlier diagnosis of NMOSD, especially in patients whose AQP4-IgG serostatus is unknown.

Disclosure

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P809

MOG-antibody- related disorders cohort description: common features and ucommon presentations

A. Cobo-Calvo[1,2], A. Ruiz[2], A.-L. Poulat[3], M. Carneiro[3], F. Durand-Dubief[1], S. Vukusic[1], V. Desportes[3], R. Marignier[1,2]
[1]Département de Neurologie,, Hôpital Pierre Wertheimer, Hospices Civils de Lyon, Lyon er, [2]Lyon's Neuroscience Research Center, Team ONCOFLAM,, INSERM U 1028 / CNRS 5292, Lyon, [3]Department Neurologie pédiatrique, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron, France

Introduction: Myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) have been recently reported mainly in acute demyelinating encephalomyelitis (ADEM) and optic neuritis (ON) in children and Neuromyelitis Optica spectrum disorders (NMOSD) in adults. Since MOG-Ab related disorders are an emerging entity, the whole spectrum has likely not been completely described.
Objectives: To delineate clinical, laboratory and radiological features in a cohort of MOG-Ab positive patients.
Methods: Twenty four consecutive paediatric (⩽16 years old) and adult patients testing positive for MOG-Ab between January 2014 through April 2016 were included. Comprehensive epidemiological, clinical, laboratory and magnetic resonance imaging (MRI) were retrospectively analyzed.
Results: Among the whole cohort, 12 (50%) were paediatric and 50% were men. MOG-Ab related disorders comprised 9 ADEM, 4 NMOSD, 5 monophasic acute myelitis (4 extensive and 1 non-extensive), 5 ON (1 monophasic and 4 relapsing) and one multiple sclerosis (MS). After a median follow-up of 14.83 months (interquartile range, 7.6-69.2), 10 (41.7%) patients presented a relapsing course. Among those with an abnormal brain MRI, 6 (40%) showed specific bilateral thalamic lesions and 5 (33%) in the fourth ventricle (increasing to 71.4% and 50% among the paediatric cohort, respectively). There were no differences between paediatrics and adults patients regarding gender, relapsing course, radiological features or outcome apart of a tendency for encephalopathy as a first clinical presentation in the paediatric group (50% vs 8.1%, respectively p=0.069). We identified unusual presentation in 5 patients: an associated teratoma (n=1), a concomitant HHV-6 myelitis (n=1), an associated neurofribromatosis-1 (n=1), seizures (n=1), and a non-extensive myelitis showing a "patchy pattern" along the whole spinal cord MRI (n=1).
Conclusion: MOG-Ab related disorders shared common clinical and prognostic features but encompasses a spectrum much wider than recently reported.

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P810

Outcomes of pregnancy in neuromyelitis optica patients:turkish multicenter study data

A. Altintas[1], U. Uygunoglu[1], M. Terzi[2], C. Boz[3], S. Saip[1], M. Koseoglu[4], N. Kale[4], M. Ozturk[4], C.F. Demir[5], A. Soysal[4], M. Ozerden[4], E.O. Dogan[1], S.Z. Ozturk[1], A. Siva[1]
[1]Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, [2]19 Mayis University, Samsun, [3]Karadeniz Technical University, Trabzon, [4]Bakirköy Education and Training Hospital of Neurology, Istanbul, [5]Neurology, Firat University Medical School, Elazıg, Turkey

Introduction: Neuromyelitis optica(NMO) is an immune-mediated, usually relapsing, inflammatory disease characterized by severe attacks of optic neuritis(ON) and myelitis.Although most of the NMO patients are female on childbearing age, there is still inefficient data regarding with the pregnancy outcomes in NMO patients and pregnancy related attacks.
Objective: To reveal the relation between Neuromyelitis Optica Spectrum Disorder(NMOSD) and pregnancy.
Methods: A total of 29 female with NMOSD whom were followed with different centers in Turkey were enrolled.Inclusion criteria was to have at least one conception.The demographic and clinical features of patients were documented. A questionnaire including the number of conception, the number of spontaneous abortion and medical abortion before and after onset of NMO were asked and the outcome of pregnancy and fetus was recorded.A total of fifty-eight conception was evaluated.The number of relapses during each trimester of pregnancy and postpartum period were also assessed.
Results: The mean age of the patients was 42.4(range:24-59).The average age at first pregnancy was 23.2 (range:15-34).The total fertility rate was found to be 1.75 in NMO group whereas 2.07 in general Turkish population according to official reports.
The number of conception before onset of NMO was 49 and 9 after the diagnosis.Regarding the outcome of the conception, six spontaneous abortion was reported prior to diagnosis(12.24%) and one(11%) after the diagnosis, which was lower than the general Turkish population(20.5%).

Seven of twenty-nine patients(24.1%) had a relapse in the first pregnancy while six of them occurred on the postpartum period(85.7%) and the remaining one was during the third trimester.Eighteen patients had second delivery and only one of them(12.5%) had relapse,which was seen in the second trimester. Five of the patients had third delivery and no relapse was observed.

Conclusion: The conception rate in NMO was found to be lower than the general population. No major congenital anomalies were detected in newborns.Similar with multiple sclerosis, NMO has a negative impact on reproductive attitudes and a higher relapse rate in the post-partum first 3 months.

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P811

Efficacy of immunotherapies and predictors of therapy response in neuromyelitis optica spectrum disorders: analysis of 397 treatment years from 150 patients

J.-P. Stellmann[1,2], M. Krumbholz[3,4], T. Friede[5], C. Trebst[6], I. Kleiter[7], on behalf of the NEMOS Group
[1]Institute of Neuroimmunology and MS (INIMS), [2]Department of Neurology, University Medical Center Hamburg Eppendorf, Hamburg, [3]Institute of Clinical Neuroimmunology, Faculty of Medicine, Ludwig Maximilian University, Munich, [4]Center of Neurology and Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, [5]Department of Medical Statistics, University Medical Center Göttingen, Göttingen, [6]Department of Neurology, Hannover Medical School, Hannover, [7]Department of Neurology, Ruhr University Bochum, Bochum, Germany

Background: Neuromyelitis optica spectrum disorders (NMOSD) are rare autoimmune disease of the central nervous system, mainly manifesting through recurrent optic neuritis and longitudinal extensive myelitis. Relapse prevention with immunosuppressive agents is the best available treatment. Data about treatment efficacy are scarce and efficacy estimates are based solely on retrospective cohort studies. The German Neuromyelitis Optica Study (NEMOS) group build up a registry with aquaporin-4-antibody (AQP4-ab)-positive and -negative NMOSD patients.
Objective: To analyse relapse prevention and predictors for relapses under immunosuppressive treatments in the NEMOS cohort.
Methods: Besides descriptive statistics and unadjusted annualised relapse rates (ARR), we computed hazard ratios (HR) from Cox proportional hazard regression models adjusted for centre effects and recurrent measurements to compare efficacy of treatments with regard to time to first relapse and to explore the dataset for predictors of treatment response defined as relapse free survival.
Results: We analysed 329 treatments from 150 patients (mean age at first relapse 40.8 years, 83.3% female). 77% fulfilled the 2006 Wingerchuk criteria and AQP4-ab testing was positive in 86.7%. Mean duration of treatment was 440 days, resulting in 397 treatment years in total. 239 attacks occurred during the treatments (ARR 0.60). The most common treatments were rituximab (RTX, 128 patient years, n=74, ARR 0.57) followed by azathioprin (AZA, 88 years, n=54, ARR 0.39) and interferon-beta (IFN, 62 years, n=31, ARR 0.75), mitoxantrone (MITOX, 38.4 years, n=38, ARR 0.78), and glatiramer acetate (GLAT, 13.5 years, n=18, ARR 1.18). AQP4-ab positive patients had a threefold increased risk for relapses (HR=2.94, p=0.018). A previous relapse under the same treatment was predictive for further relapses (HR=1.64, p=0.031). Every decade of disease duration was associated with a lower risk (HR=0.76, p=0.020). AZA (HR=0.38, p< 0.001) and RTX (HR=0.52, p=0.005) reduced the relapse risk compared to IFN therapy. MITOX did not differ significantly from IFN, while GLAT showed a trend to be less effective than IFN (HR=1.84, 95%CI 0.98-3.47, p=0.058). Dosing for all treatments was sufficient.
Conclusion: Both AZA and RTX are effective in preventing NMOSD relapses. The relapse risk decreases with longer disease duration. Previous relapses under the same therapy as well as detection of AQP4-abs are associated with higher relapse risk.

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P812

MOG-IgG in NMO and related disorders: a multicenter study. part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin

S. Jarius[1], K. Ruprecht[2], I. Kleiter[3], N. Borisow[2], N. Asgari[4], K. Pitarokoili[3], F. Pache[2], O. Stich[5], L.-A. Beume[5], M.W. Hümmert[6], C. Trebst[6], M. Ringelstein[7], O. Aktas[7], A. Winkelmann[8], M. Buttmann[9], A. Schwarz[1], H. Zimmermann[2], A.U. Brandt[2], D. Franciotta[10], M. Capobianco[11], J. Kuchling[2],

J. Haas[1], M. Korporal-Kuhnke[1], S.T. Lillevang[12], K. Fechner[13], K. Schanda[14], F. Paul[2,15], B. Wildemann[1], M. Reindl[14]
[1]Molecular Neuroimmunology Group, Department of Neurology, University of Heidelberg, Heidelberg, [2]Charité - University Medicine Berlin, Berlin, [3]Ruhr University Bochum, Bochum, Germany, [4]University of Southern Denmark, Odense, Denmark, [5]Albert Ludwigs University, Freiburg, [6]Hannover Medical School, Hannover, [7]Heinrich Heine University, Düsseldorf, [8]University of Rostock, Rostock, [9]Julius Maximilians University, Würzburg, Germany, [10]IRCCS, C. Mondino National Neurological Institute, Pavia, [11]Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano, Italy, [12]Odense University Hospital, Odense, Denmark, [13]Institute of Experimental Immunology, affiliated to Euroimmun AG, Lübeck, Germany, [14]Medical University of Innsbruck, Innsbruck, Austria, [15]Max Delbrueck Center for Molecular Medicine, Berlin, Germany

Background: Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) have been suggested to play a role in a subset of patients with neuromyelitis optica and related disorders.
Objective: To assess (i) the frequency of MOG-IgG in a large and predominantly Caucasian cohort of patients with optic neuritis (ON) and/or myelitis; (ii) the frequency of MOG-IgG among AQP4-IgG-positive patients and vice versa; (iii) the origin and frequency of MOG-IgG in the cerebrospinal fluid (CSF); (iv) the presence of MOG-IgG at disease onset; and (v) the influence of disease activity and treatment status on MOG-IgG titers.
Methods: 534 serum samples from patients with ON and/or myelitis and from controls, including 78 follow-up samples from 45 subjects, and 18 CSF samples were tested for MOG-IgG using a live cell-based assay (CBA) employing full-length human MOG-transfected HEK293A cells.
Results: MOG-IgG was detected in 83 sera from 44 patients, including 17/46 (37%) patients with a history of ON and myelitis, 21/85 (24.7%) with a history of ON but no myelitis, 5/43 (11.6%) with a history of longitudinally extensive transverse myelitis but no ON, and in 1 control patient with a connective tissue disorder, all of whom were negative for AQP4-IgG. MOG-IgG was absent in 217 further controls, including 79 AQP4-IgG-seropositive and 85 multiple sclerosis (MS) patients. MOG-IgG was found in 12/18 (67%) CSF samples from MOG-IgG-seropositive patients; the MOG-IgG-specific antibody index was negative in all cases, indicating a peripheral origin. MOG-IgG remained detectable in 28/32 (88%) follow-up samples obtained over a median period of 19 months (range 0-120). Serum titers were higher during attacks than during remission, highest during attacks of simultaneous myelitis and ON, and declined following treatment.
Conclusions: To date, this is the largest cohort studied for IgG to human full-length MOG by means of an up-to-date CBA. MOG-IgG is present in a substantial subset of patients with ON and/or myelitis, but not in classical MS. Co-existence of MOG-IgG and AQP4-IgG is highly uncommon. CSF MOG-IgG is of extrathecal origin. Serum MOG-IgG is present already at disease onset and remains detectable in the long-term course. Serum titers depend on disease activity and treatment status.

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P813

Short delay to initiate plasma exchange is the strongest predictor of outcome in attacks of neuromyelitis optica spectrum disorders

M. Bonnan[1], R. Valentino[2], S. Debeugny[1], H. Merle[2], J.L. Ferge[2], H. Mehdaoui[2], P. CABRE[2]
[1]CH Pau, Pau, France, [2]CHU Martinique, Fort de france, Martinique

Objective: To examine the consequence of plasma exchange (PLEX) delay upon outcome of severe optic neuritis (ON) and spinal cord (SC) attacks in neuromyelitis optica (NMO spectrum).
Methods: All the patients suffering from attacks in the spectrum of NMO followed in our centre were retrospectively considered for inclusion of severe attacks treated by PLEX. Primary outcome was defined as complete improvement. Secondary poor/good outcomes were respectively defined to be the higher/lower third of Delta-Expanded Disability Status Scale (EDSS) (late minus basal EDSS). Delays from clinical onset to PLEX initiation were categorized for multivariate analysis.
Results: Among the 60 patients included, NMO-spectrum disorder criteria (2015) were fulfilled in 49 (82%), anti-MOG was positive in 1, and isolated severe optic and spinal attacks in 10. 115 attacks were included (67 SC; 48 ON) and received PLEX by a mean of 11.1±9.4 days after clinical onset. The probability to

regain complete impairment continuously decreased from 50% for PLEX given at day 0-1 to 5% after day 20 ($p< 0.01$). In multivariate analysis, basal impairment and PLEX delay (delay d0-5 vs d⩾11: OR 5.3 [1.8-15.9]; $p< 0.01$) were associated with the probability to complete improvement. Shorter PLEX delay also influenced the good secondary outcome (delay d0-5 vs d⩾11: OR 2.8 [1.1-7.3]; $p=0.04$) but not the poor secondary outcome.
Conclusion: These results confirm an improved benefit of early onset PLEX during severe attacks of NMO.

Disclosure

no conflict of interest

P814

Executive function in NMOSD: the relationship with fatigue, anxiety and depression

K. Mcmullen[1], V. Kwan[2], S. Kolind[1], A. Combes[1], R. Carruthers[1], A. Traboulsee[1]
[1]Department of Medicine (Neurology), University of British Columbia, Vancouver, BC, [2]Department of Psychology, University of Calgary, Calgary, AB, Canada

Background: There are few studies assessing cognitive function in Neuromyelitis Optica Spectrum Disorders (NMOSD). Limited research suggests that NMOSD patients demonstrate cognitive impairments in the domains of attention, memory and information processing. Less is known about executive function (EF), an important cognitive process that underlies everyday tasks such as scheduling appointments, following instructions and planning and completing a task.
Objectives: To assess whether EF is affected in NMOSD and whether mood (depression/anxiety) and fatigue are associated with performance on an executive function task.
Methods: We administered neuropsychological testing to 23 NMOSD patients and 12 healthy controls, matched for age, gender and education. EF was assessed using the Wisconsin Card Sorting Task (WCST), a standardized measure of EF, which measures abstract thinking, cognitive flexibility and impulse control. Fatigue was assessed using the Fatigue Severity Scale (FSS), depression using the Centre for Epidemiology Studies Depression Scale (CESD) and anxiety using the State-Trait Anxiety Inventory (STAI). Group differences were assessed using independent t-tests (or the non-parametric Mann-Whitney where appropriate) and correlation analysis was used to determine whether cognition was related to mood and/or fatigue.
Results: The NMOSD group had significantly worse performance than healthy controls on the WCST requiring more trials to complete the task ($U = 181.5$, $p< 0.01$), making more errors overall ($U = 164.5$, $p< 0.01$), committing more perseverative errors ($U = 146.5$, $p< 0.05$) and a trend towards failing to maintain set ($U = 141.5$, $p =0.074$). The NMOSD group had higher levels of fatigue ($t =-3.76$, $p< 0.001$) and a trend towards higher levels of depression ($t= -1.693$, $p = 0.10$). There was no difference in level of anxiety between groups ($p>0.05$). There was no significant relationship between fatigue, anxiety and depression, and EF within the NMOSD group.
Conclusions: The results demonstrate that NMOSD patients have cognitive impairments in executive function particularly in maintaining or adapting responses to environmental feedback. Fatigue and depression, whilst higher in the NMOSD group, did not relate to the level of executive function. The lack of relationship between fatigue, mood and executive function suggests that there are others factors that underlie this cognitive impairment in NMOSD.

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Anthony Traboulsee is a consultant for Novartis, Genzyme and Roche and a principal investigator on clinical trials with Biogen, Genzyme, Roche and Chugai.

P815

Radiographic and clinical features of neuromyelitis optica spectrum disorder: A retrospective study within the Columbia university medical center patient population

C.-Y. Guo, C.S. Riley
Neurology, Columbia University Medical Center, New York, NY, United States

Background: Neuromyelitis Optica (NMO) is a demyelinating autoimmune disease classically defined by the presence of optic neuritis and transverse myelitis. However, since the discovery of the diagnostic biomarker aquaporin-4 immunoglobulin G antibody (AQP-4 IgG), a more diverse set of symptoms and imaging is being recognized as part of the NMO disease spectrum. Most prominently, the presence of abnormal brain magnetic resonance imaging (MRI) is now considered a diagnostic component of NMO.
Aim: We aim to characterize the radiographic features of NMO on brain MRI and understand the impact of brain imaging abnormalities on functional outcomes within the Columbia University Medical Center (CUMC) patient population.
Methods: We performed a retrospective data collection to obtain clinical information and review imaging of patients diagnosed with NMO using the 2015 revised diagnostic criteria for NMO spectrum disorder. We then used the Expanded Disability Status Scale (EDSS) to compare the functional status of those with and without brain parenchymal abnormalities.
Results: There were 31 patients with imaging available for review. 29 (90%) had spinal cord lesions, with an average lesion length of 3.6 vertebral levels, and 10 (31%) had optic nerve lesions. 25 (78%) had parenchymal findings, most prominently non-specific cerebral fluid attenuation inversion recovery (FLAIR) hyperintensities (15) and periventricular hyperintensities (13), and less prominently infratentorial (8) and corpus callosum (8) involvement. Interestingly, 4 patients had multi-lobe confluent lesions. Those with parenchymal abnormalities of any kind also had a worse average EDSS (6.0) compared to those without (3.3).
Conclusions: Though spinal cord and optic nerve involvement remain the most common features of NMO, parenchymal involvement is an increasingly recognized component of the disease, and

there is an association between parenchymal involvement and worse functional outcome within our patient population.

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Chu-Yueh Guo: nothing to disclose
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P816

MOG-IgG in NMO and related disorders: a multicenter study. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment, and long-term outcome

S. Jarius[1], K. Ruprecht[2], I. Kleiter[3], N. Borisow[2], N. Asgari[4], K. Pitarokoili[3], F. Pache[2], O. Stich[5], L.-A. Beume[5], M.W. Hümmert[6], M. Ringelstein[7], C. Trebst[6], A. Winkelmann[8], A. Schwarz[1], M. Buttmann[9], H. Zimmermann[2], J. Kuchling[2], D. Franciotta[10], M. Capobianco[11], E. Siebert[2], C. Lukas[3], M. Korporal-Kuhnke[1], J. Haas[1], K. Fechner[12], A.U. Brandt[2], K. Schanda[13], O. Aktas[7], F. Paul[2,14], M. Reindl[13], B. Wildemann[1]
[1]Molecular Neuroimmunology Group, Department of Neurology, University of Heidelberg, Heidelberg, [2]Charité - University Medicine Berlin, Berlin, [3]Ruhr University Bochum, Bochum, Germany, [4]University of Southern Denmark, Odense, Denmark, [5]Albert Ludwigs University, Freiburg, [6]Hannover Medical School, Hannover, [7]Heinrich Heine University, Düsseldorf, [8]University of Rostock, Rostock, [9]Julius Maximilians University, Würzburg, Germany, [10]IRCCS, C. Mondino National Neurological Institute, Pavia, [11]Azienda Ospedaliero Universitaria San Luigi Gonzaga, Orbassano, Italy, [12]Institute of Experimental Immunology, affiliated to Euroimmun AG, Lübeck, Germany, [13]Medical University of Innsbruck, Innsbruck, Austria, [14]Max Delbrueck Center for Molecular Medicine, Berlin, Germany

Objective: To describe the clinical and paraclinical features of a large cohort of MOG-IgG-positive patients with optic neuritis (ON) and/or myelitis (n=42) as well as attack and long-term treatment outcomes.
Results: The sex ratio was 1:2.2 (m:f). Median age at onset was 30.5 years (range 6-70). The disease followed a multiphasic course in 74% (median time-to relapse 5 months; ARR 1.02) and resulted in significant disability in 41% (mean follow-up 78±42.4 months), with severe visual impairment or functional blindness (34%) and markedly impaired ambulation (24%) as the most common sequelae. Besides acute tetra-/paraparesis, dysesthesia and pain were common in acute myelitis (70%). Longitudinally extensive spinal cord lesions were frequent, but short lesions occurred once in 46%. Thirty-eight percent had a history of simultaneous ON and myelitis. Clinical or radiological involvement of the brain, brainstem, or cerebellum was present in 50%; extra-opticospinal symptoms included intractable nausea and vomiting and respiratory insufficiency (fatal in one). CSF pleocytosis (partly neutrophilic) was present in 69%, OCB in 13%, and barrier dysfunction in 33%. IVMP and long-term immunosuppression were often effective; however, treatment failure leading to rapid accumulation of disability was noted in many patients as well as flare-ups after steroid withdrawal. Full recovery was achieved by plasma exchange in some cases, including after IVMP failure. Breakthrough attacks under azathioprine were strongly linked to the drug-specific latency period and a lack of cotreatment with oral steroids. Methotrexate was effective in 5/6 patients. Interferon-beta was associated with ongoing or increasing disease activity. Rituximab was followed by early flare-ups in several patients. Coexisting autoimmunity was rare (8%). Around one third of all patients met Wingerchuk's 2006 and/or 2015 criteria for NMO(SD) and some met the Barkhof and/or McDonald criteria for MS; MS had been suspected in 39%. Disease onset or relapses were preceded by infection, vaccination, or pregnancy/delivery in several cases.
Conclusion: Our findings from a predominantly Caucasian cohort strongly argue against the concept of MOG-IgG denoting a mild and usually monophasic variant of NMOSD. The predominantly relapsing and often severe disease course and the short median time to second attack support the use of prophylactic long-term treatments in patients with MOG-IgG-positive ON and/or myelitis.

Disclosure

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Clinical and radiological features of 12 patients with pseudotumoral demyelinating lesions

P. Sánchez[1], V. Meca-Lallana[1], A. Barbosa[2], I. Palmí[1], R. Manzanares[2], J. Vivancos Mora[1]
[1]Neurology, [2]Radiodiagnostic, Hospital Universitario de La Princesa, Madrid, Spain

Introduction: Pseudotumoral or tumefactive demyelinating lesions (TDL) are defined as large inflammatory lesions that associate oedema and/or mass effect, being sometimes misdiagnosed as tumours or other space-occupying lesions. Among all TDL, multiple sclerosis (MS) is the most frequent etiology, but the differential diagnosis encompasses a wide spectrum of diseases.
Objective: To review the clinical and radiological features of patients with TDL treated in our MS-Unit.
Material and methods: We performed a retrospective review of 12 cases of patients with TDL treated in our Unit from January 2010 to March 2016.
Results: The mean age of tumefactive lesion onset was 38 years (± 12.36 SD) with a prevalence of 9 women and 3 men. Out of the 12 patients, 8 had TDL as a first demyelinating event, whereas 3 were previously diagnosed with Relapsing-Remitting MS and 1 with Clinically Isolated Syndrome. Among those presenting with a first event, 50% *(n=4)* developed definite MS upon follow-up by McDonald Criteria, with a mean time of conversion of 4.4 months (± 1.94 SD). Interestingly, 3 patients had recurrent TDL. All 3 patients with a previous MS diagnosis had been treated with fingolimod (two after cessation and one during treatment)

Clinical presentation in most patients was polysymptomatic, including sensory (42%), visual (25%) and motor (25%) symptoms, as well as seizures (25%) and cognitive changes (17%). The most common radiological findings included solitary lesions (75%), located primarily in the parietal (42%), or in the frontal (25%) and temporal (25%) lobes. An open-ring enhancement pattern was found in 55% of the cases, followed by heterogeneous enhancement (44%). Most *(n=7)* of the 8 patients with diffusion-weighted magnetic resonance imaging available showed partial restriction. Oligoclonal bands in cerebrospinal fluid were positive in all patients with MS and were not found in those with other diagnoses. MS was the most common diagnosis in our study (*n=7,* 60%), which represents around 1.2% of MS patients in our Unit. The therapeutic management was mixed, including steroids, plasmapheresis and rituximab.
Conclusions: Prevalence of tumefactive MS in our series was higher than expected in MS patients, according to the literature. Time of conversion to MS was significantly shorter than other published series. Clinical presentation was polysymptomatic and the most common radiological findings were isolated parietal lesions, with an open-ring enhancement.

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P818
Multiple sclerosis and NMO spectrum disorder association in sisters

S.A. Hatteb, M. Bouzar, S. Daoudi
Faculty of Medicine, Tizi Ouzou University, Tizi Ouzou, Algeria

Background: Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are chronic inflammatory diseases affecting central nervous system (CNS).
Familial MS is well known, many reported cases confirmed the implication of hereditary factors in the disease. Families with NMOSD have also been reported. However the association of the two disorders in a same family seems to be exceptional.
We report here two sisters with MS and NMOSD.
Case report: A 34 years old woman from north Algeria is followed from 2011 for unilateral severe recurrent optic neuritis. Her first cerebral MRI showed a T2 and T2 Flair hypersignal on left optic nerve with gadolinium enhancement on T1. serologies (HIV, syphilis, Lyme, bartonella..). Blood metabolic and immunological tests were negative. Cerebro-spinal fluid (CSF) analysis was normal, oligoclonal bands were absent. Aquaporin 4 antibodies (AQP4-Ab) antibodies were positive. OCT showed severe thinning in prepapillary fibers, with sequelar optic nerve atrophy on cerebral MRI control. Spinal cord MRI was normal.

In 2013 our patient's sister, 30 years aged, presented cerebellar ataxia and legs weakness with paresthesia, she reported a transient episode of unilateral lower limb weakness one year ago. Cerebral MRI showed nodular disseminated white matter lesions fulfilling McDonald 2010 criteria. oligoclonal bands were present in CSF. She experienced a total of 3 relapses and was treated by interferon b1a, with clinical improvement. AQP4-Ab were negative.

The two sisters came from a family of 10 children, with a second degree parents consanguinity.
Discussion: MS is an inflammatory demyelinating disease with cellular-mediation, whereas NMO is an autoimmune humoral-mediation pathology. Familial MS is well known. Familial NMO cases have also been described, they were parent-child, aunt-niece and siblings pairs. Familial MS-NMOSD remains exceptional.
This sibling pair could make us suppose that NMOSD and MS could share some genetic background and/or same triggering environmental factors.

Disclosure

S.A.Hatteb; M.Bouzar; S.Daoudi: have nothing to disclose

P819
MOG-IgG in NMO and related disorders: a multicenter study. Part 3: MOG-IgG-associated brainstem encephalitis

S. Jarius[1], I. Kleiter[2], K. Ruprecht[3], N. Asgari[4], K. Pitarokoili[2], N. Borisow[3], M.W. Hümmert[5], C. Trebst[5], F. Pache[3], A. Winkelmann[6], L.-A. Beume[7], M. Ringelstein[8], O. Stich[7], O. Aktas[8], M. Korporal-Kuhnke[1], A. Schwarz[1], C. Lukas[2], J. Haas[1], K. Fechner[9], M. Buttmann[10], J. Bellmann-Strobl[3], H. Zimmermann[3], A.U. Brandt[3], D. Franciotta[11], K. Schanda[12], F. Paul[3,13], M. Reindl[12], B. Wildemann[1]
[1]Molecular Neuroimmunology Group, Department of Neurology, University of Heidelberg, Heidelberg, [2]Ruhr University Bochum, Bochum, [3]Charité - University Medicine Berlin, Berlin, Germany, [4]University of Southern Denmark, Odense, Denmark, [5]Hannover Medical School, Hannover, [6]University of Rostock, Rostock, [7]Albert Ludwigs University, Freiburg, [8]Heinrich Heine University, Düsseldorf, [9]Institute of Experimental Immunology,

affiliated to Euroimmun AG, Lübeck, [10]Julius Maximilians University, Würzburg, Germany, [11]IRCCS, C. Mondino National Neurological Institute, Pavia, Italy, [12]Medical University of Innsbruck, Innsbruck, Austria, [13]Max Delbrueck Center for Molecular Medicine, Berlin, Germany

Background: Little is known so far about brainstem involvement in myelin oligodendrocyte glycoprotein antibody (MOG-IgG)-positive patients.
Objective: To investigate the frequency, clinical and paraclinical features, course, outcome, and prognostic implications of brainstem involvement in MOG-IgG-positive ON and/or myelitis.
Results: Among 42 patients with MOG-IgG-positive ON and/or myelitis, 14 (33.3%) with a history of brainstem encephalitis were identified. All were negative for AQP4-IgG. Symptoms included respiratory insufficiency, intractable nausea and vomiting (INV), dysarthria, dysphagia, impaired cough reflex, oculomotor nerve palsy and diplopia, nystagmus, internuclear ophthalmoplegia (INO), facial nerve paresis, trigeminal hypesthesia/dysesthesia, vertigo, hearing loss, balance difficulties, and gait and limb ataxia; brainstem involvement was asymptomatic in two cases. Brainstem inflammation was already present at or very shortly after disease onset in 6/14 (42.9%) patients. 15/19 (78.9%) brainstem attacks were accompanied by acute myelitis and/or ON. Lesions were located in the pons (10/12), medulla oblongata (7/12), mesencephalon (cerebral peduncles; 2/13), and cerebellar peduncles (4/13), were adjacent to the fourth ventricle in 2/12, and periaqueductal in 1/12; some had concomitant diencephalic (2/12) or cerebellar lesions (1/13). MRI or laboratory signs of blood-brain barrier damage were present in 4/11. Cerebrospinal fluid pleocytosis was found in 10/13 cases, with neutrophils in 6/10 (3-34%), and oligoclonal bands in 4/13. Attacks were preceded by acute infection or vaccination in 4/12. A history of teratoma was noted in one case. Interferon-beta was followed by relapses in two patients. While one patient died from central hypoventilation, partial or complete recovery was achieved in the remainder following treatment with high-dose steroids and/or plasma exchange.
Conclusions: Brainstem involvement is present in around one third of MOG-IgG-positive patients with ON and/or myelitis. Clinical manifestations are diverse and may include symptoms typically seen in AQP4-IgG-positive neuromyelitis optica, such as INV and respiratory insufficiency, or in multiple sclerosis, such as INO. As MOG-IgG-positive brainstem encephalitis may take a serious or even fatal course, particular attention should be paid to signs or symptoms of additional brainstem involvement in patients presenting with MOG-IgG-positive ON and/or myelitis.

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P820

Psychiatric comorbidities and suicide attempt in Neuromyelitis optica spectrum disorders in Argentina

V. Fernandez[1], C. Pita[1], N. Alonso[2], L. Melamud[1], A. Villa[1]
[1]Neuroimmunology Unit, Neurology Department, [2]Psychiatry Department, Hospital Ramos Mejia, Buenos Aires, Argentina

Background: Neuromyelitis optica spectrum disorders (NMOSD) is a severe inflammatory disease affecting the Central Nervous System (CNS). Awareness of psychiatric comorbidities has increased among neurologists, however there are few reports assessing this issue, and information on psycopathological profile is sparse.
Objective: The objective of the present study is to analyze the psychopathological profile and suicide risk in patients with neuromyelitis optica spectrum disorders NMOSD in an Argentinian cohort.
Methods: 21 patients with NMOSD diagnosed according to 2015 criteria, attending follow-up medical visits at Neuroimmunology Department at Ramos Mejia Hospital in Buenos Aires, between 2006 and 2015 were included. Current depression was assessed using the self-administered Beck Depression Inventory scale (BDI) and psychiatric illness using the MINI International Neuropsychiatric Interview 5.0.0 Spanish version, performed by a psychiatrist. Disability was assessed by EDSS.
Results: We collected data from 21 patients, 76.2% were females, mean age 38.5 years (range 20-58), mean EDSS 3.5 (range 1.0-8.0). Psychiatric comorbidity was present in 9 of 21 patients (42.85%). Using the International Neuropsychiatric Interview, diagnosis of major depressive disorder was performed in 4 patients (19%), bipolar disorder in 2 (9.5%), dysthymic disorder in 2 (9.5%) and anxiety disorder in 1 (4.8%). 6/21 patients (28.6%) had one or more previous suicide attempts. In 7/21 patients current depression was evidentusing BDI, with 4 patients being

severe depressed. A direct link between severe depression and major disability was observed.
Conclusions: Our study shows that the prevalence of psychiatric comorbidities in patients with NMOSDis 42.85%. Furthermore, suicide attempts were present in 28.6% of patients. Given the high frequency, it is important to asses associated psychiatric disorders in patients with NMOSD to optimize monitoring and comprehensive treatment of these patients.

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P821
Neuromyelitis Optica Spectrum Disorders in Argentinian patients: A hospital based study
C. Pita, V. Fernández, E. Garino, L. Melamud, A. Villa
Neuroimmunology Unit, Neurology Department, Hospital Ramos Mejia, Buenos Aires, Argentina

Background: Neuromyelitis Optica Spectrum Disorders (NMOSD) is a severe inflammatory disease of the central nervous system. Diagnosis awareness has increased in recent times; however, information of NMOSD characteristics in Latin America is still sparse.
Objective: To report clinical and epidemiological data of NMOSD patients in Argentina.
Methods: We retrospectively reviewed the medical records of patients affected by NMOSD, according to 2015 revised criteria, attending Ramos Mejia Hospital in Buenos Aires, Argentina from January 2007 to April 2016.
Results: We recruited 61 patients (46 females). Out of 51/61 patients tested, 32 (63 %) were AQP4-IgG (+). Mean age at onset and disease duration was 33 (range 4-58) years and 7.6 (range 0.5-22) years respectively. At presentation, 33 patients (54 %) had optic neuritis (ON), 20 (32.7%) transverse myelitis (TM) and 8 (13 %) simultaneous TM and ON. The Annualized Relapse Rate (ARR) was 0.7. The female to male ratio was 1.4/1 for AQP4-IgG (-) and 5.2/1 for AQP4-IgG (+) patients. Association with other autoimmune diseases occurred in 20/61 (32.7%) patients, 59 % were AQP4-IgG (+). 11/61 patients were examined for psychiatric comorbidities; 6/11 showed depression, 2/11 bipolar disorder and 4/11 suicidality. Brain MRI abnormalities were present in 23 NMOSD patients (37.7 %). 13/61 (21.3%) patients have a late onset ($\geqslant$ 40 years).
Conclusions: This is the largest cohort of NMOSD patients described in Argentina. 63% of patients were seropositive for AQP4-IgG antibodies. We showed a female to male ratio higher in AQP4-IgG seropositive patients. ON was the most common presentation of the disease. 32.7% of patients had other autoimmune disease associated. We also demonstrate a high rate of psychiatric comorbidities.

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Paediatric MS

P822
Structural connectivity abnormalities underlying cognitive impairment in pediatric multiple sclerosis
E. De Meo[1], M.A. Rocca[2], E. Pagani[2], L. Moiola[3], A. Ghezzi[4], P. Veggiotti[5], R. Capra[6], M.P. Amato[7], L. Vacchi[2], A. Fiorino[3], L. Pippolo[4], M.C. Pera[5], G. Comi[3], A. Falini[8], M. Filippi[2]
[1]San Raffaele Scientific Institute, [2]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, [3]Department of Neurology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, [4]MS Center, Ospedale di Gallarate, Gallarate, [5]Department of Child Neurology and Psychiatry, C. Mondino National Neurological Institute, Pavia, [6]MS Center, Spedali Civili of Brescia, Brescia, [7]Department of Neurology, University of Florence, Florence, [8]Department of Neuroradiology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Background: A large proportion of pediatric MS patients experiences cognitive deficits, with a prominent involvement of linguistic abilities in addition to memory, attention, and executive functions.
Aims: By applying diffusion tensor (DT) MRI, we aim at describing brain structural network architecture in pediatric MS patients and to detect structural connectivity abnormalities underlying cognitive dysfunction across the different cognitive domains.
Methods: DT and dual-echo MRI scans were obtained using a 3.0 T scanner from 53 pediatric MS patients and 26 age- and sex-matched healthy controls (HC). Whole-brain networks were constructed using graph theory. Between-group differences of global and local network connectivity metrics were investigated. Partial correlations between network metrics and Z-scores for each of cognitive domain and a global Z-score of cognitive function controlling for age and sex were performed.
Results: All global network metrics showed significant differences between pediatric MS patients and HC. Compared to HC, pediatric MS patients lost hubs in the right superior frontal gyrus (SFG), middle occipital gyrus, caudate nucleus and cerebellum crus II and in the left precentral gyrus, temporal pole, thalamus and cerebellum crus I. Global cognitive functioning showed significant positive correlation with the strength of connections of hubs located in the right superior parietal lobe and the precuneus bilaterally. Impairment in language functions, as well as verbal memory impairment were significantly related to reduced strength of the hubs located in frontal and temporal, while visual-spatial memory, attention and information processing speed impairment appeared were associated to a reduced strength in several hubs located in frontal, parietal and occipital lobes.
Conclusions: This study showed abnormalities in global network metrics in pediatric MS patients with limited differences in hubs distribution, indicating a partial preservation of brain network architecture. Our findings suggest that cognitive impairment is mainly associated to a globally reduced strength of connections of the nodes identified as hubs, likely due to diffuse normal appearing white matter damage, more than to a local damage, resulting in alteration and loss of efficiency in information transmission.

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P823

Long-term follow-up of an Italian pediatric MS population treated with first-line agents: a multicentre, retrospective, cohort study

A. Ghezzi[1], D. Baroncini[1], M.P. Amato[2], P. Bellantonio[3], R. Bergamaschi[4], M. Capobianco[5], G. Costantino[6], P. Gallo[7], M.G. Marrosu[8], N. Milani[9], L. Moiola[10], F. Patti[11], C. Pozzilli[12], E. Scarpini[13], M. Trojano[14], G. Comi[10], on behalf of iMED Registry and Gruppo di Studio SM-Società Italiana di Neurologia
[1]Centro Studi Sclerosi Multipla, Ospedale di Gallarate, Gallarate, [2]Neurol. Dept, University of Florence, Florence, [3]Neurol. Dept., Ist. Scient. Pozzilli, Isernia, [4]Centro Sclerosi Multipla, Ist. Scient. Mondino, Pavia, [5]CentroRegionale SM, Ospedale Orbassano-Torino, Orbassano-To, [6]Neurol. Dept., Ospedali Riuniti di Foggia, Foggia, [7]Neurol. Dept., Univesity of Padua, Padua, [8]Centro SM, Ospedale Binaghi, Cagliari, [9]Neuropsich. Inf., Istituto Neurologico C. Besta, [10]Neurol. Dept., Ospedale S. Raffaele, Milan, [11]Centro SM, University of Catania, Catania, [12]S. Andrea MS Center, Università La Sapienza, Rome, [13]Neurol. Dept., University of Milan, Milan, [14]Neurol. Dept., Unversity of Bari, Bari, Italy

Background: Several observational studies have provided data on safety and efficacy of Interferon-beta (IFNB) and glatiramer acetate (GA) in the pediatric multiple sclerosis (ped-MS) population. Data are not available after a long-term follow-up.
Objectives: in 2009 we published the results of an Italian cohort of ped-MS patients treated with IFNB and GA and followed for a mean of 4-6 years. Now we provide data updated to 2016.
Methods: we retrospectively reviewed clinical records of ped-MSs included in our previous study (Ghezzi et al. Neurol Sci 2009), followed in many Italian MS centers. Demographic, clinical and treatments data were collected. All patients initiating GA or IFNB in pediatric age and regularly followed were included in the study.
Results: of the 130 ped-MS patients of previous cohort data were obtained of 97 of them (67 females, age of onset: 12.3±2.5 years, monofocal onset in 69). All patients started first-line drugs (IFNB: 88, GA: 9;) at a mean age of 13.9±2.1 years. At that time EDSS was 0-1.5 in 67 patients, 2-3.5 in 29 and 4.5 in one. Patients were followed for 12.5±3.3 years (72 patients for >10 years). Forty-two patients (43%) remained on first-line agents (GA, IFNs, Dimethyl fumarate, Teriflunomide), the remaining (57%) received other treatments (1 or more): second-line drugs (Fingolimod, Natalizumab, Alemtuzumab) in 47, immunosuppressants (Mitoxantrone, Azatioprine, Cyclophosphamide) in 13, intravenous immunoglobulin in 2, and steam cell transplantation in 2. Fifteen patients did not change the treatment, the others switched to a median of 3 therapies (range 2-7); 23 patients received no treatment for more than 6 months. At the last follow-up (age: 26.5±3.9 years) EDSS was 0-1.5 in 57 patients, 2-3.5 in 31 and 4-6 in 8; one patient died because of MS. Annualized relapse rate was 3.2±2.7 before the treatment, 0.7±1.5 during the first treatment and 0.5±0.3 during the whole follow-up period.
Conclusions: over 12 years of follow-up 43% of ped-MS patients remained on first-line therapies, while 57% patients switched to second-line/other treatments. The large majority of patients had an EDSS $\leqslant$ 3.5, about 8% had EDSS >4 at last observation, and one patient (≈1%) died because of MS. Relapse rate remained lower than that of the pre-treatment period in patients who continued the first line treatment and also in those who switched to second-line/other treatments.

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P824

Cognitive impairment and lower cognitive reserve increase the risk of unemployment in patients with pediatric onset multiple sclerosis

B. Hakiki[1], L. Pastò[2], B. Goretti[2], C. Niccolai[2], M. Giannini[3], I. Righini[2], L. Razzolini[2], A. Ghezzi[4], L. Pippolo[4], M. Simone[5], R.G. Viterbo[6], M.G. Marrosu[7], E. Cocco[7], G. Fenu[7], F. Patti[8], C. Chisari[8], M. Falautano[9], E. Minacapelli[9], E. Portaccio[2], M.P. Amato[2]

[1]Department of NEUROFARBA, University of Florence, Italy., florence, [2]Department of NEUROFARBA, University of Florence, Italy., Florence, [3]Department of NEUROFARBA, University of Florence, Italy., Forence, [4]Centro Sclerosis Multipla , Gallarate .Italy, Gallarate, [5]Child Neuropsychiatry, Department of Basic Medical Sciences, Neurosciences and Sens Organs Basic Medical Sciences, University of Bari, [6]Department of Basic Medical Sciences, Neuroscience and Sense Organs. Professor of Neurology. University of Bari. Italy, Bari, [7]MS Centre, Binaghi Hospital, Department Public Healt, Clinical and Molecular Medicine. University of Cagliari. Italy, Cagliari, [8]Department G.F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy, Catania, [9]IRCCS Hospital San Raffaele, Milan, Italy, Milano, Italy

Background: the concept of cognitive reserve (CR) has been suggested to clarify the discrepancies between the degree of brain damage and its clinical manifestations. While the role of CR in adult patients with multiple sclerosis (MS) is being addressed by different research groups, information in the pediatric-onset population is scarce.
Objectives: to assess socio-professional attainment in adulthood and its relationships with cognitive performance and CR in a group of patients with POMS.
Methods: MS patients with POMS (disease onset before the age of 18 years) were enrolled in six Italian MS Centres. Cognitive functioning was assessed through the Rao's Brief Repeatable Battery and Stroop Test. Cognitive impairment (CI) was defined as the failure of at least 3 tests using the Italian normative data.CR was estimated using as proxies the subject educational level and premorbid IQ based on the Italian version of the National Adult Reading Test. Socio-professional attainment was evaluated on the scale Barratt Simplified Measure of Social Status. The relationships between CR, cognitive functioning and socio-professional attainment in adulthood were assessed through linear and logistic multivariable regression analyses.
Results: to date, 48 POMS patients were enrolled (28 females, age 31.1 +/- 7.8 years, EDSS 1.9 +/-2.6). The proportion of subjects with CI was 25%. In the multivariable analysis, unemployment in adulthood was associated with the presence of CI (OR=6.0,95%CI 1.3-27.0; p=0.019) and lower educational level (OR=0.79,95%CI 0.62-0.99;p=0.05). Higher occupational competency was related to older age (B=0.35;p=0.007), and, marginally, absence of CI (B=-0.24;p=0.095).
Conclusions: CI and lower CR in MS patients with pediatric onset disease predicted higher risk of unemployment in adulthood. Our findings suggest the need for regular monitoring of cognitive functioning in subjects with POMS and potential usefulness of interventions focused on intellectual enrichment in this population.

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P825

Differential MRI lesion features in pediatric NMO and pediatric MS

R. Ameli[1], J.C. Prieto[1], M. Waltz[2], J. Tillema[3], J. Graves[4], B. Weinstock-Guttman[5], A. Belman[6], C. Olsen[2], G. Aaen[7], L. Benson[8], M. Gorman[8], L. Krupp[6], T. Lotze[9], J. Ness[10], E. Waubant[11], J. Rose[12], M. Rodriguez[3], C. Casper[2], O. Rapalino[13], F. Cotton[14,15], C. Guttmann[1], T. Chitnis[16], U.S. Network of Pediatric MS Centers
[1]Radiology, Brigham and Women's Hospital, Boston, MA, [2]Pediatrics, University of Utah, Salt Lake City, UT, [3]Pediatric MS Center, Mayo Clinic, Rochester, NY, [4]Neurology, University of California San Francisco, San Francisco, CA, [5]Pediatric MS Center, Jacobs Neurological Institute, SUNY, Buffalo, [6]Lourie Center for Pediatric MS, Stony Brook Children's Hospital, Stony Brook, NY, [7]Pediatric MS Center, Loma Linda University Children's Hospital, Loma Linda, CA, [8]Boston Children's Hospital, Boston, MA, [9]Blue Bird Circle MS Center, Baylor College of Medicine, Houston, TX, [10]University of Alabama Center for Pediatric Onset Demyelinating Disease, Children's Hospital of Alabama, Birmingham, AL, [11]Pediatrics, Benioff Children's Hospital, University of California San Francisco, San Francisco, CA, [12]Neurology, University of Utah, Salt Lake City, UT, [13]Neuroradiology, Massachusetts General Hospital, Boston, MA, United States, [14]Radiologie, Centre Hospitalier Lyon-Sud, Université Claude Bernard, [15]UMR 5220 CNRS & U1044 Inserm, Université de Lyon, CREATIS, Lyon, France, [16]Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital for Children, Boston, MA, United States

Background: Early differentiation of pediatric NMO from other childhood demyelinating disorders including multiple sclerosis and acute disseminated encephalomyelitis (ADEM) is critical for instituting appropriate therapy.
Goal: The goal of this study was to characterize and explore differential MRI features in pediatric patients with NMO spectrum disorders relative to MS and ADEM.
Methods: Brain and spine MRIs were collected from pediatric NMO patients (age at onset< 18years) identified from 9 U.S. Network of Pediatric MS Centers (NPMSC). MRIs from matched pediatric MS and ADEM were analyzed for comparison (clinical validations in Neurology 2016; 86(3):245-52). MRI lesion analysis was performed by a single evaluator blinded to the clinical diagnosis of cases, using a web-based "virtual laboratory" (https://spinevirtuallab.org). Each lesion visualized on brain MRI FLAIR and T2 SE sequence, was annotated for: Lesion signal, shape, location, gadolinium enhancement, border, size. Spine MRI lesions were categorized according to the following criteria: lesion location level, length, gadolinium enhancement.
Results: 19 NMO, 28 MS and 19 ADEM patients had baseline brain MRI scan, and 9, 13 and 7 from these respective groups had baseline cervical-thoracic MRIs. Longitudinally extensive transverse myelitis (LETM), defined as ⩾3 spinal cord segments were not differentially present in the three groups (56% NMO, 42% RRMS and 71% ADEM) Chi-squared test, p-value=0.450. Optic nerve structures were not differentially involved between groups, Chi-squared test, p-value=0.090. 29% of NMO, 76% of RRMS, and 79% of ADEM patients met the McDonald 2010 criteria for dissemination in space on their first MRI. The presence of a juxtacortical or a subcortical lesion differentiated pediatric MS (83%) from pediatric NMO (14%), Chi-squared test, p< 0.001. Other areas that were differentially affected between NMO and MS patients on initial brain MRI were corpus callosum (61% MS, 16% NMO), and the cerebellar white matter (29% MS, 0% NMO).
Conclusions: LETM was not differentially present in pediatric NMO versus MS, however cerebral lesion location features differed between groups. These findings may inform the development of diagnostic criteria distinguishing between early forms of pediatric NMO and MS.

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P826

The Future study- Quality of liFe in adolescent sUbjecTs affected by mUltiple sclerosis treated with immunomodulatoRy agEnt using self-injecting device. A multicenter, observational, prospective study

A. Ghezzi[1], A. Bianchi[2], P. Annovazzi[1], A. Bertolotto[3], V. Bresciamorra[4], R. Lanzillo[4], N. Milani[5], V. Martinelli[6], F. Patti[7], C. Chisari[7], M.R. Rottoli[8], M. Simone[9], D. Paolicelli[9], A. Visconti[10], P. Tortorella[11], Roberta Fantozzi, Paolo Bellantonio, Maria Pia Amato,Hakiki Bahia, Ruggero Capra, Simona Malucchi, Cinzia Cordioli, Maria Trojano, Paola Perini, Paolo Gallo, Luigi Grimaldi, Lucia Moiola,Carlo Pozzilli, Luca Prosperini, Sergio Stecchi

[1]A.A.O. S. Antonio Abate, gallarate, [2]A.A.O. S. Antonio Abate, Gallarate, [3]AOU S Luigi Gonzaga Neurologia 2 CRESM, Orbassano, [4]Azienda Ospedaliero Universitaria Policlinico Federico II, Napoli, [5]Istituto Neurologico Carlo Besta,, [6]Ospedale S. Raffaele, Milano, [7]Department of Medical and Surgical Sciencese, and Advanced Technologies, Neuroscience Section, Multipla Sclerosi, Center, University of Catania, Catania, [8]Neurologia USS Malattie Autoimmuni - Centro Sclerosi Multipla ASST Papa Giovanni XXIII, Bergamo, [9]Dip di Scienze mediche di Base, Neuroscienze ed Organi di Senso Università di Bari, Bari, [10]Merck, Roma, [11]Merck, Milano, Italy

Background: Rebif® R can be administered using the RebiSmart R device for the treatment of MS above the age of 12 years. However, the use of Rebif® R in adolescent patients with MS has not been studied systematically. In this study, the PedsQL (Pediatric Health-related quality of life HR-QL), a self-administered, multi-dimensional, subject-based HR-QL test specifically developed for children and internationally validated, was used to evaluate MS QoL in this special population. Treatment adherence was monitored using the RebiSmart R™ device.

Methods: Subjects with RRMS received subcutaneous IFN ß 1-a 22 mcg three times weekly by RebiSmart R for 2 years. The study was performed in 14 Italian sites with a planned recruitment of 92 subjects. Data were collected following standard clinical practice. All centers were provided with mobile tablet devices for data collection. Data recorded on the subject's RebiSmart R were uploaded and sent to a central server. Clinical data were loaded into an electronic case report form.

Results: 51 patients were screened: 1 patient was excluded and 10 patients dropped-out . 50 subjects were included: mean age was 15 years, mean disease duration 1 year, f/m 32/18. 42 subjects were treatment naïve. At the end of the study, values of PedsQL were higher but not statistically significant compared to baseline with the exception of "emotional functioning ": the PedsQL index score improved at 52 weeks by mean +0.44 (p = 0.848). Highest QoL improvement was found for "school functioning" with an improvement of +1.41 (p = 0.713). In Parent proxy PedsQL values were clearly higher at week 52 compared to baseline, indicating an improvement in QoL during the study. Changes in QoL improved significantly for "psychosocial health summary" with +5.90 (p = 0.015) and for "school functioning" with + 7.84 (p = 0.029). 80% of subjects who were in study remained relapse-free. Adherence to RebiSmart R, was high (89.7%) at 52 weeks.

Conclusions: These results showed that the use of IFN ß 1-a administered with RebiSmart R is safe and well accepted in the pediatric population

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P827

Long term outcome of paediatric onset multiple sclerosis: comparison with adult onset

T. Armangue[1,2], G. Arrambide[3], Y. Blanco[1], P. Mulero[3], M. Sepúlveda[1], C. Auger[4], N. Sola-Valls[1], A. Rovira[4], F. Graus[1], X. Montalban[3], A. Saiz[1], M. Tintoré[3]

[1]Neuroimmunology, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)-Hospital Clinic, University of Barcelona, Barcelona, [2]Pediatric Neuroimmunology, Neurology, Sant Joan de Deu Children's Hospital, University of Barcelona, Esplugues de Llobregat, [3]Neurology/Neuroimmunology, Centre d'Esclerosi Múltiple de Catalunya (Cemcat), [4]Magnetic Resonance Unit (IDI), Hospital Universitari Vall d'Hebron (HUVH), Barcelona, Spain

Objectives: To characterize clinical, demographic and long term outcomes of Paediatric Onset Multiple Sclerosis (POMS) patients, and to compare them to those with adult onset (AOMS) analyzing two hospital-based cohorts.

Methods: Cohort A included 666 patients followed prospectively since the adult age; 39 of them (6%) had the clinical onset < 18 years (POMS), and 627 (94%) ⩾18 years (AOMS). Time to second attack, and long-term disability, measured as the time to reach an Expanded Disability Status Scale (EDSS) of 4.0, were analyzed by stepwise Cox regression models including clinical and demographic variables as predictors. Annualized incidence relapse rate (AIRR) was calculated by a Cox regression model for multiple events. Due to possible recall bias for relapses during the first years of the disease in POMS patients, we compared the analysis of time to second attack of cohort A with a cohort of clinically isolated syndrome (CIS) patients (cohort B, paediatric onset CIS n=46 [4%], adult onset CIS n=1109 [96%]), followed prospectively since disease onset.

Results: In both cohorts patients had similar baseline characteristics regardless age at onset, including female predominance (cohort A: 67 vs 69%; cohort B: 65 vs 67%) and presenting symptoms at onset, except for oligoclonal bands positivity (cohort A: 90 vs 82%; cohort B: 38 vs 58%, p=0.014). In cohort A, the median (interquartile range) disease duration was 19 years (13-33) and 12 years (6-19) respectively, whereas in cohort B follow-up from onset was similar (7.0 [2-12] years vs 7.4 [2-14] years). In cohort A, the overall AIRR for both groups was similar (0.45 vs

0.43 relapse/person risk/year), but the median time to second attack was longer for POMS (34 vs 17 months, p=0.01). In cohort B, the proportion of patients experiencing a second attack (41.3 vs 40.8%), and the median time to second attack was similar between groups (19 vs 18 months, p=0.855). In cohort A, the median time to reach an EDSS of 4.0 was longer in POMS than in AOMS patients (34 vs 23 years; p=0.0001), but they reached this disability at a significantly younger age than AOMS patients (median age 48 vs 61 year old; p=0.0001).

Conclusion: Our results confirm that patients with POMS take more time to reach a similar disability score, but do so 10 years younger than patients with AOMS. The study emphasizes the importance of taking into account the existence of a recall bias for relapses at the time of analyzing prognostic outcomes.

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contributed equally (shared first authorship)
shared last (senior) authorship
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P828

Predicting paediatric multiple sclerosis in ‚MRI negative' patients: bands do aid

Y.Y.M. Wong[1], L.H. Verhey[2], E.D. van Pelt[1], J. O'Mahony[2], I.A. Ketelslegers[1], R.F. Neuteboom[3], C.E. Catsman-Berrevoets[3], D.L. Arnold[4], A. Bar-Or[4], B.L. Banwell[5], R.Q. Hintzen[1], the Dutch Paediatric MS Study Group, the Canadian Paediatric Demyelinating Disease Network.
[1]Neurology, Erasmus MC, Rotterdam, The Netherlands, [2]Pediatrics and Research Institute, The Hospital for Sick Children, Toronto, ON, Canada, [3]Pediatric Neurology, Erasmus MC, Rotterdam, The Netherlands, [4]Neurology, Montreal Neurological Institute, Montreal, QC, Canada, [5]Neurology, The Children's hospital of Philadelphia, Philadelphia, PA, United States

Introduction: A first demyelinating event in the central nervous system in children might be the first presentation of paediatric-onset multiple sclerosis (POMS). The Verhey criteria showed high predictive value for POMS in both Canadian and Dutch ADS cohorts. However, in clinical practice one is likely to encounter patients who, at clinical onset, do not fulfill McDonald 2010 criteria and are in addition negative for one or both items of the Verhey criteria. Our aim is to investigate whether OCB may be of additional diagnostic value for predicting clinically definite MS (CDMS) in paediatric patients with acquired demyelinating syndromes (ADS) who are negative for both MRI criteria at incident presentation.

Methods: Children in the Canadian and Dutch prospective ADS databases were eligible for this study if the first MRI and OCB result were both available. MRI scans at onset were evaluated according to the Verhey MRI criteria and the McDonald 2010 MRI criteria. OCB status was tested locally with isoelectric focusing in 109/113 (96%) of cases. A minimal follow-up of two years was required for inclusion, unless the patient was diagnosed with CDMS in this period. Statistical analysis was performed with Chi square, Mann-Whitney U test and the logistic regression model.

Results: One hundred and thirteen ADS patients were included who were negative for both MRI criteria. Fourteen developed CDMS. The CDMS group was significantly older (median age 14.8 years) and had more often OCB positivity than the non-CDMS group (86% vs 13%).

OCB positivity was found in 25/113 of the ADS patients of whom 12/25 (48%) developed CDMS, in contrast to 2/88 (2%) of patients without OCB. The negative predictive value of OCB was high (97%). In a logistic regression model, OCB showed a high odds ratio of 35.3 (95% CI 4.1-307.1, p< 0.000), after correction for the presence of encephalopathy, optic neuritis presenting phenotype, age of onset, gender and abnormal MRI with presence of T2/FLAIR lesions.

Conclusion: OCB in CSF can aid in prediction of POMS in patients who are negative at onset for McDonald 2010 and Verhey MRI criteria. This is most appreciated in patients with a negative OCB status. These patients have a very low risk of MS diagnosis.

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P829

Interaction of secondhand tobacco smoke exposure and HLA-DRB1*15 increases the odds for pediatric multiple sclerosis

A. Lavery[1,2], B.N. Collins[2], A. Waldman[1], A. Bar-Or[3], R.A. Marrie[4], D.L. Arnold[5], J. O'Mahony[6], B. Banwell[7], Canadian Pediatric Demyelinating Disease Network
[1]Neurology, Children's Hospital of Philadelphia, [2]College of Public Health, Temple University, Philadelphia, PA, United States, [3]Montreal Neurological Institute, Montreal, QC, [4]University of Manitoba, Manitoba, MB, [5]Montreal Neurological Institute, McGill University and NeuroRx Research, Montreal, QC, [6]The Hospital for Sick Children, Toronto, ON, Canada, [7]The Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background: Recent evidence suggests an association between secondhand smoke exposure and multiple sclerosis (MS) and a potential interaction between secondhand smoke and human leukocyte antigen (HLA) genes. This gene-environment interaction has not been assessed in children with acute demyelinating syndromes, ADS (30% of whom will be diagnosed with MS, and 70% of whom will remain monophasic).
Methods: We included monophasic, all of whom were observed for a minimum of 2 years following acute demyelination. Parents completed standardized questionnaires regarding their child's exposure to smoke in the home, classifying the child as exposed or not exposed. Genetic analyses were performed in the MS and monophasic ADS patients using PCR amplification methods to determine the presence of one or more HLA-DRB1*15 alleles. Logistic regression models (covariates of age and sex) compared SHSe associations between MS patients, monophasic patients, and healthy controls. In children with demyelination, n stratified analyses and logistic regression to examined the relationship between SHSe and the presence of at least one HLA-DRB1*15 allele.
Results: SHSe was more commonly reported in children with demyelination (MS and monophasic ADS) compared to controls (OR=2.24; 95%CI 1.08, 4.63), but the relationship with SHSe was not significant when comparing only the MS patients to healthy controls (OR= 1.84; 95%CI 0.86, 3.95). When comparing MS and monophasic ADS patients, SHSe was not an independent risk factor for MS; however, when both SHSe and one or more HLA-DRB1*15 alleles were present, the odds for MS increased threefold (OR=3.2; 95%CI 1.04, 9.79), indicating a positive additive interaction. The presence of HLA-DRB1*15 alleles did not significantly impact the odds for MS in the absence of SHSe (OR=1.68; 95%CI 0.81, 3.45). Similarly, the presence of SHSe did not significantly impact the odds of MS in the absence of HLA-DRB1*15 alleles (OR=1.22; 95%CI 0.55, 2.66).
Conclusion: In the pilot work, we show a possible interaction between exposure to secondhand tobacco smoke and HLA-DRB1*15 alleles in determining pediatric MS risk.

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P830

Immunoglobulin free light chain analysis aids the diagnosis of pediatric MS: a pilot study

E. Ganelin-Cohen[1,2], B. Kaplan[3], R. Yeskaraev[4], A. Livneh[3], S. Golderman[3]
[1]Institute of Pediatric Neurology, Schneider Children Medical Center, Petach Tikva, [2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, [3]Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, [4]Department of Clinical Biochemistry, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

Introduction: Pediatric MS may differ from the adult disease in clinical practice and in laboratory evaluation. MRI and routine laboratory tests appear to be insufficient, at times, to accurately diagnose pediatric MS. We have recently reported that analysis of immunoglobulin free light chain (FLC) monomers and dimers in the CSF might aid the diagnosis of adult MS (Kaplan et al, 2010, 2012& 2013). However, whether such approach is helpful in the diagnosis of pediatric MS still remains questionable.
Aims: To evaluate FLC monomer-dimer pattern analysis as a new diagnostic tool in pediatric MS.
Methods: Pediatric patients with definite MS (n=17) and other non-MS neurological disorders (n=24, used to determine specificity) were tested. Patients showing no evidence for demyelinating or inflammatory disease (n=8) were used as negative controls.
CSF and serum pairs were analyzed by our previously developed technique, which included quantitative Western blotting for the detection of FLC-κ and λ immunoreactive bands. Intensity of bands was measured to evaluate the levels of FLC monomers and dimers (Kaplan et al, 2010).
Results: All patients with definite MS demonstrated abnormal FLC monomer-dimer patterns, typical of MS (Kaplan et al, 2013). Three distinct pathological FLC profiles were observed. In 10 out of 17 MS patients, the highly increased CSF levels of κ monomers and dimers were demonstrated ("k type"). Four MS cases showed the abnormally increased λ dimer levels ("λ type"). In 3 MS patients, the increased κ-FLC levels were accompanied by highly elevated λ dimers ("mixed type").

MRI and clinical assessment revealed that the "mixed" and "λ" type MS cases indicated a more aggressive form of the disease. In fact, 2 out of 3 "mixed type" patients and 3 out of 4 "λ type" patients demonstrated an increased number of T2 load lesions, more active disease and higher frequency of clinical relapses. In contrast, most "κ type" MS patients showed a moderately active course of the disease.

Diagnostic utility of our technique was evaluated. Both sensitivity (100%) and specificity (91%) of the FLC monomer-dimer analysis were higher than those of OCB test (87% and 83%, respectively).

Conclusions: Our preliminary results show that FLC monomer-dimer analysis in the CSF may aid the diagnosis and prognosis evaluation of pediatric MS.

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P831

Development of a standardized approach to the care of paediatric multiple sclerosis in Canada: Implementation of a national consensus guideline of management strategies including an online pediatric multiple sclerosis care decision support tool

S. Venkateswaran[1], B. Banwell[2], R.-A. Marrie[3], A. Yeh[4], S. Hamer[1], D. Pohl[1]
[1]Children's Hospital of Eastern Ontario, Ottawa, ON, Canada, [2]Children's Hospital of Philadelphia, Philadelphia, PA, United States, [3]University of Manitoba, Winnipeg, MB, [4]Division of Neurology, University of Toronto, Hospital for Sick Children, Toronto, ON, Canada

Background: In Canada, and other countries with similar geographic and demographic challenges, some children with MS may not receive care from neurologists experienced in the management of paediatric multiple sclerosis (MS). Studies have suggested an association of standardization of care with improved health care outcomes. Therefore, management recommendations for the treatment of paediatric MS in Canada were considered necessary to standardize care regardless of treatment setting.
Objective: To develop a standardized approach for paediatric MS care in Canada, with implementation of a national consensus guideline of management strategies facilitated by an online paediatric MS care decision support tool.
Methods: A group of Canadian paediatric MS experts drafted guidelines for the management of paediatric MS, including a protocol for monitoring and for the evaluation of treatment response, as well as algorithms for treatment changes based on treatment tolerability and efficacy. Further feedback and final approval was provided by members of the Canadian Pediatric Demyelinating Disease Study Group and the Canadian Network of MS Clinics.
Results: We developed a real-time clinical decision making tool which employs a web-based password protected portal abiding to healthcare privacy regulations. This tool allows the clinician to quickly enter patient information regarding the number of clinical relapses, MRI lesions and the current EDSS score in order to receive an evaluation of disease activity level and treatment response. A summary page allows the clinician to instantly access a snapshot of their patient's current treatment, disease activity, number of clinical relapses and new MRI lesions since start of the current treatment, as well as recommendations with regards to treatment algorithms. This decision support tool will be tested at pilot sites across the country before it will be made available to Canadian neurologists involved in paediatric MS care.
Conclusion: This web-based decision making tool would be the first of its kind in the care of paediatric MS patients, with hopes of expanding it to an international population. Future studies will focus on the effect of the tool in standardizing treatment practices across the nation, and the link of these changes to health care outcomes.
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P832

Vitamin D genetic risk score is strongly associated with vitamin D levels and relapse rate in pediatric MS patients

J. Graves[1], L. Barcellos[2], A. Belman[3], M. George[2], X. Shao[2], H. Quach[2], L. Krupp[4], E. Waubant[1]
[1]UCSF, San Francisco, [2]UC Berkeley, Berkeley, CA, [3]National Pediatric MS Center, Stonybrook, Stony Brook, [4]New York University Langone Medical Center, New York, NY, United States

Background: Low 25-OH vitamin D levels have been associated with increased risk to have MS and with greater disability and lesion burdens, but establishing a causal relationship has been challenged by multiple confounding factors.
Objective: We sought to determine if an instrumental variable of a genetic risk score for functional single nucleotide polymorphisms in vitamin D pathways is associated with vitamin D levels and relapse activity in pediatric MS subjects.
Methods: Consecutive subjects seen at two Pediatric MS Centers of Excellence between 2006 and 2011 were offered enrollment if they met published criteria for pediatric MS or clinically isolated syndrome with high risk of MS. DNA samples from enrolled subjects who were also followed for relapses were typed for 29 functional polymorphisms in vitamin D pathway genes identified through the literature to be associated with 25-OH vitamin D levels in human subjects. Linear regression models were used to compare genotype to 25-OH D level and Cox regression for association of a genetic risk score for low 25-OH D with relapse hazard.
Results: Six of the 29 polymorphisms were strongly associated with vitamin D levels in pediatric MS subjects (n=181) after Bonferroni correction (p=0.0017) for multiple comparisons. An unweighted risk score of these 6 SNPs was normally distributed and explained 12% of the variance of vitamin D level in these subjects. A five-unit change in the risk score for lower vitamin D (range 0 to 12), was associated with 5.4 ng/ml lower 25-OH D level (95% CI -7.58, -3.14, p=0.0000018). This risk score was associated with a 25% increase in the hazard to relapse (HR 1.25, 95% CI 1.03, 1.49, p=0.017).
Conclusion: A genetic score of six functional polymorphisms captures risk of hypovitaminosis D and identifies those who may be at greater risk of relapse related to this risk factor. These findings support a causal association of vitamin D with relapse rate.

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P833

Visual perception tasks in paediatric multiple sclerosis patients - a pilot study

K. Karoscik, A. Lavery, R. Datta, A. Thomas, B. Banwell, A. Waldman
Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background and Purpose: Involvement of the anterior and posterior visual pathway occurs commonly in paediatric multiple sclerosis (MS). In our pilot work, we have found that despite reduced monocular or binocular acuity in some children with MS, the magnitude of binocular summation is preserved, suggesting retention of this compensatory mechanism. The purpose of this study was to explore performance on other visually-related cognitive tasks.
Methods: We evaluated 21 paediatric MS patients (onset < 18 years, mean age at testing 17, range 13-18 years; 12 female; 8 with a history of ON) and 15 paediatric healthy controls through high and low contrast acuity (1.25%) testing, the Beery-Buktenica Developmental Test of Visual Motor Integration (bVMI), the Woodcock Johnson Visual Matching (WJVM) subtest, and the Symbol Digit Modalities Test (SDMT written version). Total letters read using HCVA and LCVA charts by each eye and using binocular testing were recorded and mean counts compared between groups. Mean values of the standardized scores for the bVMI, WJVM and SDMT were compared between MS patients and controls using student t-tests. Pearson correlations were performed to determine the strength of associations between cognitive tests, as well as between each test and the magnitude of binocular summation.
Results: Of 42 pediatric MS eyes, monocular HCVA (mean 53 letters, 1.6 SD) and LCVA (mean 11 letters, 1.8 SD) differed from that of the 30 control eyes (mean 57 letters, 1.4 SD HCVA, mean 22 letters, 1.4 SD, LCVA). There was no difference in binocular summation between controls and MS patients (p=0.536). The mean standardized scores did not differ for the bVMI between pediatric MS subjects and healthy controls (p=0.8381). For the WJVM, paediatric MS patients scored 9-points lower than the control group, (p=0.057), and SDMT z-scores were significantly lower in MS patients (p= 0.006). The bVMI, WJVM and SDMT did not correlate with the magnitude of binocular summation. Within the MS group, the WJVM correlated with the SDMT (correlation coefficient 0.6093, p=0.001).
Conclusion: Children with MS have preserved magnitude of binocular summation and in general, perform well on tests of higher order visual processing. The correlation between the WJVM and SDMT favors a relationship with processing speed, rather than visual perception, which may reflect a more general disruption of white matter rather than a specific impairment in visual networks.

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P834

Low-contrast letter acuity perception matures with age in healthy children

A.T. Waldman[1], A. Lavery[2], G. Liu[2], B. Banwell[2]
[1]Children's Hospital of Philadelphia, Bryn Mawr, [2]Children's Hospital of Philadelphia, Philadelphia, PA, United States

Introduction: Low-contrast letter acuity (LCLA) is increasingly recognized as a sensitive measure of visual impairment in paediatric multiple sclerosis and optic neuritis. LCLA requires identification of letters based on the visual angle to determine acuity, but it is also a task of perception given its faint gray letters on a white background. While high-contrast letter acuity is established by age 6 years (visual acuity of 20/20), maturation of the visual pathways and cortex occur throughout childhood. Therefore, it is unknown whether LCLA scores change as a function of age. The goal of the present study is to determine normative values for low-contrast letter acuity in healthy children.
Methods: Healthy controls (without evidence of ocular or neurologic disease) between the ages of 4 and 21 were recruited for this study if their best-corrected visual acuity was 20/20 or better on Early Treatment Diabetic Retinopathy Study letter charts. Using retro-illuminated box charts, participants completed 2.5% and 1.25% Sloan LCLA charts; monocular and binocular scores (total number of letters correctly identified) were recorded. Mean values by age were calculated. Loess and spline regression models were used to compare scores by age.
Results: A total of 95 healthy controls were recruited, contributing 190 eyes for the analysis. Overall, older children correctly identified more letters than younger children. A spline regression with 3 knots identified a change at age 13.9 years. For example, mean 2.5% LCLA scores for ages 5-6 years were 27.0 letters (SD 3.2, range 20.7-33.3) compared to 35.2 letters (SD 1.8, range 31.6-38.7) at 13-14 years and remained stable thereafter. For 1.25% contrast, mean LCLA scores also increase from 18.5 letters correct (SD 2.2, range 14.2-22.8) at ages 5-6 years to 25.6 letters (SD 1.8, range 22.0-29.2) at ages 13-14 years. Right and left monocular as well as binocular testing produced similar results. Gender differences did not significantly impact the subject's scores.
Conclusion: Healthy children's ability to detect low-contrast letters increases until age 13.9 years and then remains relatively

stable into early adulthood. These results should be considered in the design of future paediatric studies incorporating low-contrast letter charts. Similarly, LCLA has also been considered as a fourth measure for the Multiple Sclerosis Functional Composite; such studies should also incorporate age into the analysis in paediatric cohorts.

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P835

Paediatric acute disseminated encephalomyelitis followed recurrent optic neuritis (ADEM-ON): disease course and treatment

Y.Y.M. Wong[1], E.D. van Pelt[1], I.A. Ketelslegers[1], C.E. Catsman-Berrevoets[2], K. Rostasy[3], R.Q. Hintzen[1], R.F. Neuteboom[2]
[1]Neurology, [2]Paediatric Neurology, Erasmus MC, Rotterdam, The Netherlands, [3]Paediatric Neurology, Vestische Kinder- und Jugendklinik Datteln, Datteln, Germany

Introduction: Acute disseminated encephalomyelitis followed by monophasic or recurrent optic neuritis (ADEM-ON) is a distinctive and rare entity in the spectrum of acquired demyelinating syndromes (ADS). Here we describe our experience with treatment in a Dutch and German cohort.
Methods: We included children < 18 years old who fulfilled criteria for ADEM, followed by at least one ON. Clinical and demographic data, including presence of antibodies directed to myelin oligodendrocyte glycoprotein (MOG-IgG), were collected.
Results: Eight patients were identified with ADEM-ON. Four of them were boys. The median age at onset was 6.7 years old . All but one were tested seropositive for MOG-IgG (88%). Number of relapses varied from 1 to 9 with a median follow-up duration of 3.0 years. In 6 patients immunosuppressive therapy was initiated with Azathioprine or Mycophenolate Mofetil (MMF) combined with an oral prednisone taper. Remarkably, all of these patients were highly responsive to corticosteroids: no relapse occurred while on high dose oral prednisone taper and there was an overall good recovery after intravenous infusion. Relapses occurred when the prednisone taper reached a low dose, or shortly after cessation. Two patients had multiple relapses under Azathioprine or MMF therapy, and therefore treatment was switched to Rituximab infusions. One patient received IvIG pulse therapy combined with Rituximab. Afterwards relapses still occurred, but with a larger interval.
Conclusion: Children with ADEM-ON are highly responsive to corticosteroids. They do not all respond to Azathioprine or MMF. In those cases Rituximab is an alternative treatment option. Further studies in international collaboration are needed to optimize treatment regimens for children with this rare variant of ADS.

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P836

High levels of the T-cell activation marker sCD27 in CSF are associated with MS in childhood acquired demyelinating syndromes

Y.Y.M. Wong[1], E.D. van Pelt[1], I.A. Ketelslegers[1], C.E. Catsman-Berrevoets[2], R.F. Neuteboom[2], R.Q. Hintzen[1]
[1]Neurology, [2]Paediatric Neurology, Erasmus MC, Rotterdam, The Netherlands

Introduction: It is hard to predict a future diagnosis of multiple sclerosis (MS) at the onset of acquired demyelinating syndromes (ADS) in childhood. MRI lesion type and CSF oligoclonal bands (OCB) contribute to prediction, but additional markers remain needed. In adult MS, elevated levels of soluble CD27 (sCD27), that is released upon T-cell activation, are found in CSF. This marker appears an accurate biomarker for MS-related neuroinflammation. We here examined whether quantification of CSF sCD27 can distinguish a monophasic versus multiphasic disease course after pediatric ADS.
Methods: Children < 18 years old included in the Dutch Nationwide ADS study were eligible if a lumbar puncture was performed within 6 months after onset. sCD27 levels were determined by a commercially available ELISA (Sanquin, Amsterdam). Mann Whitney U and Kruskal Wallis test were used to compare continuous parameters that were not normally distributed. Chi-square and Fisher exact test were used for categorical data.
Results: Sixty-seven children were included (26 acute disseminated encephalomyelitis (ADEM), 12 clinically isolated syndrome (CIS) and 29 MS). Thirty-nine patients were female (58%). Median age of onset was 10.8 years. A multiphasic disease course was observed in 21 patients (31%) with a median follow-up duration of 3.0 years.

Multiphasic patients had a higher sCD27 level compared to monophasic patients (median 43.9 pg/ml, IQR 32.8-97.6 vs median 17.8 pg/ml, IQR 9.2-38.4 ($p< 0.000$)). Monophasic CIS patients showed lowest levels of sCD27 (median 9.0 pg/ml), followed by monophasic ADEM (median 19.1 pg/ml), with the highest levels among patients that were diagnosed with MS (median 52.2 pg/ml). The sCD27 levels differed significantly among these groups ($p< 0.000$).
Conclusion: sCD27 levels in CSF of pediatric ADS patients is associated with a multiphasic disease course, with the highest levels in MS patients. This seems to be a promising new biomarker for prediction of MS at ADS onset.

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Natural course

P837

Brain reserve and age of MS diagnosis: larger maximal lifetime brain growth is linked to later diagnosis

J.F. Sumowski[1], M.A. Rocca[2], M. Inglese[1], V.M. Leavitt[3], A. Meani[2], K. Buyukturkoglu[1], P. Preziosa[2], G. Comi[2], M. Filippi[2]
[1]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [2]Vita-Salute San Raffaele University, Milan, Italy, [3]Columbia University Medical Center, New York, NY, United States

Background: Consistent with the brain reserve hypothesis, we have shown that MS patients with larger maximal lifetime brain growth (MLBG, estimated with intracranial volume, ICV) are better able to withstand disease burden (e.g., T2 lesion volume) without cognitive decline. We recently published the first evidence linking larger MLBG to lower risk for physical disability progression in MS patients over five years. Here we investigate a novel testable hypothesis of the reserve construct: that persons with larger MLBG will have an older age of MS diagnosis, consistent with the rationale that persons with larger MLBG can better withstand neurologic disease without / before suffering clinical symptoms precipitating medical attention and diagnosis.
Methods: A sample of 431 adult-onset Italian (n=341) and American (n=90) MS patients (288 women; 395 relapse-onset, 36 progressive-onset) underwent 3T MRIs of the brain to measure ICV (with SIENAX), which was adjusted for sex and scanner, and divided into quintiles. Age of diagnosis was recorded, and adjusted for onset-course, country, sex, and socioeconomic status (years of education). ANOVA investigated differences in age of diagnosis across ICV (MLBG) quintiles (Q1 = smallest).
Results: There was a link between ICV and age of diagnosis ($F[4,426]=4.65$, $p=.001$, $\eta^2=.042$), whereby patients in the largest quintile (Q5, mean age = 35.2 years; 95%CI: 33.4-37.1) were diagnosed at an older age than patients in Q4 (32.1, 95%CI: 30.3-33.9), Q3 (32.5, 95%CI: 30.7-34.3), and Q2 (32.4, 95%CI: 30.6-34.3, $Ps< .05$) and Q1 (29.5, 95%CI: 27.6-31.3, $p< .001$). Patients in Q1 (smallest ICV) were diagnosed at a younger age than patients in Q2, Q3, and Q4 ($Ps < .05$), and Q5 ($p< .001$). When Italian and American samples were analyzed separately, there was a reliable link between larger MLBG and older age of diagnosis in each sample.
Conclusion: Age of MS diagnosis is an estimate of clinical symptom onset. Consistent with the brain reserve hypothesis, persons with the larger MLBG were diagnosed later (and persons with smaller MLBG were diagnosed younger), suggesting that larger lifetime brain growth / size allows persons to better cope with MS disease burden before suffering clinical symptoms precipitating medical attention. The link between MLBG (ICV) and age of diagnosis was found in two separate geographically-remote samples. These data provide novel support for the concept of reserve against physical disability.

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M Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd. has received funding for travel from Bayer Schering Pharma, Biogen Idec, Merck Serono, and Teva Pharmaceutical Industries Ltd.; serves as a consultant to Bayer Schering Pharma, Biogen Idec, Merck Serono, Novartis, Pepgen Corporation, and Teva Pharmaceutical Industries Ltd.; serves on speakers' bureaus for Bayer Schering Pharma, Biogen Idec, Merck Serono, and Teva Pharmaceutical Industries Ltd.; receives research support from Bayer Schering Pharma, Biogen Idec, Novartis, Merck Serono, Teva Pharmaceutical Industries Ltd., Fondazione Italiana Sclerosi Multipla, the Italian Ministry of Health, CurePSP, and the Jacques and Gloria Gossweiler Foundation (Switzerland).

P838

Rethinking the importance of paroxysmal and unusual symptoms as first clinical manifestation of multiple sclerosis: they do matter!

R. Ehling, G. Bsteh, F. Di Pauli, H. Hegen, K. Roetzer, M. Auer, F. Deisenhammer, M. Reindl, T. Berger
Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Background: Paroxysmal (PS) and unusual symptoms (US) as initial manifestation of multiple sclerosis (MS) are rare and have been reported only anecdotally. Due to their mostly self-limiting nature they are often thought to indicate "benign" MS. However, there is a lack of data on further disease courses of MS patients initially presenting with PS or US.
Objective: To investigate the prevalence and long-term clinical disease course of patients who experienced PS or US as a first clinical manifestation of MS.
Methods: In this retrospective, observational study, clinical and cerebrospinal fluid data of MS patients with a minimum follow-up of five years were obtained in a large representative MS centre.

Patients presenting with PS and US were compared to patients with classical bout onset regarding gender, age at disease onset, time to first relapse, annualized relapse rate (ARR) and disability (EDSS).
Results: In a cohort of 1,396 patients with relapsing onset MS, 15 patients (1.1%) were identified having presented with PS (trigeminal neuralgia, dysarthria and ataxia, tonic spasms, paroxysmal sensory symptoms, diplopia, akinesia) and 7 patients (0.5%) with US (epileptic seizure or status epilepticus). Despite anticonvulsive and/or corticosteroid treatment mean duration of symptoms was 77 days. At symptom onset, groups were comparable with respect to gender, age at onset and intrathecal immunoglobulin synthesis (p>0.05). During a mean follow-up period of 13.6 years, all patients initially presenting with PS or US converted to CDMS after a mean duration of 3.4 years (95% CI 1.9 - 4.8) as compared to 1,295 patients (94%) presenting with classical bout onset who converted to CDMS after a mean disease duration of 2.7 years (95% CI 3.0 - 3.4; p=0.759). However, compared to patients presenting with US or classical bout onset, patients with PS had a significantly lower ARR and EDSS less clinical disability (EDSS) 10 years after disease onset (p=0.008 and p=0.001, respectively).
Conclusion: In a large cohort of 1,396 MS patients, 1.1% of individuals presented with PS and 0.5% with US at disease onset. Irrespective of the transient nature of symptoms, patients presenting with PS and US were at the same risk of developing CDMS as classical bout onset patients. Consequently, awareness of identifying PS or US as a possible first clinical symptom of MS is critical and close clinical monitoring and consequent evaluation for early DMT initiation mandatory.

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P839

More severe disability progression in north africans with multiple sclerosis

Y. Sidhom[1,2], E. Maillart[1], S. Tezenas du Montcel[3], I. Kacem[2], C. Lubetzki[1], R. Gouider[2], C. Papeix[1]
[1]Department of Neurology, Pitié-Salpêtrière Hospital, Paris, France, [2]Department of Neurology, UR12SP21, Razi Hospital, Tunis, Tunisia, [3]Biostatistics Unit, Pitié-Salpêtrière Hospital, Paris, France

Background: Few studies have reported increased multiple sclerosis severity in North Africans compared to Caucasian patients. Data available concerning first and second generation immigrants are partial. We aimed to compare multiple sclerosis disability progression between North Africans living in France (NAF), in Tunisia (NAT) and Caucasian patients born and living in France (CF).
Methods: We included Multiple sclerosis patients admitted in the day hospital in Neurology Department at Pitié-Salpêtrière Hospital (France) and Razi hospital (Tunisia). To compare delay to outcomes, logrank tests were used. Univariate and multivariate Cox models were used to determine factors influencing time to EDSS 6.
Results: We consecutively included 462 patients: 171 CF, 151 NAT and 140 NAF (54 first generation (NAF1) and 86 second generation immigrants (NAF2)). Sex ratio, disease forms and delay from disease onset to diagnosis were similar between the groups. NAF differed from other groups with a shorter median time from the onset of the disease to EDSS 3, 4 and 6 and a more frequent incomplete recovery after first relapse (p< 0·0001). Furthermore, the NAF2 differed from the others, having the highest mean progression index and the shortest median time to EDSS 6 in relapsing remitting patients. This group was also characterized by a younger median age at onset (26·5±8·8 years p=0·001) and an increased mean number of relapses during the first 5 years of the disease (6·1 ±3·7, p=0·01) compared to CF. The Cox proportional hazard models demonstrates that i) North African ethnicity is a significant predictor of a fast progression even when adjusting for major covariates, ii) the presence of spinal lesions in initial MRI was a strong predictor for ambulatory disability
Conclusions: Our study further supports severity of multiple sclerosis in North Africans and unravels the particular severity in North Africans living in France, mainly for the second generation.

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Dr. Gouider has nothing to disclose
Dr. Papeix has nothing to disclose

P840

Brain atrophy 15 years after CIS: baseline and follow-up clinico-radiological correlation

À. Vidal-Jordana[1], J. Sastre-Garriga[2], D. Pareto[3], C. Tur[4,5], G. Arrambide[4], S. Otero-Romero[6], E. Huerga[3], R. Mitjana[3], C. Auger[3], M. Tintoré[7], Á. Rovira[3], X. Montalban[1]

[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, [2]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, [3]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, Bar elona, [4]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, Spain, [5]MS Queen Square Centre, National Hospital for Neurology and Neurosurgery, London, United Kingdom, [6]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Dept & Epidemiology Dept, Vall d'Hebron University Hospital, [7]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Dept, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Brain atrophy in patients with multiple sclerosis (MS) is present since the very early stages of the disease and it has been related to long-term disability.

Objective: We aimed to estimate global and regional brain volume (BV) at 15 years after clinically isolated syndrome (CIS) and to evaluate its relationship with baseline and follow-up disease outcomes.

Material and methods: From a prospective, on-going cohort including patients presenting with a CIS, 59 patients with a brain MRI performed 15 years after CIS were included. Clinico-radiological data was collected; a baseline risk score based on multivariate Cox model was previously calculated to predict reaching an EDSS of 3.0 during the 15-year follow-up (EDSS 3.0 risk). Statistical Parametric Mapping 8 was used for BV segmentation. Brain tissue masks obtained with Brain Extraction Tool were used to correct segmentation errors. BV were normalized by total intracranial volume and brain parenchymal fraction (BPF), grey matter fraction (GMF) and white matter fraction (WMF) estimates were obtained. Linear regression analyses were conducted to predict BV loss 15-year after CIS with baseline and follow-up variables. Uni and backward multivariate logistic regression analyses were performed to predict reaching an EDSS of 3.0 at 15 years, including BPF, GMF and WMF in each model.

Results: 41 patients were female, mean age at CIS was 29.4 (SD 8.2), baseline median EDSS was 1.0 (range 0-3.0), and 20 patients (34.5%) fulfilled 3-4 Barkhof criteria (BC). Mean time of follow-up was 18.5 years (SD 1.3), 32 patients (54.2%) had a second relapse and 12 (21.4%) reached an EDSS of 3 at 15 years. Mean BPF, GMF and WMF at 15 years were 0.83, 0.44 and 0.39, respectively. Lower values of BPF were associated with presenting 3-4 BC at baseline (p=0.017), a higher EDSS 3.0 risk score (p=0.012), presenting a second relapse (p=0.014), and receiving treatment during the follow-up (p=0.022). In the multivariate logistic regression analysis to predict reaching an EDSS of 3.0, baseline EDSS and receiving treatment were retained in the three models, as well as GMF (p=0.066) and WMF (p=0.071).

Conclusion: Patients with a higher baseline risk of developing MS and of disability accrual during follow-up will show larger BV losses 15 years after CIS. Grey and white matter volumes 15 years after a CIS are associated with a trend towards an increased risk of reaching an EDSS of 3 during the same time period.

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SOR has nothing to disclose around the present work.
EH has nothing to disclose around the present work.
RM has nothing to disclose around the present work.
CA has nothing to disclose around the present work.
MT has nothing to disclose around the present work.

P841

Clinical worsening in subjects with no MRI evidence of disease activity

D.S. Conway, D. Ontaneda

Mellen Center, Cleveland Clinic Foundation, Cleveland, OH, United States

Introduction: Multiple sclerosis usually begins with a relapsing-remitting (RRMS) phase characterized by clinical relapses and inflammatory demyelination evident on magnetic resonance imaging (MRI). Disability in RRMS is thought to develop through incomplete recovery from relapses. Most patients eventually develop a secondary-progressive course characterized by a gradual increase in disability over time thought secondary to neurodegeneration. The possibility of a mild form of progression during early stages of the disease has been proposed. It is unclear if RRMS patients experience gradual worsening despite inflammatory stability.

Methods: The Knowledge Program (KP) is a patient and clinician reported outcomes database linked to the electronic medical record. Through KP query and chart review, we identified all RRMS patients seen between 1/1/2008 and 12/31/2014. We included patients who were ⩽50 years old, had disease duration of ⩽10 years, and developed no new or enlarging T2 lesions or gadolinium enhancing lesions from their first to last MRI. The Timed 25 Foot Walk (T25FW), 9 Hole Peg Test (9HPT), Performance Scales (PS), Patient Health Questionnaire-9 (PHQ9), and European Quality of Life 5-Dimensions (EQ5D) during the period of MRI stability were extracted. Mixed effects linear models were used to determine the trajectory of the outcomes. Age, gender, and time from first MRI were included as fixed effects and subject as a random effect.

Results: The initial cohort included 5735 patients. We identified 128 who met inclusion criteria with stable MRIs. The average time between first and last MRI was 4.2 years and the average number of MRIs was 4.1. A significant increase of 0.26 seconds per year was found for the T25FW (p =0.03). A non-significant increase of 0.20 seconds per year on the right (p=0.50) and 0.45 seconds per year on the left (p=0.23) was seen for the 9HPT. An increase of 0.07 points per year was seen for the PS but this was not significant (p=0.68). PHQ9 scores improved by 0.20 points per year, but this was also not significant (p=0.14). Finally, the EQ5D score worsened by 0.0021 points per year (p=0.682).

Conclusions: A subtle but significant increase was seen in the T25FW over time, but the other outcomes did not significantly change. Our findings support the notion that inflammatory pathology is primarily responsible for worsening during RRMS, however gradual worsening may be present from early stages of MS as well.

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P842

Leveraging patient-reported outcomes to assess new neurological symptoms in a prospective cohort study of individuals at risk for multiple sclerosis

R. Bove[1,2], Z. Xia[1,3], S. Clarkson[4], I. Cortese[5], D. Reich[5], L. Chibnik[1], P.L. De Jager[1]
[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Neurology, University of California, San Francisco, San Francisco, CA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, [4]Brigham and Women's Hospital, Boston, MA, [5]National Institute of Neurological Disease and Stroke, National Institute of Health, Bethesda, MD, United States

Background: The Genes and Environment in Multiple Sclerosis (GEMS) study investigates the events leading to multiple sclerosis (MS) in at-risk individuals.
Goals: Interim assessment of the rate of baseline neurological events in a prospective cohort study of individuals at higher risk for MS.
Methods: Participants having at least one first-degree relative with MS have been enrolling in the GEMS study since 2010. In March 2016, we deployed a follow-up questionnaire, including ascertainment of interim neurological events as well as the MS rating scale (MSRS), a patient-reported disability scale (8 domains, each scored 0-4, composite score 0-32; previously validated against the EDSS). The Genetic and Environmental Risk Score (GERS), an aggregate estimate of an individual's susceptibility for MS, which incorporates genetic burden (64 SNPs) and environmental exposures (smoking, sex, and mononucleosis), was calculated at study enrollment. MS diagnosis was confirmed by medical record review.
Results: Of 2540 participants enrolled in the GEMS study, 1756 completed the interim questionnaire (16 incompletely) (response rate = 67%). Questionnaire respondents did not differ from non- or partial- respondents in terms of age, sex, ancestry, or proportion with MS diagnosis. Among respondents, 139 reported diagnosis of MS.

In respondents reporting no MS diagnosis (n=1614), 155 (9.6%) reported onset of at least one new neurological symptom since 2010, including 119 (7.3%) in the preceding two years. The self-reported symptoms included visual disturbance (n=28), difficulty moving arms (n=12), difficulty moving legs (n=7), numbness (n=23), tingling (n=51), and vertigo (n=49). A subset of the participants reported more than one symptom in the prior two years (n=38).

GEMS participants with MS had higher MSRS scores than asymptomatic participants without MS (mean=0.79, SD=0.061; $p< 0.001$). Among the participants with MS diagnosis, the composite MSRS scores were low (mean=6.7, SD 0.21) relative to previously published clinic-based and online research platform cohorts, suggesting that these GEMS participants have mild disease. Among the asymptomatic participants, there was no association between GERS and MSRS in a linear regression analysis controlling for age and body mass index.
Conclusion: This study leverages patient-reported outcomes and captures an interim development of new neurological symptoms in the first prospective cohort study of individuals at risk for MS.

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P843

Benign multiple sclerosis in the era of disease modifying therapies

C. Diaz-Cruz[1], A.S. Chua[1], B.C. Healy[1,2], T. Chitnis[1,3]
[1]Partners Multiple Sclerosis Center, Brigham and Women's Hospital, Harvard Medical School, [2]Biostatistics Center, [3]Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, Boston, MA, United States

Objective: To determine factors associated with benign multiple sclerosis (BMS) at 10 years from disease onset in the disease modifying treatment (DMT) era.
Background: Predictors of BMS have been assessed in populations before DMTs were introduced as the standard of care. However, factors associated with BMS have not been reassessed after DMTs became widely used.
Methods: 293 subjects in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital (CLIMB) with disease onset between 2002 and 2005 were included in the analysis. Using the expanded disability status scale (EDSS) score to measure disability, subjects were classified as benign (EDSS$\leqslant$ 2.0) or non-benign (EDSS>2.0) at the clinic visit closest to 10 years after the first symptom date. Univariate and multivariate logistic regression models were used to test the association between benign status and age at disease onset (ADO), race, family history of MS, smoking history, number of DMTs and

proportion of time on DMTs during the first 5 years of disease (PTDMT5). PTDMT5 was categorized as none, low (0.01-0.33), moderate (0.34-0.65), and high (⩾0.66), and high was considered the reference category.
Results: 64% (95% CI: 58-69%) of subjects were categorized as BMS. In comparison to non-benign MS (NBMS), BMS subjects were more likely to be female (79% vs. 68%, p=0.04), never-smokers (63% vs. 42%, p=0.0007), and have younger mean age at disease onset (35 vs. 40, p< 0.001). In both groups more than 85% of patients were of Caucasian decent. 43% BMS patients and 52% NBMS had a family history of MS, respectively. In the first 5 years of disease, the mean number of DMTs was 1.3 for both groups, the proportion of untreated patients was 34% for BMS and 39% for NBMS and the mean percentage of time on DMTs was 46% in the BMS and 36% in the NBMS group. Sex, ADO, family history of MS and PTDMT during the first 5 years of disease (PTDMT5) were included in the multivariate model. In this model, older ADO (OR=0.95, p=0.0002) and PTDMT5 of 1-33% (OR=0.24, p=0.001) were negatively associated with BMS at 10 years. When smoking history was included in the multivariate model (n=271), ever-smokers had a lower probability of BMS at 10 years compared to never smokers (OR=0.41, p=0.002).
Conclusions: Compared to previous reports, we found a higher proportion of BMS. In our cohort, older ADO, low PTDMT5 and smoking history are negatively associated with BMS at 10 years from MS onset.

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P844

Early MS patients meeting NEDA show no significant gray matter decline

E. Morris, G. Askin, N. Nealon, T. Vartanian, J. Perumal, U. Kauzner, S. Gauthier
Weill Cornell Medical College, New York, NY, United States

Background: No evidence disease activity (NEDA) has been recently evaluated as a possible therapeutic target. MRI volumetric measurements have been considered as an addition to determine disease stability, however this may not be feasible in the clinical setting.
Objectives: The objective of this study was to investigate the rate of achieving NEDA within a population of early treatment naïve MS patients and explore how this definition relates to change in cortical thickness and thalamic volume.
Methods: Ninety seven patients within three years of first symptom (FS) and treatment naïve were enrolled in this prospective study and initiated disease modifying therapy. Annual EDSS, MRI and relapse data was collected for 36 months. NEDA at 36 months (NEDA36) was defined as no relapses, no change in EDSS, and no new contrast-enhancing or new T2 hyperintense lesions on Brain MRI. Global cortical thickness (GCT) and thalamic volume (TV) were measured using Freesurfer's longitudinal pipeline.
Results: Baseline clinical and MRI characteristics included (mean, SD): age 36.4±9.1, EDSS 1.3±1.2, TV 15,434.3 mm^3 ± 2009.1 and GCT 176.8± 177.2 . Sixty seven subjects completed annual clinical evaluations and demonstrated no change in EDSS relative to baseline (p=0.133). Of the 59 patients completing all MRI's, there was no change in GCT (p=0.393), however there was a significant decline in TV (308.3 mm^3 ± 721.9, p=0.0018). Only eighteen subjects (26.9%) met NEDA36 criteria for which none demonstrated significant change in GCT or TV.
Conclusions: Within a cohort of early MS patients TV revealed a significant decline within a period of 36 months. A relatively small percent of patients achieved NEDA, however those that did, revealed stable GCT and TV. Therefore, in early MS, MRI volumetric measurements may not be required to assume overall disease stability.

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Epidemiology

P845

A 10-year study of predictors for employment status in people with multiple sclerosis

M. Forslin[1], L. von Koch[2,3], K. Fink[4,5], S. Johansson[2,6]
[1]Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, [2]Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, [3]Dept of Neurology, Karolinska University Hospital, [4]Department of Clinical Neuroscience, Karolinska Institutet, [5]Department of Neurology, [6]Department of Physiotherapy, Karolinska University Hospital, Stockholm, Sweden

Introduction: Working life is consistently reported to be negatively affected in people living with multiple sclerosis (MS), resulting in early retirement and decreased quality of life. There is a growing number of reports concerning predictors for employment status, but long-term studies are rare. The aim of this study was to identify predictors of employment status after 10 years in a cohort of people with MS (PwMS).
Method: A total of 116 PwMS in working age were included in the study. Data on contextual factors and factors related to functioning were collected at baseline and were used as independent variables; in total 14. In the data collection both patient reported

and performance based outcome measures were used. Employment status, collected 10 years after baseline, was used as a dependent variable and was categorized in full-time, part-time and no work. A generalized ordinal logistic regression was used to analyze the predictive value of the independent variables. Separate models were generated for predictors for full- and part-time work (FPW) versus no work (NW), and predictors for full-time work (FW) versus part-time work and no work (PNW), using multivariate modeling with backward elimination of independent variables with p-value >0.20.

Results: Two thirds of the cohort were women. At baseline mean age was 41 years, 70% had mild MS-disability and mean time since diagnosis was 12 years. In the cohort 42% were working full-time at baseline and 28% part-time. Ten years after baseline 49% had mild MS-disability, 28% were working full-time and 23% part-time. In the final multivariate model, the significant predictors for FPW versus NW after 10 years were age (p=0.002), perceived physical impact of MS (p=0.02), full-time work (p=0.001), frequency of social/lifestyle activities (p=0.001) and energy level (p=0.03) at baseline. Perceived physical impact of MS (p=0.02) at baseline was the only significant predictor for FW versus PNW.

Conclusion: In this cohort of PwMS age, perceived physical impact of MS, full-time work, frequency of social/lifestyle activities and energy level significantly predicted employment status after 10 years. The predictive value of frequency of social/lifestyle activities for long-term employment in MS has not previously been reported and highlights the importance of taking PwMS whole living situation into consideration when studying working life.

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P846

Clinical characterization of patients with CNS demyelination among the muslims arabs population in Israel

L. Brill[1], O. Abramsky[1], T. Ben Hur[1], A. Karni[2], S. Israel[3], A. Vaknin Dembinsky[1]
[1]Neurology, Hadassah Medical Center, Jerusalem, [2]Neurology, Tel Aviv Sourasky Medical Center, Tel Aviv, [3]Tissue Typing, Hadassah Medical Center, Jerusalem, Israel

In worldwide analyses, Neuromyelitis optica (NMO) and opticospinal Multiple sclerosis (MS) represented at higher proportions among demyelinating conditions in African, East-Asian and Latin American populations. There are currently very poor data regarding the prevalence of NMOSD in Middle East Muslim. In our previous work, we indicate a possibly increased prevalence of NMOSD in Muslim Arabs in Israel with distinct (positive and negative) HLA associations. We performed a follow up study aimed to phenotype patients with CNS demyelination among the Muslims Arabs population followed at the Hadassah MS center.

Methods: 160 out of 199 patients files had sufficient clinical information to be included in the study. NMO diagnosis was defined according to the 2015 criteria. AQP4 seropositivity was analyzed in 250 sera samples using an ELISA assay followed by a cell based validation assay.

Results: Out of the 160 Muslims Arabs patients with CNS demyelination followed at Hadassah MS center, more than 20% were clinical definite NMO (35/160). 13% of the patients had myelitis only with no AQP4 positivity, and 52% were diagnose with MS. The 35 definite NMO patients had clinical characteristics typical of NMO spectrum disorder. No major clinical differences were found between the Muslims Arabs population and other ethnic groups in Israel. The AQP4+ positivity was 60%. The relative frequency of MS to NMO in the Muslims Arabs population (MS/NMO ratio) was 2.4. In order to overcome referral center over diagnosis, we randomly screening the last 250 sera samples tested for AQP4-Ab in the Hadassah medical center. Out of the 250 sample, 14 were positive. 40% of the positive patients were obtained from Israeli Muslims Arabs (6/14).

Conclusions: Our findings point to an increased prevalence of NMOSD in Muslim Arabs in Israel. Among patients of Muslim Arabs origin in Israel, with idiopathic inflammatory demyelinating diseases, the diagnosis of NMO is almost half of MS diagnosis.

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P847

The influence of coping on long-term employment in multiple sclerosis - a prospective study

N. Grytten[1,2], A.B.R. Skår[1], J. Aarseth[3], J. Assmus[4], E. Farbu[5,6,7], K. Lode[8], H. Nyland[7], T. Smedal[9,10], K.-M. Myhr[2,11]
[1]Norwegian Multiple Sclerosis Competence Centre, Haukeland University Hospital, [2]KG Jebsen MS Research Centre, Institute of Clinical Medicine, University of Bergen, [3]The Norwegian Multiple Sclerosis Centre, [4]Centre for clinical research, Haukeland University Hospital, Bergen, [5]Department of Neurology, Stavanger University Hospital, [6]Neuroscience Research Group, Stavanger University Hospital, Stavanger, [7]Institute of Clinical Medicine, University of Bergen, Bergen, [8]Department of Research, Stavanger University Hospital, Stavanger, [9]Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway, [10]Department of Physiotherapy, Haukeland University Hospital, [11]Norwegian Multiple Sclerosis Registry and Biobank, Department of Neurology, Haukeland University Hospital, Bergen, Norway

Background: Provided the importance of coping and advantageous adjustments to multiple sclerosis (MS) for health and psychological wellbeing, we hypothesized that coping could have an independent effect on long-term employment status.

The aim was to investigate the influence of coping styles, clinical and demographic factors on employment status during a 13 years follow-up in patients with newly diagnosed MS.

Method: All patients (n=108) recently diagnosed with MS were invited to participate in the long-term follow-up study in 2002. A total of 93 patients agreed to participate of whom 52 were unemployed at time of inclusion in 2002. Forty-one were part or full time employed and followed up with regard to employment status until 2015. At baseline, the study included disability scoring (EDSS), fatigue (FSS), depression (BDI), time delay from onset to diagnosis and questionnaire assessing coping (the COPE scale). Logistic regression analysis was used to identify factors that were independently associated with being unemployed at baseline, and cox regression analysis were used to identify factors at baseline that were independently associated with time to unemployment during follow up.
Results: A total of 41 (44%) were employed at baseline, and after 13 years, 22 (23%) patients were still part- or full time employed. Older age at diagnosis, female gender and depression were associated with patients being unemployed at baseline, and female gender, long time delay from onset to diagnosis and denial as avoidant coping strategy at baseline predicted shorter time to unemployment.
Conclusions: Avoidant coping style, female gender and long time delay of diagnosis were associated with shorter time to unemployment. In order to improve long-term employment in MS, these factors should be considered by health professionals and at the patient`s work place.

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P848

Multiple sclerosis patients perceive their illness different than neurologists

M. Kurtuncu[1], U. Uygunoglu[2], M.A. Tuncer[3], A. Kokenli[4], M. Kasap[4], Z. Caliskan[4], A. Altintas[2], S. Saip[2], M. Eraksoy[1], R. Karabudak[3], A. Siva[2]
[1]Neurology, Istanbul University Istanbul Faculty of Medicine, [2]Neurology, Istanbul University Cerrahpasa Faculty of Medicine, [3]Neurology, Hacettepe University Faculty of Medicine, Department of Neurology, [4]Novartis Turkey, Istanbul, Turkey

Introduction: Multiple sclerosis (MS) is one of the most common debilitating neurological disease in young adults. MS patients' perception of their disease may contrast with neurologists which may further complicate the management of patients.
Objective: Our study aims to understand the differences in disease perception of patients with MS compared to neurologists.
Methods: MS patients were interviewed by using a 25-question survey which included questions on their experiences after diagnosis, signs and symptoms, laboratory tests, adherence, use of alternative medicine, and expectations from treatments. The same questions were asked to neurologists to get their assumption of their patients' answers. Neurologists responses were compared with the answers of the patients.
Results: A total of 208 patients and 176 neurologists were included in the study. As opposed to neurologists, patients consider radiological investigations to be more important than physical examination during their management. Neurologists, in comparison to their patients, have a more pessimistic perception about the effect of their patients' symptoms on their quality of life. Fatigue is the most debilitating symptom for patients, whereas neurologists rank motor deficits as the most important symptom that affect the quality of life. Regarding cerebrospinal fluid (CSF) examination, the proportion of patients who believe that CSF examination may cause severe headaches was 39%, nerve damages was 36%, and worsening of their symptoms was 16%. Neurologists assume that only 24% of their patients missed a dose of their treatment during the last month. Nevertheless, the noncompliance rate of patients was 36%. In terms of side effects of corticosteroid treatment, patients suppose osteoporosis as the most important side effect, whereas neurologists were more concerned of uncontrolled diabetes and hypertension. One third of patients presumed that their treatment may be discontinued at some point during the course of their disease.
Conclusions: This study shows that there is a discrepancy between neurologists' and patients' perception of MS. A better understanding of patients' sentiments may improve patient-physician relationships.

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Mithat Kasap works for Novartis Pharmaceuticals, Turkey.
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P849

MS differences are observed by place of birth and immigration between mexican american and mxican populations: a within ethnic-group analysis

L. Amezcua[1], J.F. Rivera[2], T. Islam[3], V. Rivas[2], Y. Rito[2], B. Guerrero[1], A. Palomeque[1], C. Teresa[2]
[1]Neurology, University of Southern California, Los Angeles, CA, United States, [2]Neurology, Instituto Nacional de Neurología

y Neurocirugía, Mexico City, Mexico, [3]Preventive Medicine, University of Southern California, Los Angeles, CA, United States

Objective: o compare the clinical characteristics and treatment patterns in Hispanic MS patients residing in Mexico and in Southern USA of Mexican background.
Methods: A total of 424 Mexican and US Mexicans living in southern California participated in separate outcome registries were evaluated. US self-reported Mexican ethnicity (n=170) were abstracted from the registry with similar disease duration to Mexican cases (n=254). The cohort was then stratified by place of birth: US-born, immigrant to the US from Mexico, and Mexican. Clinical and demographic characteristics and disability (measured by EDSS) were compared between the groups using multivariable analysis (ANOVA) with adjustment for multiple testing (Tukey).
Results: There were no significant differences in gender (p=0.91) and disability (p=0.06). Family history of MS was significantly higher in the US-born (14%, p-value=0.005) compared to immigrant (7%) or Mexican (4%). Disease course varied by birth and migration status with greater progressive type of MS in Mexicans (24%) compared to others (9% in immigrants vs. 4% US-born, p =0.005). Compared to US-born and Mexicans, the immigrant had older age of MS onset (7.0-7.3 years on average, 95% CI ranged 4.4-9.7). This difference persisted after limiting the analysis to relapsing MS only and adjusting for gender and family history of MS. We also observed differences in clinical treatment by birth and migrant status. Mexicans were more frequently treated with azathioprine and cyclophosphamide (32%) compared to others (p-value< 0.0001). Clinical presentation also varied significantly (p< 0.001) by birth and migrant status. The initial symptoms for Mexicans were more likely to involve brainstem/cerebellum (47% vs. 19% vs. 19%) compared to US-born and immigrants and less likely to present with visual symptoms (24% vs. 39% vs. 37%, p=0.008) respectively.
Conclusions: Differences in disease course and clinical presentation were observed by birth and migration status, which may reflect differences in ancestry. The treatment differences observed between Mexican patients compared to US-Mexicans may reflect difference in clinical practice and accessibility to treatment to each.

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P850

Adolescent exposure to passive smoking is associated with an increased risk of multiple sclerosis

D.B. Oturai[1], H.B. Søndergaard[1], J.H. Laursen[1], S. Gustavsen[1], J. Tilsted[1], M. Magyari[1,2], E. Just-Østergaard[3], F. Sellebjerg[1], L.W. Thørner[4], H. Ullum[5], A.B. Oturai[1]
[1]Neurology, Danish Multiple Sclerosis Center, Copenhagen University Hospital Rigshospitalet, [2]The Danish Multiple Sclerosis Registry, Department of Neurology, Rigshospitalet, University of Copenhagen, [3]Department of Public Health, Unit of Medical Psycology, Copenhagen University, [4]Department of Clinical Immunology, Blood Bank, Rigshospitalet, University of Copenhagen, [5]Department of Clinical Immunology, Copenhagen University Hospital Biobank Unit, Section for Virology, Copenhagen, Denmark

Background: There is compelling evidence that both genetic and environmental factors confer susceptibility to develop multiple sclerosis (MS). Several studies have indicated that the effect of environmental factors may be especially pronounced in adolescence. Few studies have investigated the association between passive smoking and risk of MS. In this study we focused on the association between passive smoking at home and work during the age of 10-19.
Objectives: To investigate the risk of MS in Danish patients and healthy blood donor controls exposed to passive smoking during adolescence.
Methods: All Participants, included from 2009 to 2014, answered a comprehensive lifestyle-environmental factor questionnaire including questions on passive smoking.MS patients were recruited among 2775 individuals from the Danish MS Biobank, 2058 (74%) responded. The control group consisted of blood donors, recruited from five major donor locations. Two places were able to calculate the response rates of 75% and 90%. In total we have questionnaire data from 7289 individuals (2058 cases and 5231 controls). Of these, 529 were excluded due to other ethnicity than Nordic, 248 for age corrections and 35 due to missing data on passive smoking. Finally 1197 cases and 2077 controls were excluded, because of smoking prior to age 20. Thus, we included 3203 individuals (616 patients and 2587 controls). Data on MS diagnosis was retrieved from The Danish Multiple Sclerosis Registry.Logistic regression models were used to investigate the association between passive smoking at age of 10-19 years and the risk of MS between exposed and non-exposed participants. The association was adjusted for sex, year of birth, smoking after 19 years of age and alcohol intake between ages 15-19. The exposure-response relationship was evaluated by including the number of years exposed to passive smoking in the statistical analyses.
Results: Exposure to passive smoking was associated with an overall increased risk of developing MS with an odds ratio (OR) of 1.34, 95 % confidence interval (CI) 1.15-1.57, p < 0.001. Quantifying the passive smoking by measuring in years of exposure, we found an increased risk of MS (OR 1.02, 95% CI 1.007-1.040, p=0.006) for every additional year of being exposed.
Conclusions: In this study we found that exposure to passive smoking during adolescence is associated with an increased risk of developing MS. Further, the risk increases by every additional year of exposure.

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P852

Alcohol consumption in adolescence is associated with a lower risk of developing multiple sclerosis in Danish women

C. Andersen[1], H.B. Søndergaard[1], J.H. Laursen[1], S. Gustavsen[1], N.K. Larsen[1], M. Magyari[1,2], E. Just-Østergaard[3], L.W. Thørner[4], F. Sellebjerg[1], H. Ullum[5], A.B. Oturai[1]

[1]Neurology, Danish Multiple Sclerosis Center, Copenhagen University Hospital Rigshospitalet, [2]The Danish Multiple Sclerosis Registry, Department of Neurology, Rigshospitalet, University of Copenhagen, [3]Department of Public Health, Unit of Medical Psycology, Copenhagen University, [4]Department of Clinical Immunology, Blood Bank, Rigshospitalet, University of Copenhagen, [5]Department of Clinical Immunology, Copenhagen University Hospital Biobank Unit, Section for Virology, Copenhagen, Denmark

Background: Environmental factors are shown to be important in the aetiology of multiple sclerosis (MS). However, studies of the association between alcohol consumption and MS have shown conflicting results. Due to the possible existence of a vulnerable period of MS susceptibility in adolescence and the fact that Danish teenagers have a high alcohol consumption, the present study has focused on the association between alcohol consumption from age 15 to 19 and the risk of developing MS.

Objective: To investigate the association between alcohol consumption in adolescence and the risk of developing MS in Danes.

Methods: We conducted a case-control study, including Danish patients with MS and healthy Danish blood donors, who filled in a comprehensive environmental and lifestyle questionnaire.

Of 2775 patients with MS, 2058 answered the questionnaire (74 %). The donors were recruited from five major donor locations. Two of these were able to calculate the response rates of 75% and 90%. In total, data from 7289 individuals (2058 cases and 5231 controls) were collected from 2009 to 2014.

Of these, 529 were excluded due to other ethnicity than Nordic, 248 for age corrections and 3 due to missing data on alcohol consumption.

Thus, a total of 1824 cases (1295 females, 529 males) and 4685 controls (2113 females, 2572 males) were included in the analyses. The recommended amount of alcohol intake by the Danish Health Authority is below 7 units per week for women and below 14 for men. We used logistic regression to investigate the association between alcohol consumption above and below the recommendations at age 15 to 19 and the risk of MS. Analyses were stratified by sex and adjusted for selected confounders.

Results: We found a statistically significant inverse association between alcohol consumption at age 15 to 19 and risk of developing MS in females. Females who reported an average consumption above 7 units per week had an odds ratio (OR) of 0.76 (95 % confidence interval (CI): 0.62-0.92) compared to females drinking

below 7 units per week. An insignificant positive association was found among males (OR= 1.27 (95% CI: 0.98-1.63).
Conclusion: We found that alcohol consumption above 7 units per week from age 15 to 19 is associated with a lower risk of developing MS among Danish females.

Disclosure

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Finn Sellebjerg has served on scientific advisory boards for Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva, has been on the steering committee of a clinical trial sponsored by Merck Serono, and served as consultant for Biogen Idec and Novo Nordisk; has received support for congress participation from Biogen Idec, Novartis, Genzyme (Sanofi-aventis) and Teva; has received speaker honoraria from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Schering-Plough. His laboratory has received research support from Biogen Idec, Bayer Schering, Merck Serono, Sanofi-Aventis and Novartis.
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P853

Applying the revised clinical course definitions to describe the phenotype of patients from the Swedish multiple sclerosis register

E. Mentesidou[1], A. Manouchehrinia[2], K. Fink[2], J. Hillert[2]
[1]Karolinska University Hospital, [2]Karolinska Institute, Stockholm, Sweden

Background: Accurately describing the clinical phenotype in multiple sclerosis (MS) is important for communication between clinicians, choice of therapy and study design. In 2014, Lublin et al. published a revision of the existing definition, adding two modifiers: disease activity and disease progression.
Goals: Apply the revised clinical course definition in a number of patients from the Swedish multiple sclerosis register (SMSreg) and describe their new phenotypes.
Methods: SMSreg was used and patients who have been treated with natalizumab were chosen, because of their frequent evaluations. Data used were the clinical visits (recent relapses and EDSS) and radiological evaluations (brain MRI with intravenous gadolinium contrast medium). Data span was from the beginning of therapy until the most recent evaluation. Every clinical evaluation was paired with the chronologically nearest radiological evaluation counting as one follow up. A definition of the phenotype according to the revised clinical course definition was made in each follow up.
Results: 150 patients were chosen from the SMSreg and were followed from the treatment initiation. 109 (72.7%) were female. The mean age at onset of disease was 32.8 years, at the time of diagnosis 37,2 years, and at the time of the first follow up (fo0) in the beginning of the treatment 46.1 years. 119 patients (79.3%) had relapsing remitting MS (RRMS), 24 (16%) had secondary progressive MS (SPMS), 6 (4%) had progressive relapsing MS (PRMS) and 1 (0.7%) had primary progressive MS (PPMS). When the revised definitions were applied at fo0, 98 (65.4%) were RRMS with activity (RRMS-A), 18 (12%) were RRMS without activity (RRMS-NA), 4 (2.7%) were RRMS with indeterminate activity (RRMS-IA), 4 (2.7%) were SPMS without activity but also 19 (12.7%) were SPMS with activity (SPMS-A-IP). At the next follow up (fo1), 48 (49%) of the RRMS-A were defined as RRMS-NA, 37 (37,9%) remained as RRMS-A and the rest converted to SPMS. 90 RRMS-A patients had one more follow up, where there were more patients, 60 (66,6%) who showed no activity comparing to fo0.
Conclusions: Applying the revised criteria for the clinical course definition of MS gives a more dynamic description of the patient's phenotype over time. Describing the presence or absence of activity enables a more accurate definition, which can be changed in every clinical and radiological evaluation. This may contribute to changing the medical decision, e.g. the current treatment.

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Authors report no conflict of interest

P854

Rates of pregnancy among women with multiple sclerosis over time by age, region, and payer type: a US retrospective claims database analysis

M.K. Houtchens[1], N.C. Edwards[2], K. Stern[3], A.L. Phillips[4]
[1]Brigham and Women's Hospital, Harvard Medical School, Brookline, [2]Health Services Consulting Corporation, Boxborough, [3]Boston Health Economics, Inc., Waltham, [4]EMD Serono, Inc., Rockland, MA, United States

Introduction: Data regarding the rates of pregnancy in women with multiple sclerosis (MS) over time are lacking. The objective of this study was to evaluate the rate of pregnancy in women with MS from 2006 to 2014, and to determine how these trends varied with age, region, and payer type.

Methods: A retrospective analysis of women with MS (International Classification of Diseases, Ninth Revision, Clinical Modification code: 340.xx) from IMS Health Real World Data Adjudicated Claims - US data was conducted. The trends in pregnancy rates were assessed by year (2006-2014), age, region, and payer type. Baseline demographic and clinical characteristics were evaluated for women with MS with and without a pregnancy-related claim (diagnosis code or procedure) in the dataset for each year of available data.
Results: The number of women with MS included in the annual study cohorts from 2006 to 2014 ranged from 39,801 to 59,622. The average age of women with MS and a pregnancy-related claim ranged from 32.23 to 32.95 years, whereas the mean age of all women with MS ranged from 45.33 to 46.58 years. The proportion of women with MS and a pregnancy-related claim fluctuated between 2.40% and 2.55% between 2006 and 2011, declined to 2.48% in 2012, and increased to 2.57% in 2014. The proportion of women with MS with a pregnancy-related claim was highest for those aged 25-29 years (range: 11.64-13.62%) and 30-34 years (9.66-11.77%), those living in the Northeast (2.41-2.79%), and those with Medicaid health insurance (2.64-6.76%).
Conclusions: This study demonstrated there was a numerical increase in pregnancy rates in this US population of women with MS from 2006 to 2014. This is in contrast to pregnancy rates for all women in the US, which have steadily declined since 1990. More women with MS in the Northeast, aged 25-29 and 30-34 years, and with Medicaid health insurance had a pregnancy-related claim. This may reflect a change in perceptions regarding pregnancy risks in this patient population.

Disclosure

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Natalie C Edwards is an employee of Health Services Consulting Corporation. Health Services Consulting Corporation received funding from EMD Serono, Inc., to run the analysis.
Kevin Stern is an employee of Boston Health Economics, Inc. (BHE). BHE received consulting fees from EMD Serono, Inc.
Amy L Phillips is an employee of EMD Serono, Inc., Rockland, MA, USA (a business of Merck KGaA, Darmstadt, Germany).

P855

Identification of coping strategies in Multiple Sclerosis

E. James[1], R.J. Mills[2], A. Tennant[3], C.A. Young[4,5], TONiC Study Group
[1]Barts and The London School of Medicine, London, [2]Royal Preston Hospital, Preston, United Kingdom, [3]Swiss Paraplegic Research, Nottwil, Switzerland, [4]Walton Centre NHS Trust, [5]University of Liverpool, Liverpool, United Kingdom

Background: The physical, psychological and social impacts of Multiple Sclerosis (MS) require the patient to develop coping strategies in order to address the adverse outcomes of the disorder. The aim of our study was to identify how coping strategies vary according to demographic and clinical factors.
Method: As part of the UK TONiC study, MS patients completed the Coping Orientation for Problem Experiences Scale (COPE60), consisting of 15 domains of coping skills, along with data on demographic and clinical characteristics. We generated mean frequencies of each coping domain using SPSS22, to compare use between gender, age, disability and disease type using the Mann-Whitney U Test.
Results: 722 patients completed the questionnaire, with an average age of 49 years (17-82); 519 females (71.9%). The most common coping strategies used were Acceptance (mean=7.20, SD=2.94) and Active Coping (6.47, 2.89); the least common were Substance Use (1.05, 2.30) and Denial (2.15, 2.42).

Patients aged < 50 years were found to use more Humour (z=-3.602, p=0.0003) and Substance Use (z=-3.076, p=0.002) as coping strategies; whereas those aged ⩾50 years were more likely to use Religion (z=-3.508, p=0.0005), Restraint (z=-3.739, p=0.0002) and Suppression of Competing Activities (z=-2.38, p=0.017).

Women were more likely to use Focusing on and Venting of Emotions (z=-5.192, p< 0.00001), Religion (-2.014, p=0.044), and both Seeking Instrumental (z=-3.090, p=0.002) and Emotional Social Support (z=-4.732, p< 0.00001). Men used more Humour (z=-2.661, p=0.008) and Acceptance (z=-3.031, p=0.002).

Patients with an EDSS score ⩾7 or who were progressive in their disease course used more Mental (z=-2.380, p=0.17) and Behavioural Disengagement (z=-2.850, p=0.004). Progressive patients were also more likely to use Restraint (z=-2.342, p=0.019) or Religion (z=-2.350, p=0.019), whereas relapsing patients were more likely to Seek Instrumental (z=-2.029, p=0.042) or Emotional Social Support (z=-2.462, p=0.014).
Conclusion: People with MS mainly favour an active, adaptive coping approach. However, different coping strategies are deployed depending on age, gender, disability and between progressive and relapsing patients. Older and more disabled patients are more likely to use an avoidant pattern of coping.
1. Carver CS, Scheier MF, Weintraub JK. Assessing Coping Strategies: A Theoretically Based Approach. J Personal Soc Psych 1989;56(2):267-283

Disclosure

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P856

Psychological distress in Multiple Sclerosis and its correlation with coping strategies

E. James[1], R.J. Mills[2], A. Tennant[3], C.A. Young[4]
[1]Barts and The London School of Medicine, London, [2]Royal Preston Hospital, Preston, United Kingdom, [3]Swiss Paraplegic Research, Nottwil, Switzerland, [4]Walton Centre NHS Trust, Liverpool, United Kingdom

Background: Psychological distress in Multiple Sclerosis (MS) has been shown to influence quality of life. Coping strategies may help mediate the effects of psychological distress. We aimed to identify the prevalence of psychological distress, the effect of gender, and any correlation between psychological distress and coping strategies.

Method: As part of the multi-centre TONiC study, MS patients completed the Hospital Anxiety and Depression Scale (HADS) and the Coping Orientation for Problem Experiences Scale (COPE60). We calculated HADS scores to identify case frequencies using a cut off score of 8 and greater, and compared psychological distress by gender, as well as the effect of psychological distress on coping strategies, using the Mann-Whitney U Test. All analyses were done in SPSS22.
Results: 722 patients completed the questionnaire, with an average age of 49 years (17-82); 519 females (71.9%). Within the cohort there were 326 cases of anxiety (45.2%) and 216 cases of depression (29.9%). There was no gender difference for anxiety or depression.

Patients suffering from anxiety were more likely to use Venting of Emotions (z=-7.663, p< 0.00001), Denial (z=-4.898, p< 0.00001), Mental (z=-6.359, p< 0.00001) and Behavioural Disengagement (z=-6.463, p< 0.00001) and Substance Use (z=-2.837, p=0.05) as coping strategies; whereas those who are not anxious tended to use Positive Reinterpretation and Growth (z=-3.325, p=0.01), Active Coping (z=-3.095, p=0.02), Acceptance (z=-4.377, p=0.00001) and Planning (z=-2.460, p=0.014).

Patients suffering from depression used more Venting of Emotion (z=-4.725, p< 0.00001), Denial (z=-5.427, p< 0.00001), and Mental (z=-7.206, p< 0.00001) and Behavioural Disengagement (z=-7.701, p< 0.00001); whereas those who are not depressed were more likely to use coping strategies such as Positive Reinterpretation and Growth (z=-6.204, p< 0.00001), Active Coping (z=-6.414, p< 0.00001), Humour (z=-3.248, p=0.001), Seeking Emotional (z=-3.938, p=0.001) and Instrumental Support (z=-3.374, p=0.0001), Acceptance (Z=-3.710, p=0002) and Planning (z=-4.972, p< 0.00001).
Conclusion: Anxiety and depression in MS patients and are linked to several maladaptive coping strategies. This highlights the need to address stressors in these patients. These data do not show the directionality of the relationships but ongoing longitudinal analyses in TONiC will provide further data.

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P857

The use of prescription medication by individuals with multiple sclerosis (MS): A population-based linkage study

L.W. Svenson[1,2,3], N. Jette[4], R.A. Marrie[5], H. Quan[6]
[1]Community Health Sciences, University of Calgary, [2]School of Public Health, University of Alberta, [3]Surveillance and Assessment, Alberta Health, Edmonton, [4]Clinical Neurosciences, University of Calgary, Calgary, AB, [5]Department of Internal Medicine (Neurology), University of Manitoba, Winnipeg, MB, [6]Community Health Sciences, University of Calgary, Calgary, AB, Canada

Objective: The objective of this study was to quantify to the use of prescription medications by multiple sclerosis (MS) patients using population-based administrative health data.

Methods: The province of Alberta maintains a publicly funded, universally available health care system. As part of managing the system, the Ministry of Health maintains a number of linkable population-based databases. A case was defined as an individual receiving five or more physician visits or one or more hospitalizations within a two year period. Prescription drugs dispensed were extracted from the Alberta Pharmaceutical Information Network (PIN), which covers more than 95% of all pharmacies, for those with and without MS for the period January 1 to December 31, 2014. Drugs were grouped using the Anatomical Therapeutic Chemical (ATC) coding system into 12 main groups. The analysis was restricted to individuals aged 20 years and older.
Results: There were 9.607 (6,896 females; 2,711 males) MS cases included in the analysis. When adjusting for age and sex, individuals with MS were more likely to fill prescriptions for the following groups: anti-infectives (OR=1.08,95%CI: 1.03, 1.12) alimentary tract (OR=1.14, 95% CI: 1.09, 1.20), blood and blood forming organs (OR=1.15, 95% CI: 1.08, 1.22), genitourinary (OR=1.93, 95% CI: 1.85, 2.02), hormonal (OR=1.08, 95% CI: 1.02, 1.13), musculoskeletal (OR=1.56, 95% CI: 1.50, 1.63), and nervous system (excl. disease modifying therapies; OR=3.21, 95% CI: 3.07, 3.37). Individuals with MS were less likely to fill prescriptions for cardiovascular (OR=0.74, 95% CI: 0.70, 0.78), anti-parasitic (OR=0.80, 95% CI: 0.73, 0.89), respiratory (OR=0.76, 95% CI: 0.72, 0.79), and sensory (OR=0.89, 95% CI: 0.83, 0.95).
Conclusions: Individuals with MS are prescribed a larger number of medications than the general population. An understanding of medication use can help to guide practice to reduce the risk of unintended medication interactions.It can also help with understanding the burden of comorbidities.

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MS and gender

P858

Differential androgenic effects on inflammatory and degenerative processes in neuroinflammation

C. David[1], M.G. Massa[1], S. Jörg[2], J. Berg[1], B. Gisevius[1], S. Hirschberg[1], R.A. Linker[2], R. Gold[1], A. Haghikia[1]
[1]Department of Neurology, Ruhr-University Bochum, Bochum, [2]Department of Neurology, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

Multiple sclerosis (MS) is a presumably T cell-mediated inflammatory disease which is also characterized by early occurring neurodegenerative processes ultimately leading to progressive neurological deficits. In MS, there are apparent sex differences, which may depend upon sex steroid hormone levels. However, while previous research focused on estrogens, little is known about specific androgenic effects. Previous studies demonstrated that androgens may have the ability to affect inflammation and neurodegeneration depending on hormonal concentration, as well as timing and type of stressor. Furthermore, recent research has shown an effect of androgens on T cell differentiation, whose balance is disturbed in MS but crucial for an intact immune system.

In order to investigate putative differential effects of androgens on the inflammatory and neurodegenerative processes relevant in MS pathogenesis, timed hormonal treatments were administered to female C57BL/6J mice after MOG (myelin oligodendrocyte glycoprotein) EAE induction at the age of 8-10 weeks. Clinical disease course as well as histopathological analyses of inflammation and degeneration were investigated. Androgenic effects on T cell-differentiation were examined by extracting naïve T cells from female C57BL/6J mice and subjecting them to Th1- and Th17-polarizing conditions in the presence of androgens. Additionally, MS-patient derived neurons were cultured from induced pluripotent stem cells to perform apoptosis assays after hydrogen peroxide-mediated cell stress to test for testosterone mediated effects on neuronal survival.

Androgenic treatment led to disease amelioration when applied at immunization, but resulted in disease exacerbation when applied in the chronic phase of EAE. These phenotypes were reflected in the histological investigation. When added to Th1- and Th17-polarizing conditions, testosterone led to decreased levels of T cell differentiation ($p < 0.01$). Finally, MS-patient derived neurons were subjected to the stressor H_2O_2, adding testosterone after an incubation time to acquire implications with respect to neuronal death.

Our results provide evidence for a role of androgens in both T cell-modulation and neurodegeneration, thereby reflecting sex differences in MS epidemiology.

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P859

Effect of combined oral hormonal contraceptives to predict a benign course of multiple sclerosis

R. Hernandez-Clares[1,2], E. Carreon-Guarnizo[1,2], M. Cerdan-Sanchez[1,2], J. Jimenez-Veiga[1,2], J.E. Meca Lallana[1,2]
[1]Sclerosis Multiple Unit. Neurology Department. Virgen de la Arrixaca Hospital, [2]Catedra de Neuroinmunologia. Universidad Católica San Antonio., Murcia, Spain

Background: The paradox that multiple sclerosis (MS) is more frequent in women but it manifests more aggressively in men, linked to the changes observed in the disease during female hormonal periods, such as pregnancy, has taken us to study about sexual hormones as the leading cause, due to their close union with the immune system. Combined Oral Hormonal Contraceptives (OHCs), are an exogenous source of sexual hormones used by young women and also a means to study their role in this disease.

MS severity scale (MSSS) is an algorithm that provides the factor of time to the disability produced by the disease, measured by the EDSS. The benign course of the disease is defined as a MSSS < 2.5, equivalent to an EDSS lower than 3, 15 years after diagnosis.

We present a retrospective study to analyze the effect of using contraceptives during MS to predict a benign course of the disease (MSSS< 2.5).

Patients and methods: RRMS patients with an evolution of two years. Clinical, demographical and gynaecological data were collected (onset age, menarche, duration of MS, ARR, maternity and OHCs taking time). Patients were divided into two groups depending on the intake of OHC during MS, not taking (NT) and taking (T).

To study the effect of contraceptives during the disease and of the rest of variables on the benign course of the disease (MSSS< 2.5), a logistic regression was made.

Results: 167 patients: 95 NT (42 MSSS < 2.5), 72 T (54 MSSS< 2.5). Taking contraceptives during MS disease has a significant and direct effect (β=1.35; OR=3.63; p< 0.001) on the benign course of the disease.

Conclusions: In our patients, taking contraceptives during MS disease increases the probability to have a benign course (MSSS< 2.5) compared to never taking them.

Disclosure

Rocío Hernandez -Clares: nothing to declare
Ester Carreon Guarnizo: nothing to declare
Maria Cerdan Sanchez: nothing to declare
Judith Jimenez Veiga: nothing to declare
J. E Meca Lallana: nothing to declare

P860

Menarche and pregnancies are not related with MS activity or long term prognosis

M. Zuluaga[1], S. Otero-Romero[2], B. Pujal[2], L. Negrotto[2], I. Galán[2], G. Arrambide[2], J. Río[2], M. Comabella[2], C. Nos[2], M.-J. Arévalo[2], À. Vidal-Jordana[2], J. Castilló[2], B. Rodríguez-Acevedo[2], L. Midaglia[2], P. Mulero[2], R. Mitjana[3], C. Auger[3], J. Sastre-Garriga[2], Á. Rovira[3], X. Montalban[2], M. Tintoré[2]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, [2]Multiple Sclerosis Centre of Catalonia/ Neuroimmunology Dept & Epidemiology Dept, [3]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Previous studies show increased MS risk in females with early menarche and a possible protective effect of pregnancy in long-term outcomes.

Objective: The aim of this study was to investigate the effect of menarche and pregnancy in the risk of developing MS and disability accrual.

Methods: Clinical, cerebrospinal fluid, and imaging data were prospectively acquired from an ongoing CIS cohort started in 1995. A cross-sectional survey on reproductive information was conducted at follow-up or via e-mail with females of this cohort. We studied the relationship between age of menarche and pregnancy (before

and after CIS) with time to clinically definite MS (CDMS) and to confirmed EDSS 3.0. Uni- and multivariate analyses adjusted by age, CIS topography, oligoclonal bands, baseline lesions and disease modifying treatment initiation were conducted using age at menarche and pregnancy, either as a baseline or time-dependent variable, to size its effect in the risk of CDMS and EDSS 3.0. We also performed sensitivity analyses using the calculated conception date and taking into account pregnancy and abortion after CIS. Finally we confirmed our findings with propensity scores and structural marginal models analyses.

Results: 501 females completed the survey. Age at menarche was not correlated with the age at CIS (p=0.9) nor associated with the time to CDMS (p=0.5) or EDSS 3.0 (p=0.4). Pregnancy before CIS was highly protective for CDMS in the univariate analysis (HR 0.63 95%CI 0.4-0.8, p< 0.05) but this effect was marginal in the multivariate (adjusted HR (aHR) 1.4, 95%CI 1-1.9, p=0.051). Pregnancy before CIS did not modify the risk of EDSS 3.0 (HR 0.96, 95%CI 0.5-1.5, p=0.8 aHR 1.08, 95%CI 0.5-2.1, p=0.8). Pregnancy after CIS was highly protective for both outcomes in the uni- (CDMS HR 0.29, 95%CI 0.1-0.4, p< 0.005; EDSS HR 0.43, 95%CI 0.2-0.7, p< 0.05) and multivariate analyses (CDMS HR 0.32, 95%CI 0.2-0.5, p< 0.05; EDSS HR 0.38, 95%CI 0.1-0.7, p< 0.05) when considered as a baseline variable. The protective effect of pregnancy after CIS disappeared with pregnancy as a time-dependent event (HR 1.0, 95%CI 0.6-1.7, p=0.7; aHR 0.8, 95%CI 0.5-1.3, p=0.5). Propensity scores, sensitivity analyses and structural marginal analyses confirmed these results.

Conclusion: Age of menarche is not related with age at CIS or time to develop MS or disability. Pregnancy before or after CIS did not modify risk of CDMS or disability accrual.

Disclosure

M Zuluaga & C Auger report no conflict of interest related to this work.

M Tintoré has received compensation for consulting services and speaking honoraria from Bayer-Schering, Merck-Serono, Biogen-Idec, Teva, Sanofi-Aventis, Roche and Novartis.

J Río has received speaking honoraria and personal compensation for participating on Advisory Boards from: Almirall; Bayer-Schering Healthcare; Biogen-Idec; Genzyme; Merck-Serono; Novartis; Teva and Sanofi-Aventis

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

A Rovira serves on scientific advisory boards for NeuroTEC and on the editorial board of the American Journal of Neuroradiology and Neuroradiology, has received speaker honoraria from Bayer Schering Pharma, Sanofi-Aventis, Bracco, Merck Serono, Teva Pharmaceutical Industries Ltd. and Biogen Idec, receives research support from Bayer Schering Pharma, and serves as a consultant for 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 with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Pharmaceuticals and Almirall.

Susana Otero-Romero, Berta Pujal, Laura Negrotto, Ingrid Galán, Carlos Nos, María Jesús Arévalo, Angela Vidal-Jordana, Joaquim Castilló, Breogán Rodríguez-Acevedo, Luciana Midaglia, P Mulero, Raquel Mitjana, Cristina Auger report no conflict of interest related to this work.

P861

A review of observational studies of women with MS and pregnancy

M.K. Houtchens[1], N.C. Edwards[2], A.L. Phillips[3]

[1]Brigham and Women's Hospital, Harvard Medical School, Brookline, [2]Health Services Consulting Corporation, Boxborough, [3]EMD Serono, Inc., Rockland, MA, United States

Introduction: Real-world evidence involves patient healthcare data collected outside of the randomised controlled trial environment to provide information on relevant health outcomes in a real-world setting reflective of clinical practice in a large number of patients. This evidence provides insights into unmet needs, interventional pathways, and the clinical impact on patients and the healthcare systems involved. An understanding of the outcomes of women with multiple sclerosis (MS) and pregnancy is essential to improve available clinical support, healthcare services, and quality of life for women with MS of childbearing age. The objective of this study was to conduct a literature review to identify and summarize the observational studies (i.e. prospective cohort studies, retrospective chart reviews, population-based surveys, observational registries, retrospective database evaluations, etc.) that have reported on the outcomes of women with MS and pregnancy.

Methods: We conducted a search of peer-reviewed observational studies for women with MS and pregnancy using the MEDLINE (PubMed) database. Search terms used were 'multiple sclerosis' AND 'pregnancy' AND ('observational' OR 'cohort' OR 'retrospective' OR 'survey' OR 'registry' OR 'database'). Articles were restricted to those published after the year 2000. Reference lists of selected studies were also reviewed for additional literature.

Results: The literature review found that there was a paucity of observational studies reporting real-world outcomes in women with MS and pregnancy (n=39). Approximately half of the studies (n=20) reported on the impact of a specific treatment in MS. Because patients' therapy can vary with time, it is important to understand the outcomes of all women with MS who have pregnancy. Only 19 publications considered all women with MS who have a pregnancy, irrespective of treatment. Nine studies were conducted in Europe, four were from Canada, two each were from the United States and South America, and one each were from Russia and Taiwan. Most evaluated delivery and birth outcomes (n=11), five evaluated outcomes during pregnancy, and four evaluated the impact of pregnancy on MS.

Conclusions: As the demand for evidence to support decision making in women with MS of childbearing age escalates, more data from large observational studies are needed. These studies can provide information about outcomes from large numbers of patients treated in a variety of practice settings.

Disclosure

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Natalie C Edwards is an employee of Health Services Consulting Corporation. Health Services Consulting Corporation received funding from EMD Serono, Inc., to run the analysis.
Amy L Phillips is an employee of EMD Serono, Inc., Rockland, MA, USA (a business of Merck KGaA, Darmstadt, Germany).

P862

Disease activity during pregnancy and pregnancy outcomes in patients with multiple sclerosis (MS) treated with alemtuzumab - A case series from the German MS and pregnancy registry -

K. Gerbershagen[1], S. Thiel[2], V. Limmroth[1], J. Faiss[3], I. Van Loh[4], R. Loos[5], R. Gold[2], K. Hellwig[2]
[1]Hospital Cologne, Cologne, [2]University Bochum, Bochum, [3]Teupitz Hospital, Teupitz, [4]Neurological Center, Kiel, [5]Neurological Center, Alzey, Germany

Background: More than 25% of women with MS and high disease activity experience relapses during pregnancy. Data on MS relapse activity during pregnancy in alemtuzumab treated women are scarce.
Objective:

1. to assess MS disease activity during pregnancy after alemtuzumab treatment.
2. to document pregnancy outcomes in alemtuzumab exposed pregnancies (alemtuzumab < 4 months after the last menstrual period [LMP]).

Methods: 10 women, who received alemtuzumab before pregnancy were prospectively enrolled into the German Multiple Sclerosis and Pregnancy Registry. A standardized questionnaire was administered during pregnancy and postpartum. Detailed information on course of MS and pregnancy, concomitant medications, labor, delivery and outcome of pregnancy was obtained.
Results: 7 pregnancies were exposed to alemtuzumab (median days 50 [1-10]); the remaining not exposed 3 pregnancies became pregnant after a median of 164 days [125-175]). The Mean age at contraception was 29,9 years (SD 4,1). So far six babies are born, one newborn whose mother received the last alemtuzumab 2 months prior to LMP gave birth to a boy with only one kidney and hydronephrosis. Four pregnancies are ongoing and their outcome will be reported at the time of the meeting. No preterm birth occurred. Although the median relapse rate in the year before alemtuzumab was 2 (range 0-5) and 6 women were treated with second line drugs before alemtuzumab, none of our women had a relapse during pregnancy and so far none after delivery.
Conclusion: Depleting antibodies as alemtuzumab might be an interesting option for women with MS and high disease activity, who plan a pregnancy, as the drug itself is cleared shortly after the exposure but the biological effect continues. The only malformation is most probably not related to alemtuzumab (last infusion > 70 days before kidney development). However, more information on the occurrence of secondary autoimmune disorders and the specific interaction with pregnancy is needed.

Disclosure

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P863

PREG-MS: New England Multiple Sclerosis pregnancy prospective cohort study

T.D. Mahlanza[1], D. Sadovnick[2], M. Houtchens[1]
[1]Neurology, Partners MS center, Brigham and Women's Hospital (BWH), Harvard Medical School, Brookline, MA, United States, [2]Medical Genetics and Neurology, University of British Columbia, Vancouver, BC, Canada

Background: Multiple Sclerosis (MS) often affects women at the peak of their reproductive capacity.
Several studies have shown successful reproductive outcomes in women with MS. However, there is a lack of prospective disease-specific, rather then medication-specific, real-world pregnancy registries. There is also a paucity of data related to developmental pediatric outcomes in children born to mothers with MS. Here, we propose a region-specific MS pregnancy study focused on longer-term maternal and pediatric outcomes.
Methods: We developed a data repository that will follow women with MS from any stage of conception to three years post-partum. This prospective cohort investigation will recruit 600 patients from 11 Multiple Sclerosis Clinics and Centers in the New England region of the United States. RedCap database will be used for data processing and storage. The principle site will collect neurologic, obstetric, and pediatric routine care information throughout pregnancy attempts, pregnancy trimesters and for 3 years post partum. Telephone interviews will be conducted every three months during pregnancy and at specified time points post partum. Decoded, de-identified information will be made available for subsequent aggregate analysis.
Results: This unique registry will assess real world practices and outcomes in pregnant MS patients and their children. We expect that maternal outcomes may be influenced by the overall duration off disease-modifying therapy (DMT), lactation choices post-partum, and disease severity pre-partum. We anticipate that pediatric outcomes may be influenced by level of maternal neurologic disability peri-partum, exposure to immune-modulating medications in early pregnancy and socio-economic stressors.
Conclusion: This is the first prospective regional MS pregnancy registry in the United States. Results from this study will contribute to our understanding of maternal and pediatric outcomes in

MS and to the development of effective pregnancy and post-partum management programs in this patient population.

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P864

Pregnancy outcomes of women with MS in a large US claims database

M.K. Houtchens[1], N.C. Edwards[2], J. Aggarwal[3], A.L. Phillips[4]
[1]Brigham and Women's Hospital, Harvard Medical School, Brookline, [2]Health Services Consulting Corporation, Boxborough, [3]Boston Health Economics, Inc., Waltham, [4]EMD Serono, Inc., Rockland, MA, United States

Introduction: Multiple sclerosis (MS) affects women three times more commonly than men, and the clinical onset is often during childbearing years. Although healthcare claims data are collected for administrative rather than research purposes, they can provide insight into outcomes of women with MS and pregnancy in a real-world population. This study aimed to evaluate pregnancy outcomes of women with MS in a large US claims database.
Methods: This was a retrospective analysis of women aged 18-65 years with MS (International Classification of Diseases, Ninth Revision, Clinical Modification code: 340.xx), a pregnancy-related claim (diagnosis code or procedure), and 1 year continuous eligibility pre- and post-pregnancy claim from the IMS Health Real World Data Adjudicated Claims - US database (from 1/1/2006-30/6/2015). Pregnancy outcomes evaluated were: indication of a live birth; complications during pregnancy, labour and delivery, and the puerperium period; ectopic and molar pregnancies; and other abortive outcomes.
Results: A total of 205,466 women with MS were included; 10,630 had a pregnancy claim. Of those, 5022 had 1 year of continuous eligibility pre- and post- pregnancy claim. The mean (standard deviation [SD]) age of women with a pregnancy claim who met the eligibility criteria was 34.3 (8.1) years. Most patients had commercial health insurance (98.1%) and were from the Northeast (32.2%), Midwest (29.9%), or South regions (29.2%) of the US. The mean (SD) Charlson Comorbidity Index score was 0.35 (0.89) pre- and 0.34 (0.87) post-pregnancy claim. Common comorbidities included gastrointestinal disorders (17.6%), depression (14.4%), thyroid disease (14.1%), hypertension (13.5%), anxiety (12.3%), and hyperlipidaemia (10.5%). Over half had a live birth (n=2867; 57.1%). The proportions of women with claims for complications during pregnancy were: diabetes/abnormal glucose test, 12.0%; infection, 8.5%; mental health disorders, 5.0%; hyperemesis gravidarum/vomiting, 5.2%; thyroid disease, 4.2%; pre-eclampsia/eclampsia, 4.2%; and placental problems, 4.0%. The proportions of women with claims during labour and delivery were: malposition/disproportion, 31.9%; forceps/C-section, 8.5%; and haemorrhage, 8.0%. The proportion of women with claims for ectopic and molar pregnancy was 13.0% and for other pregnancy with abortive outcomes was 14.7%.
Conclusions: This study presents pregnancy outcomes of women with MS from a large US administrative claims database.

Disclosure

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Natalie C Edwards is an employee of Health Services Consulting Corporation. Health Services Consulting Corporation received funding from EMD Serono, Inc., to run the analysis.
Jyoti Aggarwal is an employee of Boston Health Economics, Inc. (BHE). BHE received consulting fees from EMD Serono, Inc.
Amy L Phillips is an employee of EMD Serono, Inc., Rockland, MA, USA (a business of Merck KGaA, Darmstadt, Germany).

P865

Levels of serum anti-Müllerian hormone in women with early stage of relapsing-remitting multiple sclerosis

M. Svobodova[1], I. Crha[2], E. Nekvapilova[1], M. Podborska[3], I. Šrotová[1,4], E. Vlckova[1,4], P. Stourac[1,4], J. Bednarik[1,4]
[1]Department of Neurology, University Hospital Brno, [2]Department of Obstetrics and Gynecology, University Hospital Brno, [3]Department of Clinical Biochemistry and Hematology, University Hospital Brno, [4]CEITEC - Central European Institute of Technology, Masaryk University, Brno, Czech Republic

Background: Multiple sclerosis (MS) is a neurological disease mostly affecting women of childbearing age.
Recent studies suggest that MS may have a negative impact on fertility. In general, decreased ovarian reserve is supposed to be one of the most important factors for fertility impairment.
Anti-Mullerian hormone (AMH) is a peptide hormone that represents a simple widely available measure of ovarian reserve unrelated to the menstrual cycle.
Objective: The purpose of this study was to determine AMH levels in females with relapsing-remitting MS (RRMS) in comparison with healthy volunteers.
Methods: A total of 25 reproductive-age females (among 25-36 years) with RRMS and 24 age matched healthy controls were included in this case control study. In females with MS the median EDSS score was 2.5 points, patients received first-line treatment (glatiramer acetat or interferon beta 1a,1b). The median disease duration was 3.1 years.

An enzymatically amplified two-site immunoassay was used to measure serum AMH level.
Results: Mean AMH level was significantly decreased in females with RRMS (1.1 ng/ml) in comparison with healthy controls (2.3ng/ml) ($p < 0.01$). In MS group 13 patients (59%) showed very low AMH values (< 0.4 ng/ml) compared to group of healthy controls. In a group of healthy controls very low AMH was diagnosed in 2 patients (9%) only ($p < 0.01$).
Conclusions: Our data show that decreased ovarian reserve is frequently found in MS patients even in early stages of the disease and may represent one of the underlying mechanisms of fertility impairment in MS.

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Stourac P: nothing to disclose
Bednarik J:nothing to disclose

MS symptoms

P866

Multiple sclerosis and cognitive function: the influence of change in depression and subjective cognitive fatigue on change in cognitive function in people with multiple sclerosis

D. Golan[1,2], O. Calisi[3], M. Gudesblatt[3], K. Wissemann[3], M. Zarif[3], B. Bumstead[3], L. Fafard[3], C. Sullivan[4,5], J. Wilken[4,5], K. Blitz[3], M. Buhse[3,6], G. Doniger[7]
[1]Department of Neurology, Carmel Medical Center, [2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel, [3]South Shore Neurologic Associates, Patchogue, NY, [4]Neuropsychological Associates, Fairfax, VA, [5]Georgetown University Hospital, Department of Neurology and Washington Neuropsychology Research Group, Washington, DC, [6]Stony Brook University, Stony Brook, NY, [7]NeuroTrax Corporation, Bellaire, TX, United States

Background: Multiple Sclerosis (MS) impacts cognition, and patient reported fatigue and depression in a complicated manner that is dynamic and evolves. Most prior studies of the association between subjective cognitive fatigue, depression and objective cognitive dysfunction in patients with MS (PwMS) were cross sectional, thus precluding causal inference.
Objective: To explore how subjective patient reported outcomes (PRO) of cognitive fatigue and depression change over time relate to changes in cognitive function in a large cohort of PwMS.
Methods: PwMS completed a standardized computerized cognitive assessment battery (NeuroTrax) with analysis of age- and education-adjusted cognitive domain scores (memory, executive function, visual spatial, verbal function, attention, information processing, motor skills) and completed PRO metrics in the course of routine clinical care. Cognitive fatigue impact (cognitive subscale of the Modified Fatigue Impact Scale) and depression (Beck Depression Inventory questionnaires) were evaluated respectively. Analysis was repeated after a time interval of 2-53 months, for each patient.
Results: 369 test-retest pairs from 282 PwMS [Female: 220 (78%0, EDSS 2.6±1.9, Education years: 15±2.8]. Both subjective cognitive fatigue and depression were significantly and negatively correlated with the same cognitive domains: memory, executive function, attention, information processing and motor function. Therefore, a fatigue and depression sensitive global cognitive score (FDS-GCS) was defined as the average of these sub-scores. Change in depression was significantly and negatively associated with change in FDS-GCS (r=-0.14, P=0.006) but change in subjective cognitive fatigue was not associated with FDS-GCS change. Change in depression explained only 2% of the variance of change in cognitive scores.
Conclusion: PwMS-PRO Depression could account for only a small degree of the variance in cognitive scores evolution over time. Changes in cognitive scores of PwMS over time, as assessed by NeuroTrax computerized battery, should not be generally ascribed to changes in depression or to changes in fatigue.

Disclosure

Glen Doniger is an employee of NeuroTrax Corporation

P867

Multiple sclerosis and cognitive function: evolution of cognitive function over time in people with multiple sclerosis

D. Golan[1,2], S. Zarif[3], M. Gudesblatt[3], K. Wissemann[3], M. Zarif[3], B. Bumstead[3], L. Fafard[3], C. Sullivan[4,5], J. Wilken[4,5], K. Blitz[3], M. Buhse[3,6], G. Doniger[7]
[1]Department of Neurology, Carmel Medical Center, [2]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel, [3]South Shore Neurologic Associates, Patchogue, NY, [4]Neuropsychological Associates, Fairfax, VA, [5]Georgetown University Hospital, Department of Neurology and Washington Neuropsychology Research Group, Washington, DC, [6]Stony Brook University, Stony Brook, NY, [7]NeuroTrax Corporation, Bellaire, TX, United States

Background: Cognitive impairment is common in patients with Multiple Sclerosis (PwMS). Cognitive impairment in PwMS can impact employment, driving, fall risk, Quality of Life (QoL). Cognitive impairment may be present and vary independently of EDSS or changes in EDSS. Few studies to date assessed the evolution of cognitive function over time in PwMS.
Objective: To explore how cognitive function changes over time in a large cohort of PwMS.
Methods: PwMS completed a standardized computerized cognitive assessment battery (NeuroTrax) with analysis of cognitive domain scores (memory, executive function, visual spatial, verbal function, attention, information processing, motor skills). The average of these domain scores was defined: global cognitive score (GCS). NeuroTrax domain scores are normalized to an IQ-style scale (mean: 100, SD: 15) in an age- and education-specific fashion by comparing the subject's specific achievements to normative data of individuals classified as cognitively healthy. Cognitive domain score < 85 was considered impaired. This procedure was repeated after a time interval of 2-52 months, for each patient.
Results: There were 369 test-retest pairs from 282 individuals with MS [Female: 220 (78%), EDSS 2.6±1.9, Education years: 15±2.8]. The average change in GCS was 2±7.3, implying that 70% of the re-test results remained stable within ±0.5SD from initial scores. The average number of impaired cognitive domains on initial testing was 1.4±1.9. 180 (48.85) test-retest pairs had no change in the number of impaired domains, the others had either increased or decreased number of impaired cognitive domains upon re-test (range: 1-6).
Conclusion: Changes in cognitive function with time of PwMS were detected by NeuroTrax. The clinical significance of these changes and their relationship to MS disease activity and treatment are being elucidated. This method of objective examiner independent analysis might provide information relevant to patient care as an adjunct to EDSS and MRI.

Disclosure

Glen Doniger is an employee of NeuroTrax Corporation

P868

Prevalence of periodic limb movements during sleep among multiple sclerosis patients: potentially beneficial effect of baclofen

P. Repovic, L. Fine
Swedish Neuroscience Institute, Seattle, WA, United States

Objective: While association of multiple sclerosis (MS) and restless leg syndrome is well-documented, relatively little is known about the prevalence of periodic limb movements during sleep (PLMS) in MS.
Methods: Polysomnography data from 99 patients with MS (73% women, mean age= 52+/-12 years) in routine clinical practice was retrospectively analyzed for the presence and frequency of PLMS. MS duration since diagnosis, use of disease-modfying therapy, and other concurrent medications were recorded. PLMS index was determined, with values greater than 5 per hour considered as significant.
Results: 41 (43%) of the patients exhibited PLMSI >5. Higher PLMSI was associated with increased age (p=0.02), but not duration of disease (p=0.171). No relationship was found between PLMSI and any disease-modifying therapy. Use of baclofen was associated with significantly lower rates of PLMS (χ^2=9.35, p=0.002). Gabapentin use showed a similar trend, but did not reach statistical significance. Use of tizanidine, ropinirole, pramipexole was not associated with PLMSI.
Conclusions: Prevalence of PLMS in MS population is higher than among healthy controls, and is correlated with older age, but not duration of disease. Baclofen use was associated with lower rates of PLMS in MS populations, suggesting a potential therapeutic benefit, that should be confirmed in a prospective clinical trial setting.

Disclosure

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P869

Distinct patterns of fatigue and sleep dysfunction by MS phenotype and disability level

R.J. Mills[1], A. Tennant[2], C.A. Young[3], TONiC Study Group
[1]Neurology, Lancashire Teaching Hospitals Trust, Preston, United Kingdom, [2]Swiss Paraplegic Research, Nottwil, Switzerland, [3]Neurology, Walton Centre NHS Trust, Liverpool, United Kingdom

Background: Previous work has demonstrated that fatigue in multiple sclerosis (MS) increases with disability level and is worse in those with progressive disease and also varies with duration of nocturnal sleep, but is not clearly related to disease duration. However, little is known about these relationships within disease subtypes or disability bands (EDSS).
Objective: To assess parameters of fatigue and sleep dysfunction in different sub-populations of MS.
Method: Fatigue was assessed by administration of the Neurological Fatigue Index (NFI-MS) and sleep dysfunction by the Neurological Sleep Index (NSI-MS) in patients with clinically definite MS as part of the TONiC study, a multicentre, UK study of factors affecting quality of life in MS. Summed raw scores were converted to interval level data by application of the Rasch measurement model. Non-linear relationships were visualised with local polynomial regression fit.
Results: 1509 records were available for analysis. 73% were female, 69% had relapsing (RR), 9% primary progressive (PP) and 22% secondary progressive (SP) disease. 48% were fully ambulatory. There was a striking divergence in fatigue levels: clearly there was an increase in fatigue once ambulation was affected for those PP and RR disease, but the relationship was lost for those with SP disease with little variation seen across disability level. In the lowest EDSS band, PP subjects had the lowest levels of fatigue (particularly cognitive fatigue). Sleep became more restorative in SP patient at higher EDSS band less fragmented when compared to PP. All disease subtypes had the same, V shaped relationship between hours of nocturnal sleep and fatigue and the non-restorative nature of nocturnal sleep. Complex relationships, again divergent between disease subtypes, were seen between both fatigue and sleep parameters and disease duration.
Conclusion: The large scale of the TONiC study has allowed subgroup analysis of the relationships between fatigue, sleep dysfunction and clinical features of MS such as disease type, disability level and disease duration. Clear relationships could be seen but they were complex and non-linear. However, it was evident that relapsing disease modifies any subsequent progressive phase to behave differently from primary progressive disease in terms of fatigue and sleep dysfunction, but this is not simply a function of disease duration.

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A. Tennant has nothing to declare.

P870

Dynamic mobility deficits in people with multiple sclerosis: a systematic review and meta-analysis

L. Comber, R. Galvin, S. Coote
Clinical Therapies, University of Limerick, Limerick, Ireland

Background: Multiple Sclerosis (MS) results in postural instability and dynamic mobility deficits. Such impairments are associated with an increased likelihood of falls; as such an understanding of these deficits will inform both assessment and treatment.
Objective: This systematic review and meta-analysis aims to quantify the effect of MS on dynamic mobility to inform the development of falls prevention interventions.
Methods: A systematic search of the literature identified case-control studies investigating differences in variables between people with MS and healthy controls. Search terms were based on

previous literature relating to similar topics and expert opinion. Meta-analysis examined the effect of MS on dynamic mobility under normal and accelerated pace conditions.

Results: Forty-one studies of people with Expanded Disability Status Scale (EDSS) 1.8 to 4.5 were included of which 32 contributed to meta-analysis. A large effect of MS was found on stride length (Standardised Mean Difference, SMD=1.27, 95% CI{0.93, 1.61}, p< 0.00), velocity (SMD= 1.12, 95% CI{0.85, 1.39}, p< 0.00), double support duration (SMD=0.85, 95% CI{0.51, 1.2}, p< 0.00), step length (SMD=1.15, 95% CI{0.75, 1.5}, p< 0.00), stance phase (SMD=0.96, 95% CI{0.36, 1.57}, p=0.002) and swing phase duration (SMD=1.23, 95% CI{0.06, 2.41}, p=0.04). A moderate effect was found on step width (SMD=0.65, 95% CI {0.36, 0.94}, p< 0.00), single support duration (SMD=0.78, 95% CI {0.35, 1.21}, p< 0.00) and stride time (SMD=0.56, 95% CI {0.35, 0.76}p< 0.00). with the smallest effect found on cadence (SMD=0.43, 95% CI {0.14, 0.72}p=0.004). All effect sizes increased for variables investigated under an accelerated walking pace (for example the effect on cadence increased to SMD=1.15, 95% CI {0.42, 1.88}, p=0.002).

Conclusions: MS has a significant effect on dynamic mobility even for those with relatively low EDSS. This effect is amplified by increasing pace suggesting this condition may be more pertinent for assessment and treatment. Further investigation relating to the predictive or protective nature of these deficits in relation to falls is warranted.

Keywords: Multiple Sclerosis; Mobility Limitations; Gait; Accidental Falls; Postural Balance

Disclosure

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P871

Cognition, fatigue and health-related quality of life in patients with multiple sclerosis: results from a european-wide study

G. Kobelt[1], J. Berg[2], M. Gannedahl[2], J. Eriksson[2], A. Thompson[3], MS BOI Study Group
[1]European Health Economics, Mulhouse, France, [2]Mapi, Stockholm, Sweden, [3]University College London, London, United Kingdom

Background: The effect of multiple sclerosis (MS) on physical functioning has been well studied, and the Expanded Disability Status Scale (EDSS) shows strong correlation with costs and health-related quality of life (HRQoL). The additional effect of mental and psychological factors on overall well-being is less well documented.

Objectives: The main study objective was to collect current information on the burden of illness of MS across Europe. Here we investigate cognition and fatigue in MS and their effect on HRQoL at all disease stages.

Methods: 16,400 patients from 16 countries provided cross-sectional data on demographics, disease severity, relapses, disease symptoms and their impact on productivity, resource use and HRQoL. Cognition and fatigue were assessed using visual analogue scales (VAS; 0=no problems, 10=extreme problems). The impact of MS on productivity was assessed with descriptive questions. HRQoL was measured with the EQ-5D and responses were evaluated for the individual domains and translated to utility weights (1=perfect health, 0=death).

Results: In the first 13,844 patients from 10 countries, mean age was 52±12 years, 74% women, 42/35/21% had EDSS 0-3/4-6.5/7-9, and 12% overall had experienced a relapse in the last 3 months. Cognitive problems and fatigue were present at all disease severity levels. 73% of patients reported cognitive problems, with mean VAS scores of 4.4±2.1 at EDSS 0-3, 4.9±2.1 at EDSS 4-6.5 and 5.3±2.3 at EDSS 7-9. Mean VAS scores for fatigue within the last 48 hours, reported by 98%, were 5.0±2.5, 5.9±2.2, and 6.0±2.4, respectively. A VAS score of ⩾5 was reported by 40% for cognitive problems and by 69% for fatigue. Among employed patients, 79% felt that their productivity at work was reduced, with fatigue being the most common reason (81%); cognition was mentioned by 42%. The most affected HRQoL dimensions were pain/discomfort (77% reporting problems), usual activities (74%) and mobility (72%). Mean utility ranged from 0.9±0.1 at EDSS 0 to -0.2±0.2 at EDSS 9. Both fatigue and cognitive problems showed moderate negative correlations with utility (r=-0.385 and -0.335, p< 0.001, respectively).

Conclusion: In this large European sample of MS patients covering the entire disease severity spectrum a majority experienced fatigue and cognitive problems. While HRQoL deteriorated with advancing disease, fatigue and cognitive problems were present at all disease severity levels and impacted HRQoL significantly.

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Mia Gannedahl: working for consultancy performing projects for pharmaceutical companies
Jennifer Eriksson: working for consultancy performing projects for pharmaceutical companies
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P872

Influence of cognitive impairment and depression on cortical thinning in patients with multiple sclerosis

L. Cacciaguerra[1], M.A. Rocca[2], P. Valsasina[2], E. Pravatà[3], G.C. Riccitelli[2], P. Preziosa[2], G. Comi[4], A. Falini[5], M. Filippi[2]
[1]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, [2]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience,, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, [3]Department of Neuroradiology, Neurocenter of Southern Switzerland, Lugano, Switzerland, [4]Department of Neurology, [5]Department of Neuroradiology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Aims: To investigate cortical thickness abnormalities associated with cognitive impairment and depression in a large cohort of MS patients.
Methods: High-resolution T1-weighted scans were acquired from 126 MS patients and 59 matched healthy controls. Patients with at least two abnormal tests at the Brief Repeatable Battery of Neuropsychological Tests were considered cognitively impaired (CI). Patients were classified as depressed (D) if their Montgomery-Asberg Depression Rating Scale score was >9. Differences of cortical thickness between controls and MS patients and between patient subgroups were assessed using FreeSurfer.
Results: Sixty-five MS patients (51%) were classified as D, while 34 MS patients (27%) were CI. Fifteen patients had the concomitant presence of depression and cognitive impairment (12%). Compared with controls, MS patients exhibited a widespread bilateral cortical thinning involving all brain lobes. Compared with CP, CI MS patients had decreased cortical thickness in several bilateral regions of the frontal, temporal and parietal lobes. Compared with non-D, D MS patients had cortical thinning of the frontal and temporal lobes. Cognitive impairment had a selective effect on cortical thinning of the bilateral superior frontal gyrus, bilateral superior parietal lobule, left entorhinal cortex and right precuneus, whereas depression affected cortical thinning of the bilateral orbitofrontal cortex and right temporal pole.
Conclusions: Cortical thickness analysis is able to detect specific effects of clinical symptoms on cortical atrophy in MS. While cognitive impairment seems to be associated with atrophy of regions located in the fronto-parietal lobes, depression is linked to atrophy of the orbitofrontal cortex.
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Disclosure

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Prospective evaluation of movement disorders in early multiple sclerosis and other CNS demyelinating diseases

H. Abboud[1,2], H.H. Fernandez[3], X.X. Yu[3], J.A. Cohen[1]

[1]Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH, United States, [2]Neurology, Alexandria University, Alexandria, Egypt, [3]Center for Neurological Restoration, Cleveland Clinic, Cleveland, OH, United States

Background: Movement disorders (MDs) are traditionally thought to be uncommon in multiple sclerosis (MS). However, several retrospective reports suggest that MDs secondary to brain and cord demyelination are not as rare as once thought.
Objective: To prospectively evaluate the incidence and clinical characteristics of MDs in early MS and other CNS demyelinating diseases.
Methods: A consecutive sample of patients attending the MS clinic was prospectively evaluated within a 10-month-period from July 2015 to April 2016. Patients who were diagnosed over 5 years before the study start date were excluded along with patients in whom a demyelinating CNS disease was not confirmed. Each eligible patient was interviewed by a movement disorder neurologist who conducted a standardized MDs survey and a focused exam. Each patient was followed prospectively for at least 1 and up to 4 follow up visits. Patients with MDs identified on clinical exam were video-recorded and videos were independently rated by a separate blinded movement disorders neurologist.
Results: Forty four patients were included (45% female, mean age=38.6+/-13.2). Of the entire cohort 82% reported 1 or more MDs, 68% developed the MD(s) after disease onset with or shortly after a well-defined clinical relapse, and only 43% had positive findings on the focused MDs exam. Patients whose MDs started exclusively before disease onset and/or thought to have a separate etiology for their MDs (e.g. essential tremor) were excluded from further analysis. In the remaining patients, the MD(s) started 6 months following a relapse on average but in 6 patients it was the presenting symptom of a new relapse or the disease itself. The majority of MDs occurred secondary to spinal relapses (63.3%), cerebellar/brainstem relapses (23.3%), or both (11.2%). MDs secondary to basal ganglia lesions occurred in only 1 patient. The most common MDs reported were: new onset RLS (16), tremors (13), tonic spasms (13), myoclonus (13), fasciculations (12), spontaneous clonus (8), focal dystonia (6), pseudoathetosis (4), hyperkeplexia (4), and hemifacial spasm (2). MDs-directed treatment was required in only 13 patients.
Conclusion: Movement disorders may be more common than previously thought even in the early stages of MS and other CNS demyelinating diseases. They typically begin a few months after spinal or cerebellar relapses but on rare occasions, may be the presenting symptom of the disease.

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P874

The CIRCLES program: accelerating solutions to neuromyelitis optica spectrum disorder

L.J. Cook[1], J.W. Rose[2], A.M. Jolley[1], J. Alvey[1], R. Kuhn[1], M. Pederson[1], M. Han[3], M. Levy[4], M. Mealy[4], J. Bennett[5], R. Carruthers[6], A. Traboulsee[6], M. Kenneally[7], D. Behne[7], R. Rodriguez[7], D. Blackway[7], B. Coords[7], T. Blaschke[8], T.J. Smith[9], M.R. Yeaman[10], J. Behne[7], the Guthy-Jackson Charitable Foundation International Clinical Consortium (GJCF-ICC)
[1]Pediatrics, [2]Neurology, University of Utah, Salt Lake City, UT, [3]Neurology, Stanford University, Palo Alto, CA, [4]Neurology and Neurosurgery, Johns Hopkins University, Baltimore, MD, [5]Neurology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States, [6]Medicine, University of British Columbia, Vancouver, BC, Canada, [7]The Guthy-Jackson Charitable Foundation, San Diego, [8]Internal Medicine and Molecular Pharmacology, Stanford University Medical Center, Stanford, CA, [9]Internal Medicine, University of Michigan Health System, Ann Arbor, MI, [10]Infectious Diseases, UCLA David Geffen School of Medicine, Los Angeles, CA, United States

Background: Neuromyelitis Optica Spectrum Disorder (NMOSD) is a rare autoimmune disease that frequently causes serious neurological disability. Generation of pathogenic antibodies targeting the water channel, aquaporin 4 (AQP4) is the hallmark of seropositive NMOSD. Many uncertainties remain concerning etiology, epidemiology, pathogenesis, and long-term outcomes. These unmet needs and the imperative to improve therapeutic options motivated the creation of a patient registry and biorepository devoted to solving NMOSD.
Methods: The Collaborative International Research in Clinical and Longitudinal Experience for NMOSD Studies (CIRCLES) registry and biorepository was established through consensus. Using a standardized protocol, patients with NMOSD or comparative controls were recruited into the CIRCLES program through clinical centers and patient advocacy events at five geographically dispersed sites across North America beginning in November 2013. At six-month intervals, demographic information and medical history were collected, including disease phenotype, comorbidity, medication, vaccination, environmental exposure, and activities of daily living. Biospecimens were collected and archived at each interval.
Results: As of April 2016, 562 participants have been enrolled: 440 NMOSD cases and 123 controls (25 comparative disease [21%] and 96 healthy individuals [79%]). Demographic features observed include: gender ratio, 6.1:1 (86% female); median age at enrollment, 43.6 (IQR 32.1, 55.2); racial distribution, 275(63%) white; 76(17%) black/African American; 41(9%) Hispanic/Latino; 37(8%) Asian; 10(2%) other. Biospecimens have been collected on 93% of cases and 97% of controls. Among cases, 82 (19%) have two longitudinal biospecimens, and 61 (14%) have three or more. Preliminary analyses show that compared to healthy controls, NMOSD patients are more likely to have a first degree blood relative diagnosed with an autoimmune disease (49% vs. 37%; P=0.02).

Interpretation: CIRCLES represents a robust registry and biorepository created using standardized methods to facilitate consistency in studying NMOSD. This program has already begun to offer new hypotheses intended to promote solutions to NMOSD.

Prospectus: As CIRCLES expands in geographic diversity and temporal experience, its impact on understanding NMOSD should increase. Thus, the CIRCLES program will accelerate solutions to NMOSD by providing a unique and much needed resource for all NMOSD stakeholders.

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Michael Yeaman is an associate editor for PLoS Pathogens, and study section reviewer for the U.S. National Institutes of Health; holds patents for vaccines and immunotherapies targeting drug-resistant pathogens & infections, anti-infective biologicals, and anti-infective small molecules; is Founder and 170 shareholder of NovaDigm Therapeutics; is Founder and shareholder of Metacin, Inc.; has received research support from the United States

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P875

oculomotor synkinesis in multiple sclerosis

G. Castelnovo[1], E. Nerrant[2], D. Renard[3], L. JeanJean[4], E. Thouvenot[5]
[1]Neurology, CHU Caremeau, NIMES, [2]Neurology, CHU Guy de Chauliac, montpellier, [3]Neurology, CHU CaremeauCaremeau, [4]Ophtalmology, [5]Neurology, CHU Caremeau, Nimes, France

Introduction: To describe oculomotor synkinesis in multiple sclerosis (MS) patients
Background: Acquired oculomotor synkinesis has been most frequently observed in association with intracranial aneurysm, trauma, compressive neoplasms, midbrain ischemic and hemorragic stroke, and idiopathic third nerve palsy. We report five MS patients presenting stereotyped oculomotor synkinesis
Case reports: We report five MS patients (three patients with relapsing-remitting MS and two patients with secondary progressive MS) presenting stereotyped oculomotor synkinesis characterised by bilateral droping eyelid during horizontal eye movements (saccades and smooth pursuit).

In all patients, MRI revealed demyelinating paramedian midbrain lesions.
Discussion: Ocular motor disorders (OMDs) are a common feature of MS, most frequently consisting of impaired smooth pursuit, saccadic dysmetria, or internuclear ophthalmoplegia. To the best of our knowledge, these are the first case reports of oculomotor synkinesis in MS patients. We suspect ephaptic neuron transmission inducing inhibition of the unpaired central caudal subnucleus during horizontal eye movements as probable explanation for oculomotor synkinesis in these patients.
Conclusion: Oculomotor dyskinesis, probable due to the presence of a demyelinating mesencephalic lesion, is one of the OMDs that can be observed in MS.

Disclosure

We have no conflict of interest to declare

P876

Hemifacial spasm and continuous facial myokymia in Multiple Sclerosis: A descriptive study on clinical features and treatment outcomes

I.V. Marin Collazo, W.O. Tobin
Neurology, Mayo Clinic, Rochester, MN, United States

Background: Hemifacial spasm and facial myokymia have been associated with multiple sclerosis, however their etiology and clinical outcome is uncertain.
Objective: To describe clinical and radiological features, along with treatment outcomes of patients with hemifacial spasm and facial myokymia associated with multiple sclerosis.
Methodology: Thirty-six patients with a diagnosis of multiple sclerosis and hemifacial spasm (7) or facial myokymia (29) seen at Mayo Clinic (Rochester, Minnesota, USA) between 1996 and December 2015 were identified by chart review. Case histories; radiologic and electrodiagnostic reports were reviewed.
Results: Twenty five women and eleven men with a median age of 40 (17-66 years old) were reviewed. MS disease duration at the time of symptom onset was 5 and 2 years in cases of FM and HFS, respectively. Clinical course was relapsing remitting MS (75%), secondary progressive MS (17%), and primary progressive MS (3%). A pontine lesion was visible in 83% of cases with brainstem lesions on MRI (14/36). Patients with facial myokymia were treated with steroids (13/29; with benefit in 11/13), carbamazepine (1/29; with benefit in 1/1) and gabapentin (1/29; with benefit in 1/1). Patients with hemifacial spasm were treated with steroids (2/7; with benefit in 1/2), oxcarbazepine (1/7; with benefit in 1/1), carbamazepine (1/7; with benefit in 0/1), gabapentin (1/7; with benefit in 1/1) and botulinum toxin injection (3/7; with benefit in 1/3). Facial myokymia resolved in 26/27 of cases within ten days to three months. One patient had intermittent myokymia for years. Hemifacial spasm resolved in 4/7 patients within 3 months to 7 years. Two patients had persistent hemifacial spasm for up to seven years.
Conclusion: Hemifacial spasm and facial myokymia are more common in relapsing remitting MS when compared to progressive MS. Pontine demyelinating lesions are common. Steroids treatment was associated with symptom improvement in the majority of cases of facial myokymia. Regardless of treatment, the majority of patients with facial myokymia had symptom resolution within 3 months. Botulinum toxin injection treatment was given in cases of hemifacial spasm with partial to good clinical response but other treatments including: intravenous steroids and oral medications could be alternatives.

Disclosure

Nothing to disclose.

P877

Meige syndrom as a first relapse of multiplesclerosis

S.A. Hatteb, S. Daoudi
Faculty of Medicine, Tizi Ouzou University, Tizi Ouzou, Algeria

Background: Multiple sclerosis is an inflammatory demyelinating disease of central nervous system characterized by dissemination of the lesions in time and space. MS evolution is rarely punctuated by the occurrence of movement disorders, except for cerebellar tremor. we report in this context a Meige syndrom revealing the disease.
Observation: A young woman aged 36 years, presented with headache, hemifacial numbness and involuntary movements interesting first left eyelid, then both. Examination showed bilateral spasms in the frontal and orbicularis muscles of the eyelids predominantly on left side making a blepharospasm. These

movements appeared to be exagerated by emotion and also to exposure to light. The examination showed the extension of spasms to the platysma muscle neck on left side and exagerated tendon reflexes. Brain MRI showed T2 and T2 Flair disseminated nodular lésions fulfilling McDonald 2010 criteria. one T2 lesion was located in midbrain. Cerebrospinal fluid (CSF) analysis showed oligoclonal bands of IgG.

Complete regression of blepharospasm with neck spasm and headache was obtained after a five-day infusion of methylprednisolone (1 g / day).

The diagnosis of multiple sclerosis (MS) was made according to the McDonald criteria 2010, after exclusion of other possible causes including infectious, autoimmune, metabolic or toxic.

Discussion: Occurence of movement disorders and MS may be coincidental or really caused by disease. In our case, MRI scans showed a midbrain demyelinating lesion, providing a potential link between symptoms and the autoimmune disorder, also suggested by oligoclonal IgG synthesis in CSF. About abnormal facial movement, blepharospasm are rarely described, but it is to our knowledge the first description of an MS case in which the sole primary manifestation was a Meige syndrome

Conclusion: Meige syndrom is a particular form of abnormal facial movement whose etiopathogenic bases remain unknown. its occurrence during MS is exceptional. In our case, there seems radiological correlation between symptoms and MRI scans. The other causal argument would be rapid and complete response to corticosteroids.

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P878

Cognitive impairment of Chinese patients with multiple sclerosis and neuromyelitis optica

S.S.T. Leung, K.H. Chan
Medicine, The University of Hong Kong, Hong Kong, Hong Kong

Introduction: Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are important central nervous system inflammatory demyelinating disorders. Cognitive impairment is increasingly recognized in both MS and NMOSD.

Methods: We studied cognitive functions of Chinese MS and NMOSD patients followed up in QMH by using a Chinese version of Rao's Brief Repeatable Battery of Neuropsychological Tests (BRBN). The BRBN consists of five groups of tests: 1) Symbol Digit Modalities Test (SDMT) and 2) Paced Auditory Serial Addition Test (PASAT) for sustained attention, concentration and speed of information processing, 3) Selective Reminding Test (SRT) for verbal immediate and delayed recall memory, 4) 10/36 Spatial Recall Test (SPART) for spatial immediate and delayed recall memory, and 5) Word List Generation Test (WLG) for verbal fluency on semantic stimulus; yielding total 9 test scores. An abnormal score is defined as below the fifth percentile of the normative value derived from healthy subjects. Patients with abnormal scores in 3 or more tests were diagnosed as having cognitive impairment.

Results: 30 healthy subjects (16 men, mean age 37.3 years, range 21-56), 17 NMOSD patients (15 women, mean age 47 years, range 28-69) and 21 MS patients (14 women, mean age 40.5 years, range 18-59) were studied. The mean disease duration was 80.5 months, the mean latest EDSS score was 2.7, 13 (76.%%) were AQP4 antibody +ve and 10 (58.8%) had MRI brain abnormalities for the NMOSD patients. The mean disease duration was 141.7 months and the mean latest EDSS score was 3.5 for the MS patients. Among the 17 NMOSD patients, 5 (31.3%) had impaired SDMT, 6 (35.3%) had impaired SRT, 7 (41.2%) had impaired SPART, 7 (41.2%) had impaired PASAT and 7 (41.2%) had impaired WLG. Overall, 8 NMOSD patients (47.1%) had cognitive impairment. Among the 21 MS patients, 15 (71.4%) had impaired SDMT, 10 (47.6%) had impaired SRT, 9 (42.9%) had impaired SPART, 14 (66.7%) had impaired PASAT and 14 (66.7%) had impaired WLG). Overall, 15 MS patients (71.4%) had cognitive impairment.

Conclusion: Cognitive impairment is common among NMOSD and MS patients.

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Clinical assessment tools

P879

Dual-tasking in multiple sclerosis - evidence for lower response selection capacities

C. Beste, M. Mükschel, M. Paucke, T. Ziemssen
University Hospital Dresden, Dresden, Germany

Background: The monitoring of cognitive functions is central to the assessment and consecutive management of MS, but especially cognitive processes central to everyday behavior, like dual-tasking, are less recognized.

Objective: To assess dual-tasking in MS using a clinically applicable computer-based method.

Methods: Dual-task performance was examined using a psychological-refractory period (PRP) task in N =21 patients and healthy controls, together with standard neuropsychological tests. In the PRP task, the difficulty of dual-tasking was scaled.

Results: MS patients performed worse on the dual-task in that they committed more response errors when dual-tasking was difficult. This means when dual tasking was difficult and the two task close presented to each other (gap of 16ms), controls committed fewer errors (10.81 ± 1.71) than MS patients (19.00 ± 12.98; $t(40) = 2.48$; $p = .018$; $d = .78$). The same was the case by slightly increasing the time gap between tasks (i.e. 133ms);, controls committed less errors (8.86 ± 1.75) than patients (16.76 ± 2.45; $t(40) = 2.63$; $p = .012$; $d = .83$). There were, however, no differences when both tasks were separated by more than half a second ($t(40) > .999$; $p > .3$). There were generally no effects on response times ($p > .8$) showing that the deficits observed do not reflect simple motor, but executive control deficits. Effect sizes obtained were considerably large with d~0.80 in mild affected patients and effects were not modulated by factors related to fatigue and depression.

Conclusions: There are cognitive control deficits in MS that are not attributable to simple motor speed deficits. Scaling of the difficulty of dual-tasking makes the test applied suitable for a wide variety of MS-patients and may complement neuropsychological testings in clinical care and research setting in MS.

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P880

Video-rating to quantify limb ataxia in multiple sclerosis

M. D'Souza[1], S. Steinheimer[2], J. Dorn[3], C. Morrison[4], J. Boisvert[3], K. Miciunaite[1], J. Burggraaff[5], C.E.P. van Munster[5], P. Kontschieder[4], A. Sellen[4], C.P. Kamm[2], F. Dahlke[3], B. Uitdehaag[5], L. Kappos[1]

[1]University Hospital Basel, Basel, [2]Inselspital, Bern University Hospital, Bern, [3]Novartis Pharma AG, Basel, Switzerland, [4]Microsoft Research, Cambridge, United Kingdom, [5]VU Medical Center, Amsterdam, The Netherlands

Background: In Multiple Sclerosis (MS) the Expanded Disability Status Scale (EDSS) is commonly used to assess disability but suffers from low inter- and intra-rater reliability. Supporting such assessments with computer systems based on machine learning is one possibility for improvement but require alternative methods to capture consistent clinical judgement. We recorded videos of patients performing the Finger-to-Nose Test (FNT) based on EDSS subscores for limb ataxia to use them as a reference.
Objective: To investigate whether the use of reference videos with predefined degrees of severity of limb ataxia can improve rating of other video clips.
Methods: Twenty-six neurologists from two participating centers rated 60 videos of MS patients performing FNT. Ratings were performed at baseline and after six weeks using the Neurostatus definitions of limb ataxia. The neurologists were randomized into two groups: one group used the reference videos for rating, the other rated without reference videos. The inter-rater consistency and long-term re-test agreement were determined.
Results: The use of reference videos made neurologists more consistent. We find that the spread of average ratings was lower when reference videos were used (standard deviation=0.12; range=0.40) than without reference videos (standard deviation=0.26; range=0.88), with a statistically significant difference in standard deviation (F-test; p=0.013). Similarly, use of reference videos increased the intraclass correlation coefficient for inter-rater agreement from 0.756 (without reference videos) to 0.816 (with reference videos). Long-term intra-rater agreement measured as percentage of identical ratings was similar between the two groups, with 69±11% without reference videos and 68±9% with reference videos.
Conclusions: The use of reference videos significantly improved consistency in rating upper limb ataxia by FNT. Hence, this may represent a method to rate movements in a more consistent way, particularly in the context of clinical research or for training of machine learning algorithms.

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Effect of transdermal application of myelin peptides on MSFC in MS patients

A. Walczak, K. Selmaj

Neurology, Medical University of Lodz, Lodz, Poland

Background: We previously reported that transdermal application of myelin peptides reduced MRI activity and relapse rate (ARR) in patients with relapsing-remitting multiple sclerosis (RRMS).
Objective: To assess efficacy of transdermal application of myelin peptides on MSFC Score in a one-year placebo-controlled clinical trial in patients with RRMS treated with a mixture of three myelin peptides.
Methods: Patients (n=26) with RRMS, were randomized in 2 groups, treated with a mixture of 1 mg of each peptide, MBP 85-99, PLP 139-151 and MOG 35-55 (n=16) and a control group that received placebo (n=10). Myelin peptides skin patches were applied weekly for first month and once monthly for 11 months. EDSS and MSFC (Multiple Sclerosis Functional Composite) were assessed every 3 months. MFSC consists of 3 parts: T25FW (Timed 25-Foot Walk), 9-HPT (9-Hole Peg Test) and PASAT (Paced Auditory Serial Addition Test), that were performed by blinded neurologist. We compared MSFC in the 1 mg peptide group with placebo.
Results: In myelin skin patches group MSFC Score showed increased values in comparison to placebo group (-0.01 v. -0.32). In particular, T25FW results were nearly at the same level in

myelin peptides treated group (1 mg) at the baseline and after 12 months of treatment 6.45 and 6.85 s respectively, whereas in placebo group T25FW increased at the end of the trial (6.35 at baseline v. 9.45 s). Similarly, in 9-HPT for dominant hand, the results in myelin skin patches group showed similar values between baseline and the end of the study v. increased values in placebo. Cognitive functions assessed by PASAT did not differ between skin patches group and placebo.
Conclusions: We have shown that myelin skin patches during 12 months of treatment showed beneficial effect on motor functions in MS patients.

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P882

Novel computer-based testing shows cognitive dysfunction in patients with MS

A.D. Smith III, C. Duffy, A.D. Goodman
Neurology, University of Rochester Medical Center, Rochester, NY, United States

Background: Cognitive dysfunction is present in a majority of patients with multiple sclerosis (MS). However, cognitive testing is infrequently performed in the clinical setting due to either time, personnel constraints, or perceived stress of current tests such as Paced Auditory Serial Addition Test (PASAT). Additionally, these tests primarily assess subcortical processing. Within the past decade there has been increased appreciation of both cortical demyelinating inflammatory lesions and cortical atrophy in both relapsing and progressive MS. The clinical correlates of this cortical pathology may not be fully captured with current cognitive tests. Cognivue, is a computer based cognitive test that was recently FDA-approved for evaluation of early signs of dementia in persons over the age of 55. Cognivue takes only 10 minutes to complete and is able to test both cortical and subcortical cognitive domains.
Objective: The primary objective was to conduct a pilot study comparing patients with clinically stable MS and healthy controls using PASAT, SDMT and Cognivue.
Methods: 23 patients with MS and 9 healthy controls between 18 and 50 years were enrolled. Baseline testing included an Expanded Disability Scale (EDSS), Perceived Deficits Questionnaire (PDQ-5), PASAT, SDMT and Cognivue.
Results: Preliminary cross-sectional data show significant differences between patients with MS and healthy controls on PASAT (Z scores -0.15 vs 0.25, p=0.0033), SDMT (Z scores -0.920 vs 1.31, p=0.0001) and composite Cognivue score (83.1 vs 92.7, p=0.02). Additionally, two Cognivue component tasks, adaptive motor (52.2 vs 74, p=0.0004) and motion discrimination (73.3 vs 82.31, p=0.02) were significantly different between patients with MS and healthy controls.
Conclusion: These results suggest that Cognivue, a cognitive test that can be easily implemented in the clinical setting, may be able to detect cognitive dysfunction in MS. Further, specific Cognivue domain performance may show a profile of cognitive dysfunction that is characteristic of patients with MS.

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Emulating neurologists' scoring of motor dysfunction with 3D depth sensing and machine learning

M. D'Souza[1], J. Burggraaff[2], S. Steinheimer[3], P. Kontschieder[4], C. Morrison[4], J. Dorn[5], S. Rota Bulo[4], P. Tewarie[2], K. Miciunaite[1], C.E.P. van Munster[2], A. Sellen[4], M.A. Johnson[4], C.P. Kamm[3], F. Dahlke[5], B. Uitdehaag[2], L. Kappos[1]
[1]University Hospital Basel, Basel, Switzerland, [2]VU Medical Center, Amsterdam, The Netherlands, [3]Inselspital, Bern University Hospital, Bern, Switzerland, [4]Microsoft Research, Cambridge, United Kingdom, [5]Novartis Pharma AG, Basel, Switzerland

Background: Motor dysfunction has a high impact on quality of life and restricts mobility in patients with Multiple Sclerosis (MS). Yet, clinical assessment remains challenging. The Assess MS system is being developed as a touch-free, consistent and potentially finer grained tool to measure motor dysfunction in MS. Assess MS is using advanced machine learning algorithms (MLAs) to analyse 3D-depth-sensor recordings of patients performing standard tests of motor function.
Objectives: To demonstrate that automated analysis of 3D depth sensing video recordings of patients performing standard neurological tests with machine learning can emulate neurologists' scoring of motor dysfunction.
Methods: Standardized finger-to-nose test (FNT) and truncal-ataxia test (TAT) were recorded in 282 patients with a 3D-depth-sensor. A pair of neurologists scored severity of dysfunction using Neurostatus-Expanded Disability Status Scale (EDSS) subscore definitions (grade 0=normal, 1=signs only, 2=mild, 3=moderate and 4=severe). Resulting scores were used to train a MLA to automatically score the 3D depth sensor recordings. The agreement between the MLA and the neurologists' scores was compared with the neurologists' short- and long-term intra-rater agreement, as well as nine-hole peg test and Arm Function in Multiple Sclerosis Questionnaire.
Results: The overall agreement between MLA and neurologists' scorings was 77.3% for FNT (78.5% for grade 0, 55.8% for grade 1, 75.7% for grade 2 and 97.4% for grade 3), based on a total of 2861 videos, and 78.8% for TAT (80.8% for grade 0, 76.5% for grade 2 and 77.8% for grade 3). The overall short-term intra-rater agreement of the neurologists, which characterizes the internal consistency of the scoring used for training, and which the MLA cannot exceed, was 86.2% for FNT and 87.1% for TAT. The overall one-month

intra-rater agreement of the neurologists, which is what the MLA should reach at minimum, was 76.9% for FNT and 67.6% for TAT. Note that retest agreement of the MLA is always 100%. We further report correlations to measurements of upper limb function.
Conclusions: Automated classification of motor dysfunction by MLAs reproduced neurologists' scoring with accuracy similar to the neurologists' own long-term intra-rater agreement, and allows an acceptable assessment of motor dysfunction that is consistent through time. Assess MS may thus improve the evaluation of disability in clinical studies and clinical practice.

Disclosure

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How to assess the upper limb function in persons with multiple sclerosis: a european RIMS multicenter study investigating convergent validity and floor/ceiling effects of measures at different ICF Levels

I. Lamers[1], I. Baert[1], J. Jansa[2], E. Santamarta[3], K. Rasová[4], L. Kallmayer[5], A. Tacchino[6], I.G. Løyning[7], A. Golewska[8], S. Nødtvedt[9], N. Filló[10], J. Raats[11], L. Kerkhofs[12], P. Feys[1]
[1]REVAL - Rehabilitation Research Center, BIOMED - Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium, [2]University medical center Ljubljana (UMCL), Ljubljana, Slovenia, [3]Eugenia Epalza Rehabilitation center, Bilbao, Spain, [4]Charles University and General faculty Hospital, Prague, Czech Republic, [5]MS hospitals, Haslev and Ry, Haslev and Ry, Denmark, [6]FISM Scientific Research (AISM), Genova, Italy, [7]Multiple Sclerosis Senteret Hakadal AS, Hakadal, Norway, [8]John Paul II rehabilitation center for people with MS, Borne Sulinowo, Poland, [9]Haukeland University Hospital, Bergen, Norway, [10]MS Center of Catalonia (Cemcat), Vall Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain, [11]AZ Klina, Campus De MICK, Brasschaat, [12]Rehabilitation and MS Center Overpelt, Overpelt, Belgium

Background: A recent review on upper limb outcome measures highlighted the need for more studies investigating their psychometric properties.
Objectives: The aim was to investigate the psychometric properties, in particular the convergent validity and floor/ceiling effects for this abstract, of frequently used as well as new upper limb outcome measures in multiple sclerosis.
Methods: 136 persons with MS from 11 centers across Europe (RIMS network) were assessed using different upper limb outcome measures on the three levels of the International Classification of Functioning (ICF). On body function and structures level, maximum isometric pinch, key, 3jaw grip strength were evaluated using a dynamometer. Visual Analogue scales (VAS) of spasticity, muscle weakness, sensory impairment, coordination and fatigability were used to evaluated the perceived presence of impairments on this level. On activity level, upper limb capacity was assessed by the nine hole peg test (NHPT), block and box test (BBT) and coin rotation test (CRT). The ABILHAND, Manual Ability Measure-36 (MAM-36) and Motor Activity Log were used to evaluate the perceived performance. Pearson correlation coefficients were calculated to investigated the validity of the outcome measures. Descriptive statistics were used to examine possible floor and ceiling effects.
Results: High correlation coefficients were found between the different grip strength measures (range R= 0.75-0.80, p< 0.001). The different VAS correlated low to moderately with each other (range R= 0.31-0.58). The NHPT, BBT and CRT are highly associate with each other (range R= 0.67-0.78, p< 0.001). A correlation coefficient of 0.80 (p< 0.001) was found between the MAM-36 and the ABILHAND. The MAL was only moderately related to the MAM-36 and ABILHAND (range R=0.41-0.45, p< 0.001). Low to moderate correlation coefficients were found between the capacity and the perceived performance measures on activity level (range R=-0.10-0.50). No floor and ceiling effects were found in any of the included measures.
Conclusion: The results suggest that one type of pinch grip provides enough information about the strength in the hand. The correlation coefficients between capacity and perceived performance measures on activity level indicated that measures on these sublevels are interchangeable. One capacity (NHPT or BBT or CRT) and one perceived performance (MAM-36 or ABILHAND) measure would be enough to evaluate the upper limb on activity level.

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The impact of visible and invisible symptoms on employment status and work and social functioning in Multiple Sclerosis

L. Lorefice[1], G. Fenu[1], J. Frau[1], G. Coghe[1], M.G. Marrosu[2], E. Cocco[1]

[1]Multiple Sclerosis Center, Department of Public Health and Clinical and Molecular Medicine, [2]Multiple Sclerosis Center, Department of Medical Sciences, University of Cagliari, Cagliari, Italy

Background: Frequently diagnosed in young adulthood, multiple sclerosis (MS) and several MS-related factors can influence patients' unemployment status and negatively affect work productivity and daily functioning.

We examined MS patients' employment status and evaluated clinical features influencing it. Furthermore, we investigated patients' burdens due to visible and invisible MS symptoms through their worsening daily functioning.

Methods: The study included outpatients affected by MS according to the 2010 McDonald criteria. The co-occurrence of invisible symptoms (fatigue, depression and apathy) was stated using validated, self-administered tools: Fatigue Severity Scale (FSS);[1] Beck Depression Inventory-Second Edition (BDI-II);[2] Apathy Evaluation Scale (AES-S).[3] Impairment in daily functioning due to MS was assessed using the Work and Social Adjustment Scale (WSAS).[4] Descriptive statistics, hierarchical regression analyses, Pearson's correlation, and the *t-test* were conducted.

Results: Of the 123 participants, 52 (42.3%) were unemployed. Results showed employment to be positively associated with higher education levels (p 0.01); female gender (p 0.03) and higher disability (p 0.02) showed negative associations with employment. No associations were found between employment and fatigue or clinically relevant depressive and apathetic symptoms. High correlations were found between WSAS score and Expanded Disability Status Scale score ($r = 565$, $p < 0.001$), BDI-II score ($r = 588$, $p < 0.001$), and FSS score ($r = 545$, $p < 0.001$).

Discussion: Our study revealed physical disability's significance in determining MS patients' unemployment. Alternatively, invisible MS symptoms negatively affected principally patients' social lives. Therefore, programs should be designed to improve MS patients' work integration and daily activities.

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Disclosure

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Multiple Sclerosis and PDDS: a true walking scale with no brains

M. Gudesblatt[1], K. Wissemann[1], B. Bumstead[1], M. Zarif[1], L. Fafard[1], S. Thotam[1], C. Sullivan[2,3], J. Wilken[2,3], M. Buhse[1,4], D. Golan[5,6]

[1]South Shore Neurologic Associates, Patchogue, NY, [2]Neuropsychological Associates, Fairfax, VA, [3]Georgetown University Hospital, Department of Neurology and Washington Neuropsychology Research Group, Washington D.C., DC, [4]Stony Brook University, Stony Brook, NY, United States, [5]Department of Neurology, Carmel Medical Center, [6]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Background: Multiple Sclerosis (MS) is a disease measured by use of EDSS, MRI changes and relapse rates. EDSS critical changes and thresholds are primarily driven by changes in walking ability in people with MS (PwMS). EDSS scores strongly correlate with the patient reported outcome (PRO) patient-reported disease progression (PDDS). Functional ability/independence, cognition, fatigue, and depression are important factors to consider when evaluating PwMS disease burden. These factors may impact PwMS independently of EDSS. Despite the fact that EDSS is a universally utilized scale to measure treatment efficacy, cognitive function does not impact EDSS or PDDS. Cognitive function can vary independently of walking ability and is an important aspect of MS disease impact.

Objective: To investigate both the relationship between PDDS and PRO-cognitive function in a PwMS cohort, and to self-reported quality of life (QoL). NARCOMS PRO-cognitive self-assessment questionnaire with higher scores reflecting worse cognitive function.

Methods: PwMS completed standardized PRO questionnaires evaluating disease progression, cognitive function, and a QoL Likert scale. Regression analyses were used to investigate the relationship between PRO-cognitive function and PDDS with PRO-QoL. PDDS groups were defined: low-PDDS (0-1), moderate-PDDS (2-4), and severe-PDDS (>4). The variability of cognitive function was calculated within each PDDS group, and degree overlap of cognitive function was evaluated across PDDS groups.

Results: 785 PwMS (73.5% female, average age = 49.3±11.3). PRO-cognitive function ($r=0.39$, $P=< 0.001$) and PDDS ($r=0.37$, $P=< 0.001$) both correlated with PRO-QoL. PRO-cognitive function scores however demonstrated marked variability: 85.4% (low-PDDS), 54.6% (moderate-PDDS), and 73.7% (severe-PDDS), and with considerable overlap (55.2%) between adjacent PDDS-groups, and between extreme PDDS-groups (66.1%).

Conclusions: Cognitive function and PDDS are both PRO-scales that impact and relate to PRO-QoL. PDDS despite widespread use and acceptance is a PRO-scale, like EDSS, is insensitive to PRO-cognitive function. PDDS use as measure of important global disability in PwMS should be reconsidered.

Disclosure

All: nothing to disclose

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Hand motor performance as a new quantitative clinical endpoint in MS: longitudinal evaluation in patients with CIS and correlation with accumulation of disability and tissue integrity at MRI

L. Bonzano[1], L. Avanzino[1], A. Bisio[1], M. Bove[1], F. Gallo[1], A. Laroni[1], G.L. Mancardi[1], M. Mueller[1], M. Pardini[1], L. Pedullà[1], L. Roccatagliata[1], C. Solaro[2], M.P. Sormani[1], A. Uccelli[1]
[1]University of Genoa, [2]Department of Neurology ASL3 Genovese, Genoa, Italy

Background: Expanded Disability Status Scale (EDSS) is mainly based on lower limb assessment; this is a limitation in the interpretation of clinical trials in multiple sclerosis (MS).
Recently we tested an engineered glove to assess finger motor performance; the motor parameters were reproducible and showed significant differences between healthy controls and people with MS with EDSS=0. This sensitivity can be crucial for monitoring the disease course and treatment effects in early MS.
The corpus callosum (CC) is one of the main structures involved in MS and is known to influence bimanual coordination.
Objective: To assess the potentiality of quantitative analysis of finger motor performance to detect subclinical disability in early disease phases and understand the role and prognostic value of CC integrity.
Methods: Thirty patients with Clinically Isolated Syndrome (PwCIS) were enrolled in a follow-up study (time-points: 0-6-12-18-24 months). They performed finger opposition movement sequences with the two hands simultaneously to assess bimanual coordination skills and underwent different instrumental evaluations. From Diffusion Tensor Imaging (DTI) (1.5 Tesla, 15 diffusion gradient directions, b=1000 sec/mm^2) we obtained parametric maps of fractional anisotropy (FA), axial diffusivity (AX), radial diffusivity (RAD), and mean diffusivity (MD). Transcranial magnetic stimulation (TMS) was used to assess the ipsilateral silent period (iSP), i.e. a marker of transcallosal motor inhibition.
Results: Inter-hand interval (IHI) significantly increased over time, indicating worsening in bimanual coordination. DTI parameters showed damage progression in the CC. From TMS data, iSP area and duration increased over time.
Twenty out of 30 subjects received the diagnosis of MS during the study period. In particular, CC FA decreased and RAD increased progressively from month 0 to 24 in the group of MS converters, whilst the two parameters remained stable in the group of MS non-converters. Related to this finding, IHI increased in the group of MS converters, indicating the occurrence of impairment in coordinating simple bimanual finger movements, whilst the MS non-converters maintained their abilities. Similarly, iSP area and duration increased only in the group of MS converters.
Conclusions: The adopted methodologies are useful to monitor the disease course in PwCIS and can be able to discriminate the group of MS converters from the group of MS non-converters.

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Multiple sclerosis and cognitive testing: the relationship between traditional measures and novel computerized analytics - a preliminary analysis

M. Gudesblatt[1], M. Zarif[1], K. Wissemann[1], B. Bumstead[1], L. Fafard[1], M. Buhse[1,2], K. Blitz[1], S. Thotam[1], R. Kane[3,4], C. Sullivan[3,4], J. Wilken[3,4]
[1]South Shore Neurologic Associates, Patchogue, [2]Stony Brook University, Stony Brook, NY, [3]Neuropsychological Associates, Fairfax, VA, [4]Georgetown University Hospital, Department of Neurology and Washington Neuropsychology Research Group, Washington D.C., DC, United States

Background: Multiple Sclerosis (MS), evaluated by EDSS, relapse and MRI, but none provide cognitive information. Cognitive function impacts: employment, Quality of Life, risk of falling. Traditional measures evaluating cognitive function: employ single score screens, limited availability, and difficult to incorporate into routine care. Computerized cognitive testing can easily incorporate into routine MS care and provide an objective method to screen and track changing disease impact. NeuroTrax computerized cognitive testing (NT) is one digital method to obtain a screening profile in people with MS (PwMS).
Objective: To evaluate the ability of NT identifying the presence of SDMT defined PwMS-cognitive impairment and the degree it correlates with traditional measures.
Methods: Prospective study to determine whether NT scores can predict cognitive impairment as defined by SDMT scores, and correlate NT scores with scores from traditional measures across a variety of cognitive domains.
Results: 46 PwMS and 15 healthy controls. NT- GCS, attention, executive function, memory differentiate cognitive dysfunction in PwMS from normal (defined by SDMT) ($p< 0.001$), and spatial and speed ($p=0.03$). NT Global score predicts level of impairment per SDMT: 83% specificity, 58% specificity, >70% positive and negative predictive values. NT cognitive domains correlate with traditional measures: NT-memory vs SRT ($p< 0.001$, $r=.54$); NT-attention vs PASAT ($p< 0.001$, $r=.46$), SDMT-oral ($P< 0.001$, $r=.64$); NT-speed vs PASAT-total ($p< 0.003$, $r=-.38$); NT-executive vs DKEFS-CS ($p< 0.001$, $r=.54$), FAS ($p< 00.01$, $r=.32$), and Animal ($p< 0.002$, $r=.38$); NT-verbal vs FAS and Animal (not significant); NT-spatial vs JLO ($p< 0.02$, $r=-.30$).
Conclusions: In a preliminary analysis of a larger study, NeuroTrax computerized cognitive testing appears to be useful as a cognitive screen in PwMS. Cognitive impairment in PwMS is common and analysis of cognitive burden of disease by NT could be incorporated into routine care to provide cognitive information that is unique/important and patient centric but not provided by EDSS, relapse rate or MRI findings.

Disclosure

All; nothing to disclose

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Exploration and verification of a patient-powered research network to provide patient insights in multiple sclerosis

P. Wicks[1], L. Julian[2], J. Han[2], T. Tian[2], J. Devenport[2]
[1]PatientsLikeMe, Cambridge, MA, [2]Genentech, Inc., South San Francisco, CA, United States

Background: Patient-powered research networks (PPRN) are an emerging source of information about patients' experiences with disease, treatments and the healthcare system. PatientsLikeMe is an online patient-focused platform that enables patients with chronic conditions like multiple sclerosis (MS) to share and find disease-related information. To assess feasibility of the use of this type of patient-reported data, it is important to verify participants' diagnoses.
Objective: To evaluate the feasibility of PPRN as a source of patient-reported data by linking the PPRN information with insurance claims to verify participants' diagnoses and summarise the overlapping and unique patient-reported data.
Methods: Active members of PatientsLikeMe, residing in the US, aged ⩾18 years, with a self-reported diagnosis of MS or Parkinson's disease were invited and consented to participate in a survey during a two-week period in December (Dec) 2014. Patient-reported data, including identity (via a HIPAA compliant third-party software generated de-identified token), diagnosis and usage of disease-modifying treatments (DMTs) were anonymously matched and compared to US medical and pharmacy claims data with dates of service between Dec 2009-Dec 2014. For matching patients, other patient-reported data was summarised descriptively.
Results: Among 603 responders, 94% had ⩾1 record in the claims dataset; of these, there was 93% agreement rate for MS diagnosis. Concordance on specific treatment usage within an imputed five-year period ranged from 73.5−100%. Within the matched dataset, ≈70% of patients reported having relapsing-remitting MS and >50% of the patients reported being treated with a DMT. Over 85% of patients in this cohort preferred to make treatment decisions jointly with their doctor or by themselves after considering their doctor's opinion. Patients reported varying degrees of interruption of physical and social function, with progressive patients reporting the lowest (worst) scores of all subtypes.
Conclusion: The high degree of concordance between patient-reported data and medical claims data supports the authenticity of consenting patients from PPRNs. The willingness of patients to share their disease information and the feasibility of matching patient-level data opens up prospects for future research using enriched datasets that combine clinical, treatment and patient-reported information that is not captured by traditional sources.
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Disclosure

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Laura Julian is an employee of Genentech, Inc.
Jian Han is an employee and shareholder of Genentech, Inc.
Tony Tian is an employee and shareholder of Genentech, Inc.
Jenny Devenport is an employee and shareholder of Genentech, Inc.

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Implications for clinical practice of employing MRI to detect ongoing disease activity in patients with non-symptomatic relapsing-remitting multiple sclerosis who are receiving therapy

S.M. Montgomery[1], J.M. Kusel[1], N. Adlard[2], A. Williams[2], J. Punn[2]
[1]Costello Medical Consulting Ltd, Cambridge, [2]Novartis Pharmaceuticals UK Ltd, Camberley, United Kingdom

Background: Patients with relapsing-remitting multiple sclerosis (RRMS) treated with disease modifying therapies (DMTs) can have ongoing disease activity as observed by magnetic resonance imaging (MRI), prior to symptomatic activity. The objective of this study was to estimate the size of the patient population who have new or enlarging lesions on MRI, but not symptomatic clinical activity, who could benefit from a switch of DMT and the cost implications of using MRI for this.
Methods: A targeted literature review of online databases and conference abstracts was performed to identify studies that report on the outcome of 'no evidence of disease activity' (NEDA-3). Studies were included if they reported both NEDA defined only by lack of clinical symptoms and also NEDA defined by lack of clinical symptoms and absence of new or enlarging T2 lesions or T1 gadolinium-enhancing lesions on MRI. The reciprocal of NEDA was taken, as this reports the number of patients who do have remaining disease activity. A basic costing model was developed to estimate the cost of employing MRI (when one MRI costs £137.23) for non-symptomatic RRMS patients receiving DMT in the UK.
Results: Nine studies reporting on 12 data points for 7 different DMTs were included. Two data points were at 6 months, 2 at 1 year, 4 at 2 years and 4 at 3 years. Across all studies, the percentage of patients with disease activity whose activity was defined only by MRI ranged from 30.3% to 72.4% (median 51.8%). For the model, the median value was used, which then estimated that 4973 patients in the UK with disease activity could be identified by MRI. If RRMS patients without symptomatic activity received an annual MRI, the cost would be £237 per additional case of active disease detected.
Conclusions: This study shows that MRI assessment could be used to detect a substantial number of patients with active disease, but prior to symptomatic activity, at a small cost per case detected. There is now a range of options for treatment escalation from first line therapies for these patients. The conclusions that can be made with regards to individual DMTs or looking at trends over time are

limited due to the small number of studies reporting the appropriate data. Further research is required to confirm the generalisability of the clinical trial results to clinical practice, and to investigate the clinical outcomes of patients with MRI-defined disease activity who switch DMT compared to those who do not switch.

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Stephen Montgomery: is a paid employee of Costello Medical Consulting Ltd which provides services to many pharmaceutical companies, including in relation to this work Novartis Pharmaceuticals UK Ltd
Jeanette Kusel: is a paid employee of Costello Medical Consulting Ltd which provides services to many pharmaceutical companies, including in relation to this work Novartis Pharmaceuticals UK Ltd
Nicholas Adlard: is a paid employee of Novartis Pharmaceuticals UK Ltd
Alison Williams: is a paid employee of Novartis Pharmaceuticals UK Ltd
Jitender Punn: is a paid employee of Novartis Pharmaceuticals UK Ltd

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BICAMS underestimates verbal memory impairment in MS patients: we propose a simple solution

J.F. Sumowski[1], M. Inglese[1], M. Petracca[1], D.M. Erlanger[2]
[1]Icahn School of Medicine at Mount Sinai, [2]NYU Langone Medical Center, New York, NY, United States

Background: Cognitive decline is common in multiple sclerosis (MS), and the need for brief, sensitive cognitive screening is widely accepted. The Brief International Cognitive Assessment in MS (BICAMS) screens the two cognitive domains most impacted by MS: processing speed (Symbol Digit Modalities Test [SDMT]) and memory (California Verbal Learning Test, 2nd Ed. [CVLT-II], Brief Visuospatial Memory Test, Revised [BVMT-R]). Due to time constraints, memory tests have been shortened to include Total Learning (TL) but omit Delayed Recall (DR). We evaluated whether use of TL in lieu of DR underestimates memory impairment in MS patients, thereby limiting the utility of BICAMS as a sensitive screening tool.
Methods: Complete versions of the CVLT-II and BVMT-R were administered to 160 MS patients (89 RR, 47 SP, 24 PP). We calculated norm-referenced T scores for CVLT-II TL and Long Delay Free Recall (LDFR), and BVMT-R TL and DR. We performed dependent t-tests to compare TL and DR for each of the two tasks. We also examined differences in the proportion of MS patients impaired ($T \leqslant 35$) on each score to see if differences existed in identification rates.
Results: There was a large (d=0.77) difference between CVLT-II TL (mean T=43.2±13.3) and CVLT-II LDFR (mean T=38.0±14.5; $p < .001$), whereby TL performance was half a standard deviation higher than LDFR. There was no difference between BVMT-R TL and DR ($p > .1$). Regarding identification of memory impairment, 28.7% of patients would be identified as impaired based on CVLT-II TL, versus 51.5% with LDFR. A similar underestimate of memory impairment was not shown for the BVMT-R: TL (59.6%) and DR (51.5%).
Conclusion: Use of CVLT-II TL may underestimate verbal memory impairment in MS patients, perhaps because CVLT-II TL can be supported by intact working memory capacity despite episodic memory problems. (Note that MS patients typically do not have working memory deficits on digit span tasks.) There may be a solution, however, as the CVLT-II also provides a Short Delay Free Recall (SDFR) score requiring patients to recall words after working memory is erased by an interference list. This adds about two minutes to the administration time. Within our sample CVLT-II SDFR (mean T=38.8±13.6) was lower than TL ($p < .001$), but comparable to LDFR ($p > .1$). Levels of impairment were similar between SDFR (46.3%) and LDFR (51.5%). CVLT-II SDFR may be a better screening measure of verbal memory function for BICAMS.

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Modification of the Tardieu scale to measure lower limb spasticity in people with multiple sclerosis

M. Liddicut, C. Valentine, K. Buchanan, S. DeTrane, R. Farrell
University College Hospital NHS Foundation Trust, London, United Kingdom

Background**:** Spasticity is a debilitating symptom for many people with Multiple Sclerosis (MS). It usually has a generalised pattern affecting several muscle groups in the lower limbs (LL), leading to spasms, pain, impaired mobility and risk of contracture. Measurements typically used in clinical trials - Ashworth/modified Ashworth (mASH) have limitations and have lacked sensitivity. The modified Tardieu scale (MTS) is generally favoured as a more valid measure as it is thought to reflect the velocity dependent component of spasticity. We sought to develop a standardised MTS protocol for the first time for use in people with LL spasticity in a clinical trial setting.
Method: Pubmed search was conducted with keywords MS, spasticity, Ashworth and Tardieu. Guidance from previously published studies regarding the use of MTS in other adult neurological populations was used as a basis for the new protocol. A manual outlining start and end postures for each movement, goniometric landmarks, handling and defined speeds of movement was developed and incorporated into training.
Results: Two trained clinicians are required to move and measure the limb. The subject rests supine for 5 minutes while goniometric landmarks are marked bilaterally.
Passive range of motion (R2) and angle of catch (R1) were measured in 1 degree increments to avoid compounding error when determining the spasticity angle.
R2 is measured at a slow speed to avoid triggering the hyperactive stretch reflex. R1 is determined by moving the limb through range quickly to a count of '1001' to elicit the stretch reflex and ascertain the 'quality of the muscle response' (graded on a scale of 0-5) and the 'angle of catch'. R2 - R1 denotes the 'spasticity angle' whereby a large value indicates greater spasticity. Six muscle

groups were assessed in each LL: hip extensors/flexors, hip adductors assessed in supine, knee extensors/ flexors assessed in prone and ankle plantarflexors in supine with knee supported over a foam roller and the hind foot free. Specifications were set so clinicians avoided handling the muscles being assessed.
Conclusion: MTS is a valid measure but there has been a lack of evidence in MS patients. We have developed a standardised protocol which can be applied to this patient population. Further work is ongoing to test the reliability and validity of the measure.

Disclosure

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P893

The clinical role of cortical lesions as a predicting factor for cognitive impairment in multiple sclerosis

E. CURTI[1], S. Graziuso[2], E. Tsantes[1], G. Crisi[2], F. Granella[1]
[1]University of Parma, [2]University Hospital of Parma, Parma, Italy

Background: Grey matter (GM) damage has been widely recognized as a fundamental aspect of multiple sclerosis (MS). Among several measures of GM disease, cortical lesions (CLs) burden, which can be detected at MRI scans with double inversion recovery (DIR) sequences, has been demonstrated to correlate with cognitive impairment (CI), an important component of MS disability.
Aims: To investigate the role of total and regional CLs number in predicting CI in a cohort of relapsing-remitting and progressive MS patients.
Methods: Thirty consecutive MS patients presenting CLs (CL+) at high-field (3T) MRI 3D-DIR sequences and an even group of MS patients without CLs (CL-) as a control, were investigated with the Rao Brief Repeatable Battery of Neuropsychological Tests (BRB), Version A plus Stroop Test. Total and regional CLs number were computed in all patients.
Results: Among the sixty MS patients enrolled, forty-seven (78.3%) had a relapsing-remitting course, while thirteen (21.7%) a progressive one. Compared to CL-, CL+ patients had a significantly higher (p=0.04) EDSS score and a greater proportion of progressive forms (p = 0.03). The most affected lobe was the frontal lobe (73.3% of patients), followed by temporal and parietal ones (both 60.0%). Total CLs number was higher in the progressive forms (p=0.03). Univariate analysis revealed a significant correlation between total CLs number and deficit at SRT-LTS (p=0.02), SRT-CLTR (p< 0.001), PASAT 3 (p=0.004), SRT-D (p< 0.001), SPART-D (p< 0.001). Similar results were found for frontal and temporal lobes. Multivariate analysis revealed total CLs number as an independent predictor of deficit at SRT-LTS (p=0.01) and PASAT 3 (p=0.05).
Conclusions: We confirmed the important role of CLs number, evaluated with a technique quite commonly available in clinical practice, in predicting CI in MS patients, in order to make an early diagnosis and monitor the evolution of CI and the potential neuroprotective effects of novel drugs.

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P894

Optic nerve ultrasonography in multiples sclerosis

S. Pérez-Sánchez, S. Eichau-Madueño, M. Rus-Hidalgo, A. Domínguez-Mayoral, G. Navarro-Mascarell, G. Izquierdo
Multiple Sclerosis Unit. Neurology., Virgen Macarena University Hospital, Seville, Spain

Background: Axonal and neuronal degeneration are important features of multiple sclerosis (MS) that may lead to permanent neurological and visual impairment. Optic nerve provide a useful clinical model to study these characteristics and could be used to measure and monitor the pathology of the disease process
Nowadays, we have observed the emergence of ultrasonography like a novel technique to study this structure. It allows assessment the thickness of the optic nerve through the orbit.
Objective: To assess difference between optic nerve thickness of MS pantients and healthy subjects.
Methods: We performed a case-control study. In order to perform the sonography, patients may lead in supine position and eyes may be closed and relaxed. We used the lowest power possible to achquieve a great image. In a longitudinal view of the nerve, we did three measures with meningeal sheaths at 3 mm of the papilla. Subsequently we used the average. ROC (Receiver Operating Characteristic) was done to identify a cut-off point.
Results: We performed ultrasounds in 63 MS patients and 11 healthy subjets. 43 of 63 patients were women and mean age at diagnosis was 35,37 years. Mean duration of disease was 8.03 years. 85,74% of the patients were relapsing phenotypes, and the rest of them, were progressive. Mean EDSS was 2.71. Mean diameter of right optic nerve was 4.54 mm and 4.63mm for left eye. In healthy subjets, these measures were 5,74 mm for right eye and 5.66 mm for left one. COR showed that values above 5.20mm had a sensitivity of 91% and a specificity of 75% to identify a subject into the healthy group. Lower values identified patients with a sensitivity of 73% and specificity of 95%. Positive predictive value was 62% and negative predictive value was 99%.
Discussion: Optic nerve thickness measured by ultrasounds allows differentiate between healthy subjets and MS patients It is a simple, fast and safe technique that can be performed by neurologist.

Disclosure

Nothing to disclose

P895

What are the optimal walking tests to assess disability progression?

S. Piérard, M. Van Droogenbroeck
INTELSIG, University of Liège, Liège, Belgium

Background: Therapy success is assumed when there is no evidence of disease activity. Clues to show it include an MRI, the

relapses history, questionnaires, and clinical measures to assess the disability progression. Especially gait analysis plays a major role as gait impairment is considered by patients as the most disabling symptom. Too often only the walking speed is measured. New technologies (e.g. GAIMS, see ECTRIMS 2012-15) measure many spatiotemporal gait parameters, even during long tests (e.g. 6min, 500m), without equipping patients with markers or sensors. Moreover, various tests can be done, depending on the length and type of walk (comfortable pace --C--, as fast as possible --F--, tandem gait --T--).

Objective: Determine if there is an advantage to perform various walking tests, and which test or combination of tests brings the higher amount of information about the patient state in a reasonable amount of acquisition time.

Methods: The system GAIMS provided 434 recordings of the gait parameters of healthy people and 60 recordings of MS patients with EDSS< =4. They performed 12 tests (25ft C+F+T each twice, 20m C+F+T, 100m C+F, 500m F). To assess the ability of these clinical outcome measures to detect disability progression, we evaluate the possibility of differentiating people below a given EDSS threshold (0.25) from those above it based only on the measured gait parameters. For individual tests, we use the classifier of Azrour (ESANN 2014). All subsets of the tests are also considered, by combining the individual classifiers and determining automatically the optimal relative importance of the tests with the linear support vector machine (SVM) technique. The ability to detect the disability progression is quantified by the performance (area under the ROC curve --AUC-- and the maximum achievable balanced accuracy --MBA--) of the corresponding classifiers.

Results: The best test alone is the 500m F (note that the walking speed measured during it is the gait parameter best correlated with the EDSS). Combining several tests leads to a better performance. A performance (MBA=95.7%, AUC=0.983) close to the best achievable one can be obtained with 6 tests only (25ft C twice, 25tf F twice, 20m C, 20m T).

Conclusions: The clinical gait analysis can help to detect disability progression. While considering different types of walking tests improves the ability of taking decisions, we showed that performing 6 tests for a total of 70.48m suffices.

Disclosure

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P896

Towards a Tele-MSDS: an iterative method to assess the MS patient remotely

R. Bove, P. Garcha, C. Bevan, E. Crabtree, D. Goodin, A. Green, J. Gelfand

Neurology, University of California San Francisco, San Francisco, CA, United States

Background: The delivery of clinical care via in-home telemedicine is important for optimizing the care of patients with multiple sclerosis (MS). The UCSF MS Center routinely provides the option for in-home telemedicine follow-up visits using a secure web-based system. However, the accuracy of telemedicine assessments has only been reported with a trained examiner assisting with evaluation at the patient's bedside, paralleling the acute tele stroke model, which cannot be used to validate a practical approach to in-home assessments.

Goals: To develop and optimize an accessible, MS-specific telemedicine neurological examination that leverages new technologies and does not require the presence of a trained examiner in the patient's home setting.

Methods: Patients aged 18-70 years with MS presenting for routine neurological evaluations at the UCSF MS Center are recruited to participate in the study. After the standard in-clinic EDSS examination, each participant completes a patient-reported EDSS (with previously reported 0.96 correlation coefficient with in-clinic EDSS) and receives a low-cost "neuro exam kit" (including vision card and tuning fork). Within 72 hours of the clinic visit, the participant is then evaluated in their home environment by another study clinician via secure video chat. Patients requiring an aide to attend their clinic evaluation have an aide for their in-home examination.

Results: After the first 12 visits (EDSS range 0 to 6.0), we reached a correlation coefficient of >0.90 between in-clinic and tele-EDSS scores. Correlation across most functional systems exceeded 0.60, with the exception of vision and sensation. After 15 visits, we are beginning to incorporate enhanced digital tools (e.g. digital visual acuity tool, sensor) and patient-reported outcomes to optimize precision in specific domains. This iterative process will allow for the efficient development of a more accurate and sensitive remote assessment of MS-related functional domains, a tele-MSDS (MS Disability Score). We are also identifying specific barriers to telemedicine access and utilization.

Conclusions: This proof of principle study of clinic to in-home telemedicine examinations demonstrates that we can replicate important features of the EDSS remotely, which will support clinical and research purposes. Further incorporation of technological solutions will allow us to measure features of MS-related disability not included in the EDSS.

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A. Green: research grants from NMSS, NIH, Novartis and Inception 5 Sciences. He has served on end point adjudication committee for MedImmune and a steering committee for OCTiMS. He has served as an expert witness for Mylan and Anneal. He is also on the Scientific Advisory Board of Bionure and Inception Sciences. He is as Harry Weaver Fellow of the NMSS.

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P897

Predicting conversion to secondary progressive multiple sclerosis using a clinical decision tree

R. Ramanujam[1,2], J. Hillert[1], A. Manouchehrinia[1]
[1]Karolinska Institute, [2]KTH Royal Institute of Technology, Stockholm, Sweden

Conversion to secondary progressive (SP) multiple sclerosis (MS) typically occurs after approximately 20 years of disease duration. This generally is a gradual process which is determined retroactively by a neurologist after examining clinical records over a period of several years. Improving prediction of secondary progressive disease and standardizing parameters which define this transition could benefit clinicians, patients and researchers. The aim of this study was to use clinical measures as a predictive tool to indicate SPMS.

Data included 11,234 MS patients from the Swedish MS registry (SMSReg), of whom 3904 had reached the secondary progressive stage as determined by a neurologist using patient records. These records contained clinical data such as the last EDSS measurement, age at last EDSS, date of disease diagnosis, date of disease onset, and sex. We used these measurements as inputs into a decision tree with SP as a binary output. The final variables included in the decision tree were last EDSS measurement and the age at last EDSS.

The model achieved 87.7% internal accuracy, and over 86% internally cross-validated accuracy. Furthermore, each of the resultant decision branches contains a certainty estimate which can be used clinically to make rapid judgements about whether a patient has reached secondary progressive disease. Since the last EDSS and corresponding age are readily available, this demonstrates that an easy method to accurately estimate patients' current SP status is possible. This has strong potential to be a clinically relevant tool which can both reduce required to evaluate the transition to secondary progress multiple sclerosis and also standardize the basis of SP across diverse clinical groups.

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RR and AM have nothing to disclose
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P898

Can mean platelet volume predict the risk for atherosclerosis in RRMS patients?

B. Yuksel[1], E. Ozaydin Goksu[1], P. Koc[2], F. Kurtulus[1], E. Karacay[1], Y. Cekin[3], Y. Bicer Gomceli[1]
[1]Neurology Department, [2]Radiology Department, [3]Microbiology Department, Antalya Research and Training Hospital, Antalya, Turkey

Objective: Multiple sclerosis (MS) is an inflammatory demyelinating disease of central nervous system (CNS). Inflammation episodes limited to CNS result in neurological symptoms that partly or completely improve. Platelets play an important role in the pathogenesis of atherosclerosis, also mean platelet volume (MPV) reflects inflammation. MS patients may have an increased risk of atherosclerotic diseases owing to reduced physical activity, smoking, use of glucocorticoids for acute relapses. No data have been reported on the relationship between MPV and risk of atherosclerosis in relapsing remitting MS (RRMS) patients.
Methods: Blood samples of 36 RRMS patients, age-sex matched 34 healthy controls (white blood cell count, thrombocyte count, MPV, neutrophil lymphocyte ratio, platelet lymphocyte ratio), EDSS, duration of disease were recorded. The history of other vascular diseases as hypertension, diabetes mellitus, peripheric artery disease and acute relapses were excluded.
Results: 36 RRMS patients (mean age 36.7±7.6) and 34 healthy controls (mean age 34.3±6.4) were included. In patient group, 20 were female (55,6%), 16 were male (44,4%). Control group contained 21 female (61,8%), 13 male (38,2%). There were significant differences between the values of MPV in patient groups than controls (p=0,04). There were no significant differences between neutrophil lymphocyte ratio or platelet lymphocyte ratio in patient groups than controls (p=0,65; p=0,31, respectively)
Conclusion: We aimed to suggest a simple tool to predict atherosclerosis risk in young RRMS patients. Elevated MPV values were found to be highly associated with atherosclerotic disease in recent studies. In multiple sclerosis, a systemic effect of an inflammatory process might predominantly affect the CNS, thus early diagnosis of the risk may prevent catastrophic results. Although a significant difference between the values of MPV in patient groups than controls was found in our study, further investigation in a large MS population is still needed to assess the definite risk of atherosclerosis.

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P899

OPTIMISE: User-guided solutions for harmonized clinical and patient-centred data capture

M. Yong[1], L. Yang[1], J. Raffel[1], M. Craner[2], C. Hemmingway[3], G. Giovanonni[4], J. Overell[5], R. Hyde[6], J. van Beek[6], F. Thomas[6], Y. Guo[1], P. Matthews[1]
[1]Imperial College, London, [2]University of Oxford, Oxford, [3]Great Ormond Street Hospital for Children, [4]Queen Mary University London, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, [5]Glasgow MS Clinical Research Centre, Institute of Neurological Sciences, Glasgow, [6]Biogen, Inc., Maidenhead, United Kingdom

Objective: Optimisation of Prognosis and Treatment in Multiple Sclerosis Portal (OPTIMISE) is a clinician and patient data entry tool. Development work has been guided by user requirements through a deliberative process, with the objective of designing time and cost-saving data collection solutions to support improvements in patient care.

Background: Current UK data collection efforts for pharmacovigilance and clinical effectiveness research in multiple sclerosis (MS) are not comprehensive or ideally standardised.
Desing/Methods: OPTIMISE features include secure data entry, project customization of data collection elements, ability for data sharing and access in offline and online modes. An iterative programme embedding technical design with evolving user requirements was undertaken over 2015-16. For this, clinicians, research nurses and patients participated in stakeholder meetings to review the software capabilities and refine requirements for harmonised MS clinical and patient centred data capture sustainable as part of routine MS clinical care delivery.
Results: The OPTIMISE platform is an open-sourced, cross platform application that works on PCs and tablets. It provides an entry tool for secure data sharing, with pipelines to other data management tools such as XNAT for imaging, and tranSMART for data analysis.

Stakeholder meetings led to addition of capabilities for generation of clinic notes and visualization of individual clinical trajectories to support care decisions. Current development work is further simplifying the user interface, adding fields to better support pharmacovigilance and including reminder "flags" for scheduling safety monitoring tests.

Additional requests from researchers will ensure that OPTIMISE data can be mapped onto data from other sources such as iMED and MS Registry, so that data collated using OPTIMISE can be aggregated easily with that from other sources.
Conclusion: A public instance of a clinician portal will have been available for open distribution in May 2016 at http://www.optimise-ms.org/portal. An audit of software users taking into account user experiences, data quality and perceived clinical value will be performed before release of OPTIMISE V2.0 in late 2016.

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P900

Is Multiple Sclerosis a risk factor for atherosclerosis?

B. Yuksel[1], P. Koc[2], F. Kurtulus[1], E. Ozaydin Goksu[1], E. Karacay[1], Y. Cekin[3], Y. Bicer Gomceli[1]
[1]Neurology Department, [2]Radiology Department, [3]Microbiology Department, Antalya Research and Training Hospital, Antalya, Turkey

Objective: Multiple sclerosis (MS) is an inflammatory demyelinating disease of central nervous system (CNS). In this study, we aimed to discuss the possible predisposing factors to atherosclerosis in multiple sclerosis as carotid intima media thickness (CIMT);an early and sensitive indicator for sublinic atherosclerosis and high sensitive C-reactive protein (hs-CRP) levels; a non-specific inflammatory sitokine accelerates the formation of atherosclerotic plaque.
Methods: 36 RRMS patients and age-sex matched 34 healthy controls were included to this study. Blood cell counts, cholesterol levels (total cholesterol, LDL, TG, HDL), vitamine D and B12, hs-CRP levels, body mass index (BMI) and CIMT of both groups, EDSS scores, duration of disease, history of smoking were all recorded. The history of other vascular diseases as hypertension, diabetes mellitus, peripheric artery disease and acute relapses were excluded.
Results: 36 RRMS patients (mean age 36.7±7.6) and 34 healthy controls (mean age 34.3±6.4) were included. In patient group, 20 were female (55,6%), 16 were male (44,4%). Control group contained 21 female (61,8%), 13 male (38,2%). There were significant differences between the values of mean IMT in patient groups than controls ($p =< 0.001$). There were no significant differences between IMT values in smoking (n:23) and non-smoking (n:47) groups ($p=0.86$). There were no significant differences of hs-CRP levels in patient group than controls ($p=0.13$). 4 controls and 4 patients' (n:8) hs-CRP levels were not achieved due to missing blood samples. There were no significant differences between hs-CRP values and IMT in the remaining 62 participants. Low-medium correlation was found in IMT and hs-CRP and very low correlation was found in IMT and EDSS or duration of disease.
Conclusion: In multiple sclerosis, a systemic effect of an inflammatory process might predominantly affect the CNS, thus early diagnosis of the risk may prevent catastrophic results. We found significant differences between the values of mean IMT in patient groups than controls and this made us to consider that multiple sclerosis patients may have predisposition to atherosclerosis. Further investigation in a large MS population is still needed.

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P901

Increased multiple sclerosis impact scale-29 score is associated with reduced survival in multiple sclerosis

A. Wallace[1], J. Raffel[1], R. Reynolds[1], T. Friede[2], R. Nicholas[1]

[1]Imperial College London, London, United Kingdom, [2]University Medical Center Göttingen, Göttingen, Germany

Introduction: Patient reported outcome measures (PROMs) are increasingly used in clinical trials in multiple sclerosis (MS) but as yet have not been shown to have an impact on survival unlike the Expanded Disability Status Score (EDSS), a clinical scale favoured by regulators despite a number of limitations. We surveyed the population-based cohort of the United Kingdom MS Tissue Bank (UKMSTB) using the PROM Multiple Sclerosis Impact Scale (MSIS-29) to assess if it correlated with survival.
Methods: MSIS-29 questionnaires were sent to the UKMSTB population in 2004 and again in 2005, and survival data collected until 2014. Survival times were modelled using Cox proportional hazards regression to investigate the effects of MSIS and EDSS on survival with adjustment for age, gender and disease duration. Pairwise correlation between the MSIS subscales and EDSS were assessed by rank-based Spearman's correlations; the reported p-values are related to test of the null hypothesis that the correlation is zero.
Results: MSIS-motor and MSIS-psych were found to have statistically significant effects on survival adjusted for age, gender and disease duration with higher scores on the MSIS subscales indicating higher risk of death (both $p < 0.0001$). These trends were more pronounced for the motor subscale than the psychological subscale. Similarly, EDSS showed a statistically significant effect on survival after adjustment for age, gender and disease duration with higher EDSS scores indicating higher risk of death ($p < .0001$). Pairwise correlations between EDSS and MSIS-motor amounted to 0.50 ($p < .0001$) whereas correlation between EDSS and MSIS-psych was 0.17 ($p < .0001$). The correlation between the two MSIS subscales was 0.71 ($p < .0001$).
Conclusion: This is the first demonstration that a PROM correlates with survival in MS and argues for their inclusion in future clinical trials due to their ease of use and administration.

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P902

Paced Auditory Serial Addition Test (PASAT 3") as a cuantitative measure of cognitive fatigue in patients with Multiple Sclerosis

Y. Higueras[1], M.L. Martínez-Ginés[2], J.M. García-Domínguez[2], J.P. Cuello[2], F. Romero-Delgado[2], H. Goicochea-Briceño[3], V. Meca-Lallana[4], J. Vivancos[4], F. García-Vaz[5,6]
[1]Neuropsychology, Fundación para la Investigación del Gregorio Marañón, [2]Neurology, Hospital General Univeristario Gregorio Marañón, [3]Nursery, Fundación para la Investigación del Gregorio Marañón, [4]Neurology, Hospital Universitario de La Princesa, [5]Procesos Básicos II, Universidad Complutense, [6]Universidad Autónoma de Madrid, Madrid, Spain

Introduction: Multiple sclerosis (MS) patients associate cognitive impairment (CI) in 50-65% of the cases. One of the classic measures of CI is the Paced Auditory Serial Addition Test (PASAT 3") also referred in the literature been used as a quantitative measure related to cognitive fatigue.
Objectives: We aim to study the effect of fatigue in PASAT performance in patients with MS and different degrees of CI.
Methods: A sample of 81 MS patients from the clinic (35,8% men, mean age of 43 years old (SD=10,5)) was divided into three groups: 25 with no cognitive impairment (NCI) when all cognitive functions (CF) were preserved; 25 with mild cognitive deficit (MCD) when one or more CF were affected with a Z score of -1 to -1.5 or one CF scored -2; and 31 with moderate cognitive deficit (ModCD) when two or more CF scored -2. Comprehensive neuropsychological assessment was administered to fulfil this classification. 30 healthy controls (HC) with same age and educational level were included in the study. We scored both correct (hits and dyads) answers and errors (omissions, interference, sum-errors, perseverative errors and chunking responses) in two blocks: first from item 1 to 30 and second from item 31 to 60. We used these two steps to assess cognitive fatigue according to previous literature. Patients' results were compared with 30 healthy controls (HC) with same age and educational level.
Results: HC group showed a significant decrease in correct responses from first to second block ($p=.024$), and increasing number of omissions. Equivalent profile was found in NCI patients ($p=.001$ for hits and $p< .001$ for dyads). MCD showed only differences in dyads ($p=.05$) in the second block when compared with the first. ModCI produced less correct responses and more omission and perseverative errors in the second block ($p< .001$ for correct responses; $p< .001$ and $p=.04$ for errors)
Conclusions: HC group performance suggested that PASAT could be sensitive to a decrement in accuracy on the second block of this test that, together with a higher omissions error could count on a worsening of performance in a high cognitive demanding task. When compared with our MS sample, NCI patients showed a quite similar performance, nevertheless MCD and ModCD groups show different error patterns. We suggest that these changes might be related with a decrement on attention and updating abilities probably due to fatigue.

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P903

Assessment of brain atrophy in multiple sclerosis patients with fat-suppressed T1 weighted and FLAIR subtracted images utilising Comparative Brain Imaging software

M. Hojjati[1], T. Richards[1], C. Tatsouka[2], F. Thiele[3], L. Wolansky[1]
[1]Radiology, University Hospital Case Medical Center, [2]Neurology, Case Western Reserve University, Cleveland, OH, United States, [3]Philips GmbH, Aachen, Germany

Background: In the BECOME study, 75 multiple sclerosis (61 with relapsing remitting and 14 with CIS) were treated for up to 26 consecutive months. The clinical outcomes of the study have been reported.The Comparative Brain Imaging (CoBI) software developed by Philips Healthcare aids in visual detection of brain parenchymal changes.
Goals: The goal of this study is to compare the efficacy of magnetic resonance (MR) fat-suppressed T1 weighted and fluid-attenuated inversion recovery (FLAIR) subtracted images in detecting brain atrophy in multiple sclerosis (MS) patients by using the CoBI software.
Methods: This retrospective study included 10 patients with MS. The patients underwent MRI brain at 3-Tesla at the start of the study and at 12 and 24 months (2 patients did not follow up at 24 months). The CoBI software (Intellispace Discovery, Philips Healthcare, Best, The Netherlands) was used to support visual qualitative assessment of brain atrophy between two axial images. The software was used to create digitally subtracted images comparing the follow-up scans with the initial scan displayed on a color scale. A total of 20 slices at and cranial to the foramen of Monro were evaluated for both the FLAIR and T1 sequences comparing each follow up scan to the patient's original scan. The mean difference between the number of slices demonstrating atrophy on FLAIR versus T1 sequences was analyzed using Wilcoxon signed rank test. The severity of each patient's global brain atrophy on the 24-month subtracted images for both the FLAIR and T1 was graded on a scale of zero to three. The mean difference of slices showing atrophic changes was correlated to the radiologist's global atrophy score for both sequences using the Spearman correlation.
Results: Subtracted FLAIR images identified more atrophy than T1 at both the 12 and 24-month time intervals (respective p-values of .005 and .030). There was 52% more atrophy detected at 12 and 41% more atrophy detected at 24 months with FLAIR. The correlation analysis showed the mean difference in atrophy detection was correlated with the global atrophy score on both FLAIR ($r = 0.90$) and T1 ($r = 0.82$) sequences.
Conclusion: In this population of 10 patients with RR MS, FLAIR showed to be more efficacious in detecting brain atrophy utilizing CoBI software than fat-suppressed T1 images.

Disclosure

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P904

Outcome measures for clinical trials on spasticity: preliminary recommendations from the Italian MS Spasticity Consensus Task Force

L. Leocani[1], A. Solari[2], D. Centonze[3], M. Rovaris[4], C. Trompetto[5], A. Ghezzi[6], C. Solaro[7], M. Marrosu[8], S. Otero[9], G. Comi[1], the Italian MS Spasticity Consensus Task Force

[1]Neurology Dep.t and INSPE-Institute of Experimental Neurology Hospital San Raffaele, [2]Istituto Neurologico C. Besta, Milan, [3]University of Rome "Tor Vergata, Rome, [4]Don C. Gnocchi Foundation, Milan, [5]University of Genova and IRCCS AOU San Martino-IST, Genova, [6]AO S. Antonio Abate, Multiple Sclerosis Study Center, Gallarate, [7]Neurology Unit, ASL 3 Genovese, Genova, [8]Neurological Dep.t, University of Cagliari, Cagliari, Italy, [9]Centre d'Esclerosi Múltiple de Catalunya, Cemcat, Barcelona, Spain

The present study represents a preliminary work of the Italian MS Spasticity Task Force, aimed at determining the direction and strength of the recommendations on the treatment of spasticity in Multiple Sclerosis (MS). We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is based on a sequential assessment of the quality of evidence, followed by assessment of the balance between advantages and disadvantages, and finally judgement about the strength of recommendations. A panel of MS experts including clinicians and researchers and one MS patient identified nine clinical questions, and rated their importance based on relevance to patients for decision making. A literature search updated to 15th February 2016 was conducted for each of the interventions considered in the PICOquestions, looking for systematic reviews and randomized clinical trials and using MEDLINE, Embase and Scopus. For those interventions with inexisting or very few RCT available, the search was extended to observational studies. Those studies that fulfilled our inclusion criteria (population: MS patients with spasticity, intervention: those considered in the questions, comparator: any; outcome: any) were considered for the outcome evaluation process. A working group of the Task Force analyzed and graded the importance of the outcomes, based upon their relevance to spasticity, classified as unrelated, direct, indirect or as a global measure influenced by spasticity, and upon the level of validation of the measure, classified as full (level A), partial (level B), insufficient (R-rejected). Outcomes were classified as objective/instrumental measures (n=22), or requiring judgment by the assessing physician (57), or requiring judgment by the patient, i.e. patient reported outcome (n=40). Among the identified instrumental outcomes, 7 were judged as Class A direct measures, 4 among the physician subjective outcomes and 4 among the patient reported outcomes. Although ongoing work will determine the validity and relevance of treatment recommendations, these results suggest that outcome selection and standardization is recommended in the view of planning clinical trials for the treatment of spasticity, in order to allow comparability of results, performing meta-analysis and identify clinical and instrumental predictors of treatment response, towards treatment validation and individualization.

Disclosure

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P905

Compressive pain: A new predictor of myelitis in Neuromyelitis optica (NMO)?

A.C. Aguilar, T. Grippe, C. Tauil, P. Ramona, E. Maciel, R. Dias
Hospital de Base do Distrito Federal, Brasilia, Brazil

Background: NMO and Neuromyelitis optica spectrum disorders (NMOSD) are uncommon neuro-inflammatory syndrome disorders with specific physiopathology and clinical course. The symptoms and presentations are still being explored and not well stablished or described.
Objective: To describe unpublished common clinical features in NMO and NMOSD and evaluate the prevalence of this symptoms in our sample.
Method: Clinical evaluation of 22 patients from a neuroimunology specialized ambulatory with diagnosis of NMO ans NMOSD.
Result: In our sample, 87% (19) of the patients were female, with a mean age of 40 (19 - 59) y.o. The mean disease duration time was of 68 (1 - 244) months , with a mean delay of 23 (1 - 44)months from the initial symptoms to the disease diagnosis. Regarding anti-aquaporin antibodies 87% (19) were seropositive and 13% (3) negative. 50% had neuritis as initial presentation, followed by 30% with myelitis and 20% with are postrema radiologial envolvement and clinical symptoms. Considering all the disease presentation time, 80% had neuritis, 70% had myelitis and 30% had area postrema symptoms and 60% reported disautonomic symptoms. Among the 82% (18) patients with medullary involvement, 100% had painful tonic spasms, 67% (12) reported a compressive chest or abdominal pain, 44%(8) had lhermite signal. Moreover, 61%(11) reported urinary incontinence and 61% (11) unresponsive neuropathic pain. Regarding the patients with neuritis, 57% (11) had continous eye pain. Pruridous was also a complain of 36% (8) of all the patients.
Conclusion: Our results showed an important delay from the symptoms onset to the diagnosis. Therefore is importante to describe the most prevalente symptons as compressive chest or abdominal pain and continuos eye pain that may facilitate the diagnosis of the NMO and NMOSD. Since these features are not described in other diseases and might increase the sensibility for the disease investigation.

Disclosure

nothing to disclose

P906

Responsiveness of laboratory- and clinically-based measures of postural performance following balance rehabilitation in patients with multiple sclerosis

H. Negahban[1], S. Monjezi[2], M. Mehravar[2], N. Mostafaee[2], A. Shoeibi[3]
[1]Department of Physical Therapy, School of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, [2]Musculoskeletal Rehabilitation Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, [3]School of Medicine, Mashhad University of Medical Sciences, Mashhad, Islamic Republic of Iran

Background: Evaluating responsiveness has an important role in the design and interpretation of results and the consequent clinical decisions obtained in the randomized controlled trial studies.
Purpose: To determine the responsiveness of some commonly-used outcome measures of postural performance following balance rehabilitation in patients with Multiple Sclerosis (MS, n=38) and to determine the minimally clinically important difference (MCID) in change score of balance measures that is perceived beneficial from the patient's perspective.
Method: Postural performance measures were evaluated at baseline (pre-intervention) and after 4 weeks balance rehabilitation (post-intervention) using a standardized test protocol. Moreover, the 7-point global rating scale was completed by the patients at 4 weeks. Laboratory-based measures were center of pressure (COP) parameters. Clinically-based measures were Activities-specific Balance Confidence (ABC), Berg Balance Scale (BBS), Functional Gait Assessment (FGA), 2 Minute Walk (2MW), 10 Meter Timed Walk (10MW) and Timed Up and Go (TUG). To evaluate responsiveness, we calculated the receiver operating characteristics (ROC) and the area under the ROC curve (AUC) with its 95% confidence interval (CI). The optimal cutoff points for the MCID were determined from the point on the upper left hand corner of the ROC curve.
Results: While the change scores were not statistically significant for all COP parameters in all postural conditions, the AUC values for mean velocity and SD velocity were above the cutoff point of 0.50 in all postural conditions. For the clinically-based outcome measures, the AUC_S ranged from 0.36 to 0.64, the highest values were found for the ABC, and 2MW, followed by the BBS and 10MW.
Conclusions: Among laboratory-based measures of postural performance, the mean and SD velocity could be considered as responsive measures of static posturagraphy to detect changes following balance rehabilitation. Also, among clinically-based measures of postural performance, the ABC, 2MW, BBS, and 10MW were responsive outcome measures that quantify balance confidence, walking endurance, functional balance, and walking speed in patients with MS undergoing balance rehabilitation.
Key words: Responsiveness, Postural measures, Balance rehabilitation, Multiple sclerosis

Disclosure

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Economic burden

P907

Increasing rates of employment in the Australian MS longitudinal study

I. van der Mei[1], A. Kirk-Brown[2], B. Taylor[1], P. van Dijk[2]
[1]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, [2]Monash Business School, Monash University, Melbourne, VIC, Australia

Background and objectives: Previous studies have documented far lower participation rates in paid employment for people with Multiple Sclerosis (MS) compared to the general population. In a large national sample of people with MS, we examined employment status, longitudinal changes in employment, and the provision of required modifications to work roles and work environment from 2010 to 2013.
Methods: The Australian MS Longitudinal Study collects data from a representative sample of Australians with MS. Employment data were collected from 2010 to 2013 (n=2143 (2010), n=1846

(2011), n=2291 (2012), and n=2182 (2013), with 1260 people responding to all four surveys. Employment rates were compared (z-tests) with the general population using data from the Australian Bureau of Statistics. The survey included questions on the organisational provision of modifications to employees' work role and work environment.

Results: The longitudinal loss of employment was 5.8% over the four years. The age and sex standardised rates of employment (full and part-time) increased over the four years from 48.8% in 2010 to 57.8 in 2013 which was associated with a decrease in the difference between people with MS and the general population from 14.3% in 2010 to 3.5% in 2013. The majority of people with MS (2013) who required adjustments to their work role (38.8%) received those adjustments (94.8%) with slightly less of those requiring adjustments to their work environment (21.1%) receiving them (81.6%).

Conclusions: The gap in employment between people with MS and the general population has substantially reduced from 2010 to 2013. It is also encouraging to find that organisations are responding positively to requests for work role/environment adjustments. It is important to understand the relative contribution of factors that may have reduced this gap, such as possibly the role of immunotherapy and employment support services.

Disclosure

The authors have no relevant disclosures

P908

Inability to work and need for social and family support drive costs in multiple sclerosis

G. Kobelt[1], J. Berg[2], M. Gannedahl[2], J. Eriksson[2], A. Thompson[3], MS BOI Study Group

[1]European Health Economics, Mulhouse, France, [2]Mapi, Stockholm, Sweden, [3]University College London, London, United Kingdom

Background: Multiple sclerosis (MS) often results in adults reducing or abandoning their workforce participation and relying heavily on support from the health care system, community and family.

Objectives: Within a European-wide burden of illness study, we assessed the impact of production losses, community and family support on total costs, and explored the factors that may affect their level of use.

Methods: Patients provided data on their disease, resource use, fatigue, cognition, work productivity and health related quality of life. Resources were valued from the societal perspective using publicly available unit costs. Production losses (sick leave, invalidity and early retirement) were valued using the human capital approach with gender specific employment cost. Informal care costs were calculated as the opportunity cost of time using disposable income. Factors affecting workforce participation were explored using logistic regression.

Results: 16,400 patients from 16 countries participated, covering all Expanded Disability Status Scale (EDSS) levels. Based on 13,844 patients from 10 countries, mean age was 52±12 years, with 80% of working age, mean disease duration 15±10 years and 74% were women. Production losses, community and family support accounted for 39-74% of total costs and were all directly related to disease severity. Depending on the country, employment rate was 52-78% in mild MS (EDSS $\leq$ 3), 27-50% in moderate MS (EDSS 4-6.5) and 10-23% in severe MS (EDSS 7-9). 43% worked part-time and in 41% of these, it was due to MS. 79% of working patients reported difficulties at work due to MS, predominantly related to fatigue, concentration and mobility. Loss of work capacity, community support and informal care use were related to disease severity in all countries, but the level of service use differed considerably: community services were used by 2-16%, 9-39% and 17-69% and informal care by 17-34%, 52-74% and 62-93% of patients in mild, moderate and severe disease, respectively. Controlling for age, disease severity, gender and country, patients in the workforce used fewer services but had a higher use of disease modifying treatments ($p>0.001$).

Conclusion: MS affects workforce participation and the need for services at all disease levels, resulting in one of the major cost components in MS in all countries. Direct comparisons between countries can however not be made without taking into account sample differences and economic conditions.

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P909

Predictive validity of the MS work instability scale

C.R. Wicks[1], A. Tennant[2], A. Stroud[1], H.L. Ford[1]

[1]Centre for Neurosciences, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [2]Swiss Paraplegic Research, Nottwil, Switzerland

Background: Maintaining paid work is a key issue for people with MS (PwMS). The concept of Work Instability - the mismatch between a person's current abilities and the demands of their job, has the potential to identify those where intervention may facilitate job retention. A scale for this (MS-WIS) was recently introduced, but evidence needs to be obtained for its predictive validity before confidence can be placed in its role as a screening instrument for risk of job loss [1].

Methods: A three year longitudinal study used validated self-completed measures, including the MS-WIS as well as psychological factors, impact of MS, quality of life and fatigue assessed PwMS at four time points. The questionnaire was administered at baseline, 8, 18 and 28 months.

Results: 208 employed PwMS were entered into the study at baseline, and 177 completed the final time point, month 28. Mean

age was 40.7 years (SD 9.2; range 20-60) with disease duration of 7.0 years (SD5.7; range 0-27). 74.5% were female and the majority (89.9%) were of the relapsing remitting type. This was a highly qualified working group with 62.9% achieving a diploma, degree or professional qualification.

Of those still participating at the final time point, over one-in-ten (11.4% - 95% CI 6.9-15.9) were no longer in paid work. Of all the scales used in the study, the highest proportion of variance explained (0.157) with respect to the loss of paid work came from the MS-WIS. The unadjusted odds ratio for being in paid work at month 28 when patients reported high Work Instability risk at baseline was 0.118 (p=0.001). Thus the odds of being in paid work 28 months after recruitment into the study were reduced by 8.5 times where high risk was initially reported.

Conclusions: Maintaining paid work is a key objective for those living with MS. The MS-WIS was developed to help screen for the risk of job loss, and the current study provides initial evidence that is has strong predictive validity over the short term (i.e. < 3 years). Thus the scale could be used routinely to monitor working PwMS to inform clinical management and appropriate referral to facilitate job retention.

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P910

Multiple sclerosis and disease modifying therapies:if you prescribe it, will they take It? -a population analysis of predicted self-administration of medication adherence behavior

K. Wissemann[1], M. Gudesblatt[1], B. Bumstead[1], M. Zarif[1], L. Fafard[1], S. Thotam[1], M. Buhse[1,2], D. Golan[3,4], S. Becker[5], C. Sullivan[6,7], J. Wilken[6,7], D. Morisky[8]
[1]South Shore Neurologic Associates, Patchogue, [2]Stony Brook University, Stony Brook, NY, United States, [3]Department of Neurology, Carmel Medical Center, [4]Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel, [5]The Chicago School of Professional Psychology, Washington, D.C., DC, [6]Neuropsychological Associates, Fairfax, VA, [7]Georgetown University Hospital, Department of Neurology and Washington Neuropsychology Research Group, Washington D.C., DC, [8]UCLA Fielding School of Public Health, Los Angeles, CA, United States

Background: People with Multiple Sclerosis (PwMS) and prescribers have multiple treatment choices. Disease modifying therapy (DMT) non-adherence and delaying DMT initiation impact outcomes. PwMS DMT non-adherence might increase long-term economic costs. Adherence can be measured by direct observation, patient report, prescription refills and other measures. With varied DMT route and frequency, "predicted PwMS adherence behavior" for self-administered treatments needs investigation to evaluate how this might impact prescribing practice and MS care. The Morisky Medication Adherence Score (MMAS-8), a validated 8 point questionnaire, is predictive of medication adherence, pharmacy fill data, relevant for treatments of varied routes/frequency, and correlates with efficacy and economic outcomes. DMT choice reflects many factors but adherence directly impacts therapy efficacy and perhaps safety. The long term MS economic impact demands treatment safety, efficacy, and adherence.

Objective: Explore PwMS predicted adherence behavior to medication if self-administered.

Methods: Single site cross sectional analysis of PwMS who completed Morisky Medication Adherence questionnaire (MMAS-8) during routine care.

Results: 788 PwMS, 73% female, average age 48. Predicted self-administered adherence behaviors for treatments were: 38% high, 34% medium, and 28% low adherence. The difference in predicted adherence behavior was significant ($p < 0.01$). Gender and age by themselves had no significant impact on predicted adherence profile. Prescribed DMT route did not appear to impact overall predicted PwMS self-administered adherence profile.

Conclusions: Patient adherence is a significant problem in MS care. Reduced DMT efficacy might reflect sub-optimal adherence for those self-administered treatments. High potency DMT, requiring safety monitoring, might have sub-optimal patient adherence. High frequency prescribed self-administered DMT prescribed to PwMS who are likely low adherent might reflect a poor choice of available DMT options. Treatment required for chronic disease requires ongoing efficacy, tolerability and high adherence. Analysis of individual adherence behavior might impact treatment decisions and alter DMT choices. Factors improving adherence or DMT choice might improve efficacy/outcome and reduce long term care costs.

Disclosure

All: nothing to disclose

P911

Income among multiple sclerosis patients with different disease phenotypes

A. Kavaliunas, A. Manouchehrinia, V. Danylaite Karrenbauer, H. Gyllensten, A. Glaser, K. Alexanderson, J. Hillert
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Background: Multiple sclerosis (MS) is a disease with profound heterogeneity in clinical course. Data from natural history series support the notion that secondary and primary progressions are more similar, than they are different, nevertheless differences exist and these are distinct forms of the disease.

Objectives; To analyse sources and levels of income among MS patients in relation to disease phenotype with a special focus on identifying differences/similarities between primary progressive MS (PPMS) and secondary progressive MS (SPMS).

Methods: A cross-sectional study was conducted linking data from Statistics Sweden and the Swedish Multiple Sclerosis Register. A total of 6890 MS patients aged 21−64 years and living in Sweden in 2010 were identified. Descriptive statistics, logistic and truncated linear regression models were used to estimate differences in annual income of earnings and social benefits between SPMS, PPMS and relapsing-remitting MS (RRMS) patients, including disability pension, sickness absence, disability allowance, unemployment compensation, and social assistance. Means, medians, and regression coefficients were reported in Swedish Krona (EUR 1 = SEK 9.5 in 2010). Proportions and probabilities, expressed as odds ratios and prevalence ratios, were analysed. Multivariable regression models were adjusted for age, disease duration, sex, geographical region, family composition, type of living area, country of birth, and education.
Results: RRMS patients earned almost twice as much as PPMS and SPMS patients (on average SEK 204,500, SEK 114,500, and SEK 79,800 in 2010, respectively). The difference in earnings between PPMS and SPMS was not statistically significant when analysed with multivariable regression. The estimated odds ratio for PPMS patients for having income from earnings was not significantly different ($p > 0.05$) from SPMS patients (95% confidence interval 0.98 to 1.59). PPMS and RRMS patients were less likely to receive benefits when compared to SPMS patients (by 6% and 27% lower, respectively).
Conclusion: Controlling for most important confounders, RRMS patients had significantly more earnings and less benefits than PPMS and SPMS patients, who in term differed very little from each other. These findings argue for similarities between PPMS and SPMS and highlight the socioeconomic importance of preventing RRMS patients convert to SPMS.

Disclosure

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P912

Differences in employment of people with MS across Europe

T. Meißner[1], D. Ellenberger[1], P. Flachenecker[2], J. Hillert[3], K. Buckow[1], for the PRO working group of EUReMS
[1]University Medical Center Göttingen, Georg-August-Universität Göttingen, Göttingen, [2]Neurological Rehabilitation Center, Bad Wildbad, Germany, [3]Karolinska Institute, Stockholm, Sweden

Background and Goals: A challenging consequence of MS is the economic burden since many patients need to quit working early because of MS related challenges. The PRO (Patient-Reported Outcomes) study of the EUReMS (European Register for Multiple Sclerosis) project focusses on the identification of differences in quality of life and employment between the participating MS registers.
Methods: Three registers have been elected to participate in the PRO study: the MS-Register der DMSG (Germany), the REJSM - Polish MS register (Poland) and the SMSreg - Svenska Multipel Skleros registret (Sweden). A total of 1965 patients met the study's inclusion criteria. Since SMSreg has been collecting PRO data for years, it contributed the largest amount of patients (n=1386) while PRO data collection in Poland (n=245) and Germany (n=334) was started in 2013. Data collected up until summer 2014 was analysed in the abstract. A data handling routine has been developed to process and harmonize the heterogeneous data. To adjust for differences in baseline patient characteristics statistical analyses involve multivariable logistic regressions with employment status as outcome.
Results: Substantial differences in the employment rate were found between the registers ($p < 0.001$). In Germany and Poland one third of the PwMS (People with MS) are employed, in Sweden more than 70%. The majority of the employed Pole has a progressive disease course. In Sweden 85% and in Germany 53% are relapsing-remitting. Of the unemployed PwMS the distribution of disease course is similar to that of the employed PwMS. In Germany, though, the progressive form of MS is now dominating (about 75%). Female ($p=0.004$) and older ($p= 0.025$) MS patients were more likely to be without employment.
Conclusion: The data indicate how sensitive employment can be to underlying circumstances. A lot of progress has already been made to keep PwMS longer in employment, but our results indicate that there's still room for improvement. Especially the Swedish data show that high employment rates of PwMS are possible. Findings of our study might be slightly biased due to different definitions of income-generating work. Also selection biases may remain even after adjustment for covariates due to different data sources, e.g. the analysed data of Germany was primarily collected at a rehab-facility. However, the usage of a variety of data sources offers an underrated potential in assessing heterogeneity and sensitivity of results.

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P913

The best clinical correlates of employment status in patients with multiple sclerosis

B. Benova[1], L. Sobisek[2], T. Uher[1], K. Kucerova[1], E. Havrdova[1], D. Horakova[1]
[1]Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, First Faculty of Medicine and General University Hospital, [2]Department of Statistics and Probability, University of Economics, Prague, Czech Republic

Background: Unemployment is a fundamental negative outcome of multiple sclerosis (MS). Currently we do not have any reliable predictors for a change of employment status.
Objectives: Our main aim was to identify the best clinical markers that could distinguish between employed and unemployed patients.
Methods: This was a cross-sectional study with 1226 patients in the original cohort. Every patient was evaluated by the Expanded Disability Status Scale (EDSS), 25 Foot Walk Test (25 FWT), Nine Hole Peg Test (9HPT), Brief International Cognitive Assessment for MS (BICAMS), Paced Auditory Serial Addition Test (PASAT), Beck Depression Inventory (BDI) and Sloan charts (SLOAN). In the first step, we chose patients with full time job (n=787) and unemployed patients with disability pension (n=210). In the second step we matched both groups according to gender, age and education. Logistic regression analysis was used to select the best predictors. The fitted models were compared using the Akaike Information Criterion (AIC), the Nagelkerke R2 (R2), as well as Odds Ratio 95% confidence interval (OR).
Results: The final selected groups accounted for 307 full time job patients (F 248, M 59; mean age 41.2y; mean disease duration 9.64y) and 153 unemployed patients with disability pension (F 127, M 26; mean age 42.21y; mean disease duration 14.36y). Both studied groups were significantly different in all tested variables ($p < 0.05$). In the univariate analysis the significant predictors of vocational status were EDSS (AIC 364.3; R2 0.54), SDMT + BDI (AIC 474.5; R2 0.31), 9HPT (AIC 489.8; R2 0.27; OR 1.16-1.28) and 25FWT (AIC 471.6; R2 0.30; OR 1.81-2.63). OR for SDMT was 0.91-0.95 and for BDI 1.07-1.1. EDSS was then excluded from a multivariate model because it was not an independent variable (in the Czech Republic a value of EDSS is used for providing a disability pension). In the multivariate model 25FWT+SDMT+BDI was the best combination of predictors (AIC 414.9; R2 0.44; OR 25FWT (1.51 - 2.22), SDMT (0.93 - 0.97), BDI (1.06 - 1.14)).
Conclusions: Walking ability (25FWT) and cognitive performance (SDMT) adjusted for depression are reliable independent predictors of vocational status. Taking them together increased our ability to identify unemployed patients. This study provides the first step towards our main goal: finding predictors for employment status and employability in longitudinal data analysis.

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P914

Evaluating the increase in the cost of Multiple Sclerosis drugs in the United States between 2010-2015: Market price vs inflation based analysis

B.L. Vollmer[1], K.H. Chong[2], J. Campbell[2], J. Corboy[1], T. Vollmer[1], K.V. Nair[2]
[1]Rocky Mountain Multiple Sclerosis Clinic at University of Colorado, [2]Skagg's School of Pharmacy and Pharmaceutical Sciences, University of Colorado - Anschutz Medical Campus, Aurora, CO, United States

Background: Recently, a number of Multiple Sclerosis(MS) disease modifying therapies(DMTs) have become newly available, including the introduction of oral therapies such as dimethyl fumarate and fingolimod. Rituximab has been used to treat MS although as off label therapy. Regardless of the increase in options, cost of MS DMTs, including older DMTs have increased dramatically.
Objectives: To compare cost increases for market based versus inflation adjusted MS DMTs by route of administration including oral, infusion or injectable between 2010-2015.
Methods: All FDA-approved MS drugs were included in this analysis, except for mitoxantrone. Rituximab was included, however analyzed individually. The Average Wholesale Price(AWP) was used as a conservative and accepted estimate for the market price of a DMT per year and was compared to the inflation adjusted annual price(or expected price) per year using the Consumer Price Index(CPI) for Prescription Drugs. Changes in annual AWP pricing for each DMT was estimated from the RED BOOK® for each year following the approval of a DMT and adjusted for a 15% discount rate. Similarly, CPI rates, obtained from the Bureau of Labor Statistics were used to estimate the expected increase of each DMT per year since approval based on the inflation rate for prescription drugs. The actual rate of increase versus expected rate of increase in DMT costs were compared using descriptive statistics and estimates of annual relative increase from 2010 AWP values.
Results: The averaged discounted AWP annual prices in 2015 for FDA-approved oral, infusion, injectable medications were $71,922,

$69,153, $62,396 respectively. Off label infusion administered rituximab(4g/year) was much lower at $30,514. From 2010-2015, the average rate of increase in the market price of all DMTs (excluding rituximab) was **8.82** times higher compared to their expected increases. Injectables, infusion(excluding rituximab) and oral DMTs increased in market price at a rate of **11.60**, **4.20**, and **6.00** more per year compared to expected price, respectively. Rituximab had the lowest increase in market price, increasing only at rate of **1.75** times more compared to expected price.

Conclusions: Market cost increases for MS DMTs is substantially greater than the CPI rates of inflation for prescription drugs. Rituximab has not followed this trend. There is a critical need to address these dramatically increasing MS DMT prices.

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P915

The impact of patient out-of-pocket costs and satisfaction with therapy on adherence to disease-modifying drugs in patients with multiple sclerosis

L. Mayer[1], J. Smrtka[2], S. Gupta[3], A.L. Phillips[4]
[1]Central Texas Neurology Consultants, Round Rock, TX, [2]University of Miami Multiple Sclerosis Center of Excellence, UHealth at Boca Raton, Boca Raton, FL, [3]Kantar Health, Princeton, NJ, [4]EMD Serono, Inc., Rockland, MA, United States

Introduction: Several studies of varying design and methodology have evaluated factors associated with disease-modifying drug (DMD) adherence in multiple sclerosis (MS); however, literature evaluating the influence of patient-centred outcomes on adherence to DMDs is scarce. This study aimed to evaluate the impact of patient out-of-pocket (OOP) costs and satisfaction with therapy on adherence to DMDs in patients with MS.

Methods: Patients with MS (n=1112) and currently being treated with a self-injectable or oral DMD from the US National Health and Wellness Survey or Lightspeed Research panel and its affiliates completed an internet survey between April and October 2015. The survey included questions about demographics, disease severity and symptoms, treatments, health behaviours, and comorbidities. MS-related OOP costs for doctor visits, medication, and other costs were reported as monthly estimates. DMD adherence was evaluated using the 4-item Morisky Medication Adherence Scale (MMAS-4). The Treatment Satisfaction Questionnaire for Medication (TSQM) assessed satisfaction (i.e. effectiveness, convenience, and satisfaction) with current DMD.

Results: Of 805 survey respondents meeting study criteria, 429 reported high adherence (MMAS-4=0) and 376 reported low adherence (MMAS-4=1-4). Bivariate analyses showed no statistically significant differences in OOP costs between high and low adherers. TSQM scores for effectiveness, convenience, and satisfaction were significantly higher in high adherers compared with low adherers (all $p< 0.05$). The data were further delineated to elucidate if relationships could be uncovered with different adherence categories. Patients previously categorised as low adherers were re-categorised as either moderate (MMAS-4=1-2) or low (MMAS-4=3-4) adherers. New patterns did emerge with the increased granularity. Compared with high adherers, (newly defined) low adherers had higher monthly MS-related OOP doctor visit costs ($42.60 vs $23.75 for moderate adherers and $24.07 for high adherers; $p< 0.05$) and other OOP costs ($71.37 vs $42.34 for moderate adherers and $35.57 for high adherers; $p< 0.05$). Compared with high adherers, (newly defined) low adherers had lower satisfaction TSQM scores (44.53 vs 56.51 for moderate adherers and 57.26 for high adherers; $p< 0.05$).

Conclusions: In this real-world population, lower OOP costs and greater treatment satisfaction were associated with higher levels of adherence to DMD treatment.

Disclosure

Lori Mayer served on advisory boards for EMD Serono, Inc., Genentech, Sanofi-Genzyme, and Teva Neuroscience, and served as a speaker for Biogen, Genentech, Novartis, and Sanofi-Genzyme.
Jennifer Smrtka served on advisory boards for EMD Serono, Inc., Genentech, Sanofi-Genzyme, and Teva Neuroscience, and served as a speaker for Mallinckrodt, Sanofi-Genzyme, and Teva Neuroscience.
Shaloo Gupta is an employee of Kantar Health, Princeton, NJ, USA. Kantar Health received funding from EMD Serono, Inc., to conduct and report on this study.
Amy L Phillips is an employee of EMD Serono, Inc., Rockland, MA, USA (a business of Merck KGaA, Darmstadt, Germany).

Neuro-ophthalmology

P916

Poor visual functioning and quality of life in multiple sclerosis are associated with retinal atrophy

L. Balk[1], D. Coric[1], J. Killestein[1], B.M.J. Uitdehaag[1], A. Petzold[1,2]
[1]Neurology, VU University Medical Center, Amsterdam, The Netherlands, [2]UCL Institute of Neurology, Queen Square, London, United Kingdom

Background: Inner retinal layer atrophy in patients with Multiple Sclerosis (MS) has been validated as a structural imaging biomarker for neurodegeneration. There is however only limited data on the impact on the patient's visual function related quality of life (QoL).

Objective: To determine how inner retinal layer thickness relates to low and high contract visual acuity and vision-related quality of life, and to investigate whether previous episodes of optic neuritis (MSON) affect this relationship.
Methods: This cross-sectional observational study included 246 patients with MS. Spectral-domain OCT images were segmented for the peripapillary retinal nerve fibre layer (pRNFL) and the macular ganglion cell inner plexiform layer (GCIPL). Ophthalmological evaluations included history on MSON, high and low contrast visual acuity (VA) and vision-related QoL. Generalized estimation equations and linear regression analyses were used to analyze group differences and associations with clinical measures.
Results: Patients had a mean disease duration of 19.3±7.5 years (range 8.5 - 48.0), 67.5% were female. Previously clinically identified episodes of MSON were present in 37% of patients (N=91), of which 22.8% unilateral and 14.2% bilateral. Macular GCIPL thickness was significantly associated with high (β=0.2, p=0.007) and low (β=0.3, p=0.001) contrast visual acuity. In patients with a history of bilateral MSON, the association was strongest with low contrast VA (β=0.7, p< 0.001). Findings for the pRNFL were consistent with the macular GCIPL. Patients with bilateral MSON had a lower vision related QoL ,compared to patients who never experienced MSON (mean difference 7.4 points, p=0.024). Preliminary analyses in a subset of patients (N=142) revealed that in patients without previous MSON, thinning of the macular GCIPL, but not the pRNFL, was significantly associated with lower visual quality of life (β 0.2, p=0.04).
Conclusion: This study showed that retinal atrophy has a significant impact on visual functioning in patients with MS. Both visual acuity and vision-related quality of life were decreased in patients with atrophy of the macular ganglion cells. OCT may therefore give useful insight in patients with visual dysfunction and our findings support including OCT and visual QoL measures into optic neuritis treatment trials.

Disclosure

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BMJ Uitdehaag: has received personal compensation for consulting from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche en TEVA.
A Petzold: is member of the steering committee for the OCTiMS study (Novartis), no consulting fees. Performs OCT QC for the Passos study (Novartis), receives consulting fees.

P917

Atypical immune-mediated optic neuritis at onset: antibodies, differential diagnoses and prognoses

E. Carnero Contentti[1], M. De Virgiliis[2], J.P. Hryb[1], F. Leguizamon[3], J. Celso[3], J.L. Di Pace[1], M. Perassolo[1]
[1]Neurology Department, University of Buenos Aires, Hospital Carlos G. Durand, [2]Neuro-Ophthalmology Section, University of Buenos Aires, Hospital P. Lagleyze, [3]Neurology Department, Hospital Alvarez, Buenos Aires, Argentina

Background: Severe isolated, bilateral and/or recurrent optic neuritis (ON) may herald neuromyelitis optica spectrum disorders (NMOsd). However, a broad range of etiologies can be observed. Thus, establishing the correct diagnosis can have an impact in terms of disease specific treatment and prognosis.
Objectives: To report the features, differential diagnosis and prognosis of atypical ON patients at onset in an Argentine population.
Methods: Retrospective study that included 22 sequential patients with atypical features of first acute ON inmmune-mediated at onset, without signs concern for systemic disease, who were referred for consideration of NMOsd, multiple sclerosis ON (MSON), chronic relapsing inflammatory ON (CRION), single isolated ON (SION) or any other inflammatory CNS disorders. Aquaporin-4 antibody (AQP4-Ab) was performed in all patients.
Results: AQP4-ab seropositive proportion was 41%. AQP4-ab was only detected in NMOsd patients and in none of the MSON, CRION and SION patients. Visual acuity (VA) baseline was poor (68%) and 100% of these patients were associated with worse VA outcome as VA of counting fingers only at 6 months with a median time of follow-up of 3.30 (±1.61) years. VA severity is not associated with serological status and no correlation was found between serological status and number of ON relapses. However, 31% of AQP4-ab negative patients developed relapses ON, 40.9% bilateral ON, 18.18% longitudinally extensive transverse myelitis and 75% of CRION patients were associated with better VA outcome (VA of 20/30 to 20/59).
Conclusion: We emphasize the high specificity of AQP4-ab to distinguish patients with a complete clinical diagnosis of NMO/NMOsd from those with other etiologies. All of patients with VA baseline poor were associated with VA counting finger only at follow-up. AQP4-ab status is not associated with the number of ON relapses and severity disease as has been previously shown in other countries.

Disclosure

nothing to disclose

P918

Visual performance in patients with neuromyelitis optica correlates with anti- aquaporin-4 antibody level

M. Gurevich[1], A. Feldman[2,3], A. Gal[1], A. Achiron[2,3]
[1]Sheba Medical Center, [2]MS Center, Sheba Medical Center, Ramat Gan, [3]Tel Aviv University, Tel Aviv, Israel

Background: Neuromyelitis Optica (NMO) is an autoimmune demyelinating disease that affects the optic nerve and spinal cord. Anti-Aquaporin-4 antibody (AQP-4 Ab) has been found to be a highly specific and sensitive diagnostic marker for NMO. However there are only a few studies analyzing the relations between the level of AQP4-Ab and NMO clinical presentation.
Objective: To investigate the correlation between AQP4-Ab titter and visual performance of NMO patients at disease onset.
Methods: We evaluated NMO patients with single or recurrent episodes of optic neuritis or transverse myelitis or both having positive AQP4-Ab test. The levels of AQP4-Ab in patients with (N=23) or without (N=27) radiologically active lesions in the optic nerve were tested using *ElisaRSRTM AQP4 Ab Version 2* kit (RSR, UK, positive cut off ⩾3.0 μg/ml). Pearson correlation between AQP4-Ab titer and visual acuity in the most affected eye

was also calculated. AQP4-Ab levels were compared between patients with low vision (visual acuity 6/120 or less including finger counting, light perception and blindness), patients with medium vision loss (6/12 to 6/60) and NMO patients with normal vision (6/6 to 6/12). Additionally, AQP4-Ab levels were compared between patients with and without radiologically active lesions in the optic nerve.

Results: Forty AQP4-Ab positive NMO patients, 23 females, age 38.5±2.4 years, EDSS=3.3±0.3, were included in the analysis. AQP4-Ab titer range was 3.2 to 199.0, and positively correlated with visual acuity in the affected eye (r= 0.52, p=0.005). Low and medium vision patients (n=18) were characterized by significantly higher AQP4-Ab titer than patients with normal vision (n=22), 81.1±17.0 vs 17.0±4.7 μg/ml, p=0002, respectively. Higher AQP4-Ab titer at onset was associated with bilateral optic nerve involvement as well as with motor involvement. Comparison of AQP-4 Ab levels between patients with and without radiologically active lesions demonstrated higher titers in the group with active lesions 61.5±10 vs 19.8±3.2, μg/ml p=0.01, respectively.

Conclusion: Measuring AQP4-Ab titers is of significance to the severity of NMO ocular involvement. NMO patients with higher AQP4-Ab levels demonstrate more severe disease both clinically and radiologically.

Disclosure

Nothing to disclose

P919

The role of multifocal visual evoked potentials in understanding disability in multiple sclerosis

E.H. Martinez-Lapiscina[1], A.I. Tercero-Uribe[1], S. Alba-Arbalat[1], N. Sola-Valls[1], M. Andorra[1], M. Sepulveda[1], A.M. Guerrero-Zamora[1], R. Torres-Torres[2], S. Llufriu[1], I. Zubizarreta[1], Y. Blanco[1], B. Sanchez-Dalmau[2], A. Saiz[1], J. Santamaria[1], P. Villoslada[1]

[1]Neurology, [2]Ophthalmology, Hospital Clinic and Institut d´Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Background: In multiple sclerosis (MS), there is an increasing interest in drugs promoting myelin repair (e.g. Opicinumab or Clemastine). Multifocal visual evoked potentials (mfVEPs) have been suggested as an appropriate technology to monitor the efficacy of these drugs. Addressing the relationship between mfVEPs and disability as well as with markers of neuroaxonal damage in MS is important to define the role of mfVEPs as surrogate endpoint in clinical trials and evaluate the impact of myelin repair strategies to prevent disability in MS.

Goal: to evaluate the relationship of mfVEPs with disability and markers of neuroaxonal damage in patients with MS.

Method: We performed a crossectional analysis in 76 patients with MS. Patients underwent examination including global and visual disability scales (low contrast visual acuity (LCVA) and color vision measured by Hardy, Rand Ritter pseudoisochromatic plates (HRR), mfVEPs and spectral domain optical coherence tomography (Spectralis-SD-OCT). We evaluated the association between the mean latency and amplitude of mfVEP and disability and neuroaxonal injury markers using Spearman´s rank correlation test in eyes unaffected with prior optic neuritis (non-ON eyes) and affected eyes (ON-eyes).

Results: We found inverse associations between the mean latency of mfVEPs and visual disability (2.5%LCVA (rho=-0.311; p=0.010 and HRR (rho=-0.423; p< 0.001)) and retinal neuroaxonal injury measured by peripapillary retinal nerve fiber layer (pRNFL) thickness (rho=-0.237; p=0.050) in non-ON eyes. Regarding the amplitude of the mfVEP, we found associations in non-ON eyes with the Expanded Disability Status Scale (rho=-0.277; p=0.020), 2.5%LCVA (rho=0.232; p=0.057), 1.25%LCVA (rho=0.239; p=0.052), HRR (rho=0.329; p=0.007), and pRNFL thickness (rho=0.263; p=0.029). In ON-eyes, there were associations between the mean latency of mfVEPs and 2.5%LCVA (rho=0.310; p=0.079) and HRR (rho=-0.438; p=0.010) as well as associations between mean amplitude of mfVEPs and 2.5%LCVA (rho=0.419; p=0.014), 1.25%LCVA (rho=0.355; p=0.043), HRR (rho=0.562; p=0.001) and pRNFL thickness (rho=0.561; p< 0.001).

Conclusion: The significant structural-functional correlations between mfVEP, SD-OCT and visual disability in both non-ON and ON-eyes found here supports the use of mfVEP as a marker of axonal and myelin damage in MS as well as its use as a surrogate end-point of efficacy of drugs promoting remyelination

Disclosure

Elena H Martinez-Lapiscina is a researcher in OCTIMS study, an observational study for validating OCT as a biomarker for MS sponsored by Novartis (this study is not involving any specific drug). She has received personal compensation for activities with Biogen Idec and Genzyme as a speaker. She has received grants from the Instituto de Salud Carlos III (CM13/00150 and MV15/00012) and Fundació Marató TV3 (20142030). She has received speaking honoraria from Biogen and Genzyme and travel reimbursement from TEVA, Bayer, Merck-Serono and Roche for international and national meetings over the last 3 years.
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Albert Saiz has received compensation for consulting services and speaking from Bayer-Schering, Merck-Serono, Biogen-Idec, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd and Novartis. He is a researcher in OCTIMS study. Founding: He received grants from the Instituto de Salud Carlos III (RD12/0032/0002)
Joan Santamaria has nothing to disclose
Pablo Villoslada has received consultancy fees from Heidelberg Engineering regarding the clinical applications of OCT; serves as academic editor of Current Treatment Options in Neurology, Neurology & Therapy, Multiple Sclerosis & Demyelinating Disorders, PLOS One, and MS in focus; is founder and hold stocks in Bionure and Spire Bioventures; has received consultancy fees from Roche, Novartis, Health Engineering, and stock options from Mint-Labs; has received unrestricted grants from

Genzyme, Roche and Novartis; and is a researcher in OCTIMS study. Founding: He received grants from the Instituto de Salud Carlos III (PI15/00061 and RD012/0060/01)

P920

Longitudinal assessment of retinal integrity in multiple sclerosis using 3D OCT imaging and intra-retinal layer segmentation

A. Droby[1,2], L. Zaubizer[1], M. Paradis[1], L. Klotz[3], S. Meuth[3], H. Wiendl[3], F. Zipp[1,2], V. Fleischer[1]

[1]Department of Neurology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany, [2]Neuroimaging Center (NIC), the FTN- Focus Program Translational Neuroscience, the Johannes Gutenberg University, Mainz, Germany, Mainz, [3]Department of Neurology, University of Münster, Albert-Schweitzer-Campus, Münster, Germany, Münster, Germany

Background: Optical coherence tomography (OCT) is emerging as a promising imaging method for monitoring retinal pathologies in multiple sclerosis (MS) patients. Depicting retinal degeneration patterns is feasible via the segmentation of intra-retinal layers from 3D OCT datasets.
Objective: Longitudinal evaluation of volume changes of the intra-retinal layers throughout the disease course in relapsing-remitting MS patients.
Methods: N=71 patients (Age [mean ± SD] = 31±8.5 y, disease duration [mean ± SD] = 5.75 ± 3.6 y, median EDSS [range] = 1.5 [0-3]) fulfilled the inclusion criteria and were enrolled in the study. Of these, N=17 had a unilateral optic neuritis episode (ON+) at least six months prior to the baseline OCT acquisition. OCT data from N=10 healthy controls (Age [mean ± SD] = 35 ± 11 y) were also recorded. All participants underwent a follow-up (FU) OCT scan session within an 18 ± 4 month interval. OCT data was acquired using a SD-OCT (Heidelberg Spectralis, Heidelberg Engineering, Germany). Segmentation was performed using an automatic 3D-segmentation algorithm developed in-house.
Results: At baseline, significant thinning of the total retinal volume (TRV), retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) (Mann-Whitney-*U*-test, p= 0.001; 0.008; 0.0001 respectively) was detected when comparing ON+ vs. ON- eyes. The longitudinal analysis across the FU period revealed a significant reduction in TRV, GCL and the inner nuclear layer (INL) (Wilcoxon signed-rank test; $p < 0.0001$ in all cases) in ON- eyes. In ON+ eyes, a significant reduction in TRV, RNFL and INL layers was detected ($p < 0.02$ in all cases) throughout the FU time period as well. Compared to ON- eyes, the RNFL in ON+ eyes demonstrated a significant rate of change across the FU period (T-test, $p = 0.003$).
Discussion: The present findings demonstrate that OCT is a sensitive tool for detecting subtle pathological processes taking place in MS retinas. Following the acute ON attack, significant damage to the cell bodies layer (GCL) was mainly observed in ON+ eyes at baseline, whereas in later stages it was found to be less prominent in this eye-group. In ON- eyes, GCL thinning was detected only in later stages. Moreover, subtle damage to RNFL was observed in both eyes throughout the FU period. These findings highlight that as in the central nervous system, both demyelization and degenerative processes can be viewed in the MS retinas throughout the disease course as well.

Disclosure

None.

P921

Retinal thickness and visual disability in patients with multiple sclerosis and disease-free controls with myopia

R. Nolan[1], D. Laura[1], P. Calabresi[2], E. Frohman[3], S. Galetta[4], L. Balcer[4]

[1]NYU School of Medicine, New York, NY, [2]Johns Hopkins School of Medicine, Baltimore, MD, [3]University of Texas Southwestern Medical Center, Dallas, TX, [4]NYU Langone Medical Center, New York, NY, United States

Objective: We determined the relation of myopia, as measured by spherical equivalent, to retinal thickness in the nerve fiber layer and macula in patients with multiple sclerosis (MS) compared to disease-free controls using optical coherence tomography (OCT).
Background: Myopia is associated with thinning of the peripapillary retinal nerve fiber layer (RNFL) by OCT in healthy patients, and longer axial length, captured by spherical equivalent (spherical correction + 0.5*cylinder), produces RNFL thinning. The extent to which myopic spherical equivalent could affect the relation between MS vs. disease-free control status and RNFL and ganglion cell layer (GCL+IPL) thickness has not been investigated.
Methods: Participants with MS and disease-free controls enrolled in an ongoing collaborative study of MS visual outcomes completed spectral-domain OCT to determine peripapillary RNFL and GCL+IPL thicknesses. The 25-Item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) and 10-Item Neuro-Ophthalmic Supplement, as well as high-contrast visual acuity and low-contrast letter acuity were administered.
Results: Among disease-free controls (n=65 eyes), greater spherical equivalent in the myopic direction was a predictor of thinner RNFL ($p< 0.001$) and GCL+IPL ($p=0.005$, GEE models, accounting for age and within-patient, inter-eye correlations). In the MS cohort (n=291 eyes), greater degrees of myopia were also associated with RNFL thinning ($p< 0.001$). These associations were similar among MS eyes with (n=101 eyes) and without a history of optic neuritis (n=180 eyes). Accounting for MS vs. control status in the models lessened the significance of the association of greater myopia with RNFL and GCL+IPL thinning, but did not account for this relationship completely.
Conclusions: Myopia is a significant contributor to RNFL and GCL+IPL thinning in both disease-free controls and among patients with MS. Even among eyes with a history of optic neuritis, the potential influence of myopia should be taken into account when interpreting group and individual data from OCT measurements.

Disclosure

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P922

Changes in oxygen saturation and the retinal nerve fiber layer in patients with optic neuritis - a pilot study

T. Svrcinova[1], J. Mares[1], P. Otruba[1], V. Sladkova[1], Z. Matejcikova[1], M. Sin[2], P. Kanovsky[1]
[1]Department of Neurology, [2]Department of Ophthalmology, Palacky University in Olomouc, Olomouc, Czech Republic

Background: Optic neuritis (ON) is an optic nerve disease, manifested by decline in visual functions and relative pupillary afferent defect of the affected eye. ON is the presenting feature of multiple sclerosis (MS) in 15-20% patients and almost half of the patients develop ON during the course of disease.
Objective: Assessment of retinal oxygen saturation, of the thickness of retinal nerve fiber layer (RNFL) and of functional changes occurring in the optic nerve during ON.
Methods: Twenty-five patients with ON were enrolled during 2015 (17 females, 8 male, age 34.7 ± 8.9 years, 17 patients with the clinically isolated syndrome - CIS, 8 patients with relapsing-remitting from of MS). All patients were examined using optical coherence tomography (Cirrus HD-OCT 4000, Carl Zeiss, Jena, Germany), automatic optical oximetry (Oxymap, ehf. Reykjavik, Island), and using visual evoked potentials (Metronic Keypoint®, Minneapolis, USA).
Results: We detected statistically significant larger difference between arterial and venous saturation in the retina of ON patients, whereas there were no significant changes of the RNFL thickness. There were no effects of gender or the form of the disease. We found significantly lower optic nerve conduction velocity in affected eye.
Conclusion: Lower level of oxygen saturation in the retinal vessels is apparently caused by a higher metabolic demand. We suggest that in the early stage of ON, oximetry reflects the inflammatory changes in the affected eye earlier and is more appropriate to assess pathological changes than optical coherence tomography. Our next goal is to assess the long-term changes after the recovery of ON.
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Disclosure

nothing to disclose

P923

Descriptive study of a series of optic neuropathies at the moment of diagnosis and predictive factors of its evolution to Multiple Sclerosis

E. García Molina, R. Hernández-Clares, E. Carreón Guarnizo, M. Cerdan-Sanchez, J. Diaz Pérez, G. Valero López, A.E. Baidez Guerrero, J.E. Meca Lallana
Neurology, Virgen de la Arrixaca University Hospital, Murcia, Spain

Goals: The main objective of our study is to characterize the optical neuropathy (ON) at the moment of diagnosis as well as to assess factors that may predispose to evolve to Multiple Sclerosis (MS).
Methods: We performed a cross-sectional, descriptive and retrospective study of a series of 98 patients of our unit whose first symptom of their disease was visual deficit, being diagnosed as optic neuropathy. We picked up their main features in a database and performed an analysis of frequencies, as well as a multivariate analysis to assess which characteristics were associated with the evolution to MS.
Results: We analysed 98 patients, 70 (71%) females and 28(29%) men, with an average age of 33 years. The affected eye was right 34(35%), left 49(50%), and both in 13(13%); retro-bulbar location in 85%.

Only 76(77%) patients were studied when ON occur, within these, oligoclonalfb bands (OCB) in cerebrospinal fluid (CSF) were positive in 59%, the Aquaporin-4-specific serum autoantibodies in 2 cases, and the serology was positive in another 2; with respect to the magnetic resonance imaging (MRI) in 24(35%) was normal, 31(45%) findings compatible with ME, 10(15%) lesions suggestive but not defining ME, and in 4(6%) cases other pathologic findings.

Of all the patients analysed the final diagnosis in 63(64%) patients was MS, in 7(8%) Isolated clinical syndrome (ICS), in 2(2%) Neuromyelitis Optica (NMO), in 4 (4%) chronic relapsing inflammatory optic neuropathy, in 5(5%) ischemic optic neuropathy, and in 9 (9%) other less frequent diseases.

If we analyse only patients who were finally diagnosed of MS we observed that there are significant differences with the rest of patients in regard to the following characteristic: 93.7% retrobulbar location ($p< 0.002$), 93.7% monocular presentation (p 0.002), the OCB was positive in 84.6% ($p< 0.0001$), and lesions in MRI were suggestive of MS in 85% of the patients ($p< 0.0001$).
Conclusion: We have performed a describing and detailed analysis of our series of patients with the diagnosis of ON, in another hand we have observed that in the patients finally diagnosed with MS, the clinical presentation is more frequently monocular and retrobulbar, the lesions in MRI are suggestive of MS and have presence of OCB in CSF, so this data can be used to establish a prognosis at the moment of diagnosis of ON.

Disclosure

No conflict of interest

Pathology

P924

Pathological heterogeneity in the multiple sclerosis post mortem cohort of the Netherlands brain bank relates to clinical course and gender

I. Huitinga[1], M. Mason[2], N. Fransen[3], C.V. Eden[3], S. Luchetti[3]
[1]Neuroimmunology and Netherlands Brain Bank, [2]Neuroregeneration, [3]Neuroimmunology, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

Methods: Two hundred thirty six MS cases (4500 tissue blocks) were included. Lesion types were scored according to demyelination, microglia morphology and anatomical location. Reactive, active, chronic active, chronic inactive and shadow plaques were distinguished in white matter and demyelination in grey matter lesions. Inflammatory activity of lesions was scored based on three types of microglia morphology based on size and ramifications. The proportion of lesion types was inferred from indexes (relative presence). Analysis was performed on total lesion load and indexes in relation to clinical characteristics and gender.

Results: We found large heterogeneity of lesion load, lesion activity, lesion location and remyelination between patients but not within a patient. Total white matter lesion load correlated positively with disease severity ($p=7x10^{-7}$). The active lesion index correlated positively with disease severity (R^2: 0.14 p=1.9e-06), the reactive site index (p=0.018) and the foamy microglia morphology index (p=0.00029). More males had cortical grey matter lesions (p = 0.004). The presence of cortical grey matter lesions was predicted by disease severity (p=0.006) and sex (p=0.016), while grey matter lesion incidence was significantly reduced in females with a mild clinical course of MS. The chronic active lesion index was higher in males than in females (p=0.04).
Interpretation: The large heterogeneity in MS neuropathology between patients observed is related to heterogeneity in clinical disease course of these patients. More severe MS was characterized by a higher total lesion load, presence of cortical grey matter lesions and a higher proportion of active lesions. Importantly, sex differences are present in the neuropathology of MS; males show more grey matter lesions and a higher proportion of chronic active lesions. This heterogeneity of MS pathology with gender as an important factor, is in line with the known clinical and radiological heterogeneity and gender differences in MS.

Disclosure

I. Huitinga; nothing to declare
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C. van Eden: nothing to declare
S. Luchetti: nothing to declare

P925

Significant meningeal inflammation and cortical neurodegeneration in a post-mortem cohort of short disease duration multiple sclerosis

R. Bevan[1], L. Griffiths[1], L. Watkins[1], R. Evans[1], B. McInerney[1], M. Rees[1], M. Calabrese[2], R. Magliozzi[2], R. Reynolds[3], I. Allen[4], D. Fitzgerald[4], O. Howell[1,3]
[1]Swansea University School of Medicine, Swansea, United Kingdom, [2]Neurological and Movement Sciences, University of Verona, Verona, Italy, [3]Brain Sciences, Imperial College London, London, [4]Experimental Medicine, Queen's University, Belfast, United Kingdom

Introduction: Increasing evidence supports a role for meningeal inflammation in sustaining MS cortical grey matter (GM) pathology in the later stages of the disease. Understanding if meningeal inflammation is associated with cortical GM pathology in the early stages of MS would allow us to devise strategies to identify and target this inflammation to reduce the severity of disease.
Aims: To characterise the extent of cortical GM demyelination, parenchymal and meningeal inflammation and neurodegeneration in a cohort of short disease duration MS.
Methods: We characterised the extent of cortical GM demyelination (anti-PLP immunostaining), microglial activation (anti-CD68), meningeal and perivascular inflammation (anti-CD68, CD3 and CD20) and neurodegeneration (Nissl stain, anti-HuC/D and anti-neurofilament-H) in a cohort of multiple sclerosis that died within 4 years of diagnosis (11 cases, 1 male, median age at death 33yrs (range 22-53), median duration 2yrs (range 0.3-4)). All slides were digitised for quantitative analysis.
Results: Subpial, intracortical and lesions affecting the deep cortical GM (Type I and IV) were noted in 9 of eleven cases. GM lesions occupied 2-37% of the total cortical GM in a sample (mean lesion area of total GM area, 16%); subpial lesions and type I/IV cortical lesions accounted for 46% and 51.6% of the demyelinated GM, respectively. The density of CD68+ cells was increased in subpial and deep GM lesion centres in comparison to matched normal GM (by 1.8- and 3.3-fold, respectively; p< 0.01), whilst the density of CD68+ macrophages was elevated in meninges overlying GM lesions (2.5-fold, p=0.01)). CD3+ T-cells were increased in number in GM and overlying meninges (>2-fold increase, p< 0.03). Meningeal accumulations of macrophages and lymphocytes (CD3+ and CD20+) resembling the follicle-like structures seen in later disease were noted in four cases. We noted a significant loss of neurons (29.7% and 34.7%; p< 0.02) and neurites (23.6% and 19.6%) in subpial and deep cortical GM lesions, whilst Spearman analysis revealed a significant inverse relationship between parenchymal GM CD68+ cell numbers and neurons (r=-0.7, p=0.02).
Conclusions: We show for the first time the presence of putative meningeal follicle-like structures and significant neurodegeneration in a post-mortem cohort of short disease duration MS. Our data could help to define important pathological events in early MS relevant to the long-term outcome of disease.

Disclosure

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P926

The influence of *HLA-DRB1*15* on motor cortical neurodegeneration in multiple sclerosis

R.L. Yates, M.M. Esiri, P. Orlowski, Q. Li, J. Palace, G.C. DeLuca
University of Oxford, Oxford, United Kingdom

Background: Multiple Sclerosis (MS) is a common and heterogeneous inflammatory demyelinating disease of the central nervous system. Evidence suggests that the *HLA-DRB1* locus influences clinical outcome, but the influence of this allele on the neuropathology of the disease is relatively unexplored. We have previously shown that younger *HLA-DRB1*15*+ MS cases have more severe microglia/macrophage inflammation in motor cortical parenchyma. Recent evidence has suggested that activated microglia in the cortex can protect neurons from apoptosis in the context of neuroinflammation by displacing inhibitory synapses. We sought to investigate the influence of *HLA-DRB1*15* status and ageing on the relationship between microglia/macrophage inflammation and cortical neurodegeneration, and the potential role of inhibitory synaptic stripping on neuroprotection therein.
Methods: A post-mortem cohort of MS cases (n=47) and non-neurologic controls (n=10) was used. Adjacent sections of motor cortex were stained for microglia/macrophages (Iba1+), activated

microglia/macrophages (CD68+) and neurons (NeuN). The influence of *HLA-DRB1*15* status and ageing on the relationship between microglia/macrophages and neuronal density was evaluated. A subset of MS cases (n=20) and controls (n=7) were double-labelled for neurofilament and glutamic acid decarboxylase 65/67 (GAD) to assess the extent of GAD+ synaptic coverage on layer 5 neurons.

Results: Cortical degeneration was a feature of our MS cohort (MS: 414 ± 17 neurons/mm^2 vs. control: 517 ± 32 neurons/mm^2, p=0.018). Iba1+ microglia/macrophages positively associated with neuronal density in all MS cases (r=0.706, p< 0.001), except *HLA-DRB1*15*+ MS cases that died below the median age of the cohort (r=0.307, p=0.460). In contrast, activated CD68+ microglia/macrophages positively associated with neuronal density only in *HLA-DRB1*15*- MS cases that died over the median age of the cohort (r=0.873, p< 0.001). GAD synaptic coverage was reduced in MS cases (MS: 3.9 ± 0.6% vs. control: 7.1 ± 0.7%, p=0.031).

Conclusions: The relationship between cortical microglia/macrophage inflammation and neurodegeneration is complex. Microglia/macrophages may be able to protect neurons from inflammation via mechanisms influenced by HLA genotype and age-related changes. Neuroprotective strategies employed by microglia/macrophages may include stripping of inhibitory synapses from neuronal cell bodies, and this now warrants further study.

Disclosure

RLY has nothing to disclose. MME has nothing to disclose. JP serves on the scientific advisory board for the Charcot Foundation and has performed advisory work for Biogen Idec, Merck Serono Ltd, Bayer Schering Pharma, Novartis Pharmaceuticals UK Ltd, Teva Pharmaceutical Industries Ltd, Gilenya, Ono Pharmaceutical Co Ltd, Primary i-research, Chugai Pharma Europe and CI Consulting. JP receives research support from the MS Society, QIDIS, Merck Serono Ltd and Bayer Schering Pharma, and has received conference expenses from Novartis and Merck Serono Ltd. GCD has received honoraria and travel expenses as an invited speaker for Bayer Schering and travel expenses from Novartis Pharmaceuticals UK Ltd.

P927

Expression of bone morphogenetic proteins in the central nervous system lesions of multiple sclerosis

C. Costa[1], E. Martínez-Sáez[2], L. Calvo-Barreiro[1], H. Eixarch[1], M. Calucho[1], A. Ortega[2], S. Ramón y Cajal[2], X. Montalban[1], C. Espejo[1]

[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, [2]Pathology Department, Vall d'Hebron University Hospital, Barcelona, Spain

Introduction: Bone morphogenetic proteins (BMPs) are secreted proteins that belong to the TGF-beta superfamily. In the adult brain they modulate neurogenesis, favour astrogliogenesis and inhibit oligodendrogenesis. Thus, BMPs could potentially be involved in the regulation of remyelination in MS lesions.

Objectives: To study the expression of BMP2, 4, 5, 7, BMPRII and pSMAD in MS lesions aND in other white matter-damaging diseases.

Methods: Forty-two MS lesions were selected from 5 patients, 12 acute ischaemic (AI) lesions from 8 patients, 8 progressive multifocal leucoencephalopathy (PML) lesions from 4 patients, and 10 central nervous system (CNS) areas from 4 non-neuropathological patients (control cases, CC). All samples were stained with haematoxylin-eosin and Klüver-Barrera, and immunostainings for BMP2, 4, 5, 7, BMPRII, pSMAD, NeuN, Olig2, GFAP, CD68 and CD3 were performed.

MS lesions were histologically classified in three groups, according to the presence and amount of macrophages and lymphocytes: chronic inactive (CI, n=8), chronic with low inflammatory activity (CALIA, n=9), and chronic with high inflammatory activity (CAHIA, n=25). These histological parameters were also evaluated in AI and PML lesions included in the study.

Results: In MS lesions, astrocytes, macrophages and neurons expressed BMP2, 4, 5, 7, pSMAD and BMPRII, and oligodendrocytes only showed BMP2, 7 and pSMAD expression. In general, the expression of these proteins was higher in CAHIA than in both CALIA and CI MS lesions. In PML lesions, macrophages and astrocytes were immunostained with BMP4, 5, 7 and BMPRII, whereas BMP2 and pSMAD were only observed in macrophages. BMP4, 7 and pSMAD were also expressed in oligodendrocytes. In AI lesions, macrophages and astrocytes expressed BMP2, 5 and 7; BMPRII and pSMAD were only detected in macrophages, and BMP7 and pSMAD were also observed in oligodendrocyte. CC had low expression of BMP4, 7 and BMPRII at oligodendrocytes and neurons, and BMP5 and pSMAD were only observed in neurons. CAHIA MS lesions showed higher expression of BMP2, pSMAD and BMPRII than PML and AI lesions. Moreover, CAHIA MS lesions expressed more BMP5 than PML and more BMP7 than AI lesions.

Conclusion: BMP expression correlates with the inflammatory activity in MS lesions; moreover BMP signalling seems to be more relevant in MS lesions than in other white matter-damaging diseases. BMP signaling may play an important role in the progression of demyelinating MS lesions.

Disclosure

- Carme Costa declares no competing financial interests.
- Elena Martínez-Saez no competing financial interests.
- Laura C Barreiro declares no competing financial interests.
- Herena Eixarch declares no competing financial interests.
- Maite Calucho declares no competing financial interests.
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Inflammation and tissue damage

P928

CSF contents of IL-17 predicts disability progression and neurodegeneration in relapsing remitting Multiple Sclerosis

L. Brambilla[1], C. Zecca[2], V. Torri Clerici[1], L. Pareja[1], G.

Camera[1], J. Perugini[1], R. Frangiamore[1], F. Andreetta[1], P. Confalonieri[1], G. Brenna[1], F. Torelli[3], C. Gobbi[2], R. Mantegazza[1], S. Rossi[1]
[1]IRCCS Fondazione Istituto Neurologico Carlo Besta, MIlan, [2]Neurology Department, Regional Hospital Lugano (EOC), Lugano, Switzerland, Lugano, [3]Merck Spa, via Casilina 125, Rome, Italy

Background: Multiple sclerosis (MS) is characterized by inflammation driven by Interleukin 17 (IL-17). However the recently developed monoclonal antibody therapies against IL-17 have not still reached solid efficacy results.
Objective: To investigate the role of cerebrospinal fluid (CSF) levels of IL-17 in the inflammatory and degenerative processes of MS.
Methods: CSF determination of IL-17 in 200 treatment-naïve relapsing-remittent MS (RRMS) patients with at least 2 years of follow-up at the Neurological Institute Carlo Besta in Milan (Italy) and at the Hospital of Lugano (Switzerland). All RRMS patients started immunomodulatory treatment (interferon beta-1a 43%, interferon beta-1b 8%, glatiramer acetate 39%, fingolimod 10%) at the time of diagnosis, after CSF withdrawal. Treatment was considered as covariate in regression analysis. Clinical, Magnetic Resonance Imaging (MRI) and optical coherence tomography follow-up was performed, after patients stratification according to their CSF IL-17 levels. Average retinal nerve fiber layer thickness (RNFL) for 360° around optic disk was recorded and analyzed using the Fast RNFL analysis.
Results: IL-17 levels were not different between patients with active/not active MRI scans performed at the time of lumbar puncture ($p>0.05$). No significant difference between IL-17+ and IL-17- were revealed by survival analysis considering time to first clinical relapse ($p>0.05$) and the time to detect an active MRI scan at the follow-up ($p>0.05$). Conversely, mean progression index was significantly higher among subjects with detectable CSF IL-17 ($p< 0.05$). In line with this, the frequency of subjects with sustained EDSS worsening was higher in IL-17+ group ($p< 0.05$). A multiple logistic regression model showed that the probability to reach EDSS 3.0 or 4.0 was significantly affected by the CSF presence of IL-17, together with the duration of the disease. A significant main effect of IL-17 CSF contents was revealed analyzing both RNFL thickness ($p< 0.05$) and macular volume ($p< 0.05$), indicating a damage of neuronal structures among IL-17+ group.
Conclusion: CSF IL-17 detection is not associated to early inflammatory activity, but to neurodegenerative processes in relapsing-remittent MS.

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Dr Mantegazza acted as an Advisory Board member of Biomarin. He received funding for traveling and honoraria for speaking from Sanofi-Aventis, Grifols, Teva, Bayer, Biomarin, Alexion, Argenx. He is involved as principal investigator in clinical trials for Alexion, Merck Serono, Hoffman-La Roche, Teva, Biogen, Biomarin, Almirall, Novartis, Genzyme, Catalyst.
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The other authors have nothing to disclose.

P929

IL-10 in multiple sclerosis: unexpected excitotoxic effects and clinical implications

J. Perugini[1], V. Torri Clerici[1], C. Zecca[2], L. Pareja[1], G. Camera[1], L. Brambilla[1], S. Bonanno[1], F. Andreetta[1], C. Antozzi[1], F. Torelli[3], C. Gobbi[2], R. Mantegazza[1], S. Rossi[1]
[1]Neuroimmunology and Neuromuscular diseases, IRCCS Fondazione Isitituto Neurologico Carlo Besta, Milan, Italy, [2]Regional Hospital Lugano, Lugano, Switzerland, [3]Merck Spa, via Casilina 125, Rome, Italy

Background: Relapsing-remitting multiple sclerosis (RRMS) has extremely variable clinical course, and limited availability of disease severity predictors at an early stage of the disease challenges the clinical practice. We have previously shown that pro-inflammatory cytokines, as Interleukin-1β (IL-1β), have the potential to drive inflammatory neurodegeneration, and their levels are useful for the identification of rapidly progressing patients. The effects of central anti-inflammatory cytokines are still elusive.
Objective: To investigate the role of IL-10 in the inflammatory and degenerative processes of MS.
Methods: Cerebrospinal fluid (CSF) determination of IL-10 in 200 RRMS patients with at least 2 years of follow-up at the Neurological Institute Carlo Besta in Milan, Italy, and at the Hospital of Lugano, Switzerland. Clinical, MRI and optical coherence tomography (OCT) follow-up in patients stratified according to their CSF IL-10 levels
Whole-cell patch clamp recordings and cell swelling measurements in mouse brain slices to assess neuronal effects of cytokines.
Results: The mean annualized relapse rate CSF withdrawal, the number of subjects with 2 or more clinical relapses in the first two years of the disease, the number of subjects with an active MRI scan in the first two years of the disease, were slightly but not significantly lower in group with detectable CSF levels of IL-10 (IL10+ group; $p>0.05$ for each comparisons). Mean progression index was significantly lower among subjects with undetectable IL-10 ($p< 0.05$) and the frequency of subjects with sustained EDSS worsening was higher in IL-10+ group ($p< 0.05$). RNFL and macular volume were lower in IL-10+ group ($p< 0,05$), suggesting a major damage of neuronal structures. Given these effects of central IL-10 on neurodegenerative processes and disability

progression in RR MS, we investigated the direct effects of Il-10 on neurons. The duration of glutamate-mediated excitatory post-synaptic currents increased in the presence of IL-10. In parallel, time-dependent neuronal swelling was significantly more pronounced in slices incubated with IL-10.
Conclusion: IL-10 showed an unexpected excitotoxic effect in vitro in parallel to association with markers of disability progression and neurodegeneration in RRMS patients, despite its anti-inflammatory action.

Disclosure

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Dr Mantegazza acted as an Advisory Board member of Biomarin. He received funding for traveling and honoraria for speaking from Sanofi-Aventis, Grifols, Teva, Bayer, Biomarin, Alexion, Argenx. He is involved as principal investigator in clinical trials for Alexion, Merck Serono, Hoffman-La Roche, Teva, Biogen, Biomarin, Almirall, Novartis, Genzyme, Catalyst.
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P930

Signature of neurodegeneration due to primary cytodegeneration and adaptive immune responses

R. Haag, T. Hochstrasser, C. Roggenkamp, F. Kramer, C. Schmitz, M. Kipp
Department of Anatomy II, Ludwig Maximilian University, Munich, Germany

Multiple sclerosis (MS) represents more than an inflammatory disease: it harbors several characteristic aspects of a classical neurodegenerative disorder, i.e. damage to axons, synapses and nerve cell bodies. While several sophisticated treatment options exist to dampen inflammatory-driven tissue damage, modalities to prevent early and late neurodegeneration are still in their infancy. A better understanding of the neurodegenerative signature in MS patients and respective animal models is therefore urgently needed.

In this study we use three distinct gold-standard methods to investigate the magnitude and morphological appearance of neurodegeneration in the cuprizone model. In this model, neurodegeneration occurs in the absence of peripheral immune cells. Furthermore, such foci can form the basis for secondary immune cell recruitment (see Scheld et al and Kipp; J Neurosci. 2016 Jan 27;36(4):1410-5). Loss of neuronal cell bodies was addressed by design-based stereology. Dendritic trees, spines and synapses were reconstructed in a 3-dimensional (3D) environment. Serial block-face scanning electron microscopy was used to detect different morphological features of axonal damage. Finally, genome-wide array analyses were performed to correlate morphological alterations with the transcriptome.

First analyses show that neuronal elements are subjected to degenerative processes in both, the grey and white matter. Demyelination and adaptive immune responses are not just evident in the white matter (corpus callosum) but as well occur in the cortex in a layer-specific fashion. Several pro-inflammatory genes are up-regulated in the cortex including chemokines, protease inhibitors, complement component receptors, and synaptic proteins. 3D-reconstruction of callosal fibers on the ultrastructural level reveals different types of axonal injury among (i) focal swellings of axon with intact myelin sheaths, (ii) splitting of the innermost myelin lamella from the axon with focal swelling, or (iii) complete axonal transection. Furthermore, morphological and transcriptomal changes suggestive of synaptic plasticity were detected in the cortex.

This study, which is ongoing, shows the complex nature of neurodegeneration in a progressive, non-immune cell driven, MS animal model. A better understanding of how such morphological changes occur, and which factors regulate them, will pave the way for the development of novel, holistic neuroprotective strategies.

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P931

At clinical onset CXCL13 identifies MS patients with higher intrathecal IgG production and cortical atrophy

M. Puthenparampil[1], L. Federle[1], S. Miante[1], E. Toffanin[1], S. Ruggero[1], M. Ermani[2], F. Rinaldi[1], P. Gallo[1]
[1]Multiple Sclerosis Centre of Padua, Department of Neuroscience, University of Padua, [2]Department of Neuroscience, University of Padua, Padua, Italy

Background: Since B-cells play a relevant role in multiple sclerosis (MS) pathology, CXCL13 may be a marker for naïve B cells recruitment in the CNS.
Objective: To evaluate the correlation between locally produced IgG, CXCL13 and MRI cortical parameter in patients with clinically isolated syndromes (CIS) suggestive of MS or early relapse-onset MS (eRRMS) at clinical presentation.
Methods: Paired serum and CSF were obtained from 44 patients with CIS/eRRMS and 18 healthy controls (HC). Routine examination of CSF and serum included Intrathecal IgG synthesis evaluation by means of quantitative formulae (IgG Index, IgG Hyp. Function for IgG intrathecal synthesis fraction (IgGIF) and Local Production (IgGLoc)) and demonstration of IgG oligoclonal bands (IgGOB). CXCL13 were detected by means of a highly

sensitive ELISA. CXCL13 ratio (CSF-CXCL13/serum-CXCL13, Q_{CXCL13}) and Indexes (Q_{CXCL13}/Q_{Alb}, CXCL13Index) were evaluated. Global Cortical Thickness (gCTh) were also calculated on 3D-T1 sequences by means of Freesurfer.
Results: Compared to HC, MS patients presented higher intrathecal IgG indexes (higher IgG-CSF, IgG Index and IgGIF values (all p-values < 0.01); higher frequency of IgGOB, p< 0.0001)). We confirmed the lower BAFF-Index value in MS patients (12.3±5.5) compared to HC (17.5±5.2, p< 0.005), while CXCL13-CSF concentration and Index were higher in MS patients (22.3±31.6pg/mL and 82.8±121.3 respectively) than in HC (0.8±1.5 pg/mL and 4.2±6.3 respectively, p< 0.001 for both comparisons). CXCL13 values explained CSF features (IgG intrathecal synthesis) better than the presence of IgGOB. Therefore, we divide MS patients in 2 groups: 23 CXCL13+ patients (CSF-CXCL13 concentration > 7.8 pg/uL) and 21 CXCL13-. CXCL13+ presented higher IgG-CSF, IgG Index and IgGIF values (all p-values < 0.05) and lower CSF-BAFF concentrations (65.5±26.0 pg/uL) when compared to CXCL13- (49.3±18.7 pg/uL, p< 0.05). While IgG intrathecal synthesis strongly correlated with CSF-BAFF in CXCL13- (r: -0.7, p< 0.001 for IgGIndex; r: -0.5, p< 0.05 for IgGLoc and IgGIF), in CXCL13+ they correlated with Q_{CXCL13} (r: +0.6, p< 0.005 for IgGIndex; r: +0.5, p< 0.05 for IgGLoc and r: + 0.6, < 0.005 for IgGIF). Finally, CXCL13+ presented lower gCTh (2.41±0.1 mm) compared to CXCL13- (2.49±0.1 mm, p< 0.05).
Conclusions: CSF-CXCL13 can be considered a promising biomarker to distinguish early MS patients with higher B-cell recruitment, higher IgG parameters in the CSF and higher cortical atrophy.

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P932

Bone morphogenetic protein signaling as a potential therapeutic target for Multiple Sclerosis

H. Eixarch[1], L. Calvo-Barreiro[1], M. Castillo[1], A. Gutiérrez-Franco[1], V. Gil[2], J.A. De Río[2], X. Montalban[1], C. Espejo[1]

[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, [2]Department of Cell Biology, Universitat de Barcelona, Barcelona, Spain

Introduction: Bone morphogenic proteins (BMPs) are critical regulators of brain development, cell proliferation and cell fate. BMPs are involved in neurogenesis and in oligodendrocyte maturing. Moreover, they are differentially expressed in the immune system of multiple sclerosis (MS) patients. Thus, BMP signaling might be a potential therapeutic target for MS.
Objective: i) To elucidate the effect of BMP4 and noggin in neurogenesis and the immune response. ii) To characterize the expression of BMP2, 4, 5, 6, 7, BMPRII and their antagonist, noggin, in the experimental autoimmune encephalomyelitis (EAE) model, in both the CNS and the immune system.
Methods: For *in vitro* studies, neurospheres were obtained from P15 pups. The effect of BMP4 and noggin on cell lineage commitment was assessed by immunochemistry. Splenocytes were cultured, challenged with BMP4 and/or noggin, and their proliferation capacity was evaluated. In *in vivo* studies, EAE was induced in C57BL/6J mice with the MOG_{35-55} peptide. Spinal cords and spleens were removed before EAE induction (basal condition), and in the induction (7 post-immunization; p.i.), inflammatory (15 p.i.), early chronic (30 p.i.) and late chronic (50 p.i.) phases of the disease. After RNA extraction, levels of expression of BMP2, 4, 5, 6, 7, BMPRII and noggin were assessed by RTqPCR.
Results: *In vitro*, neurosphere cultures challenged with BMP4 presented more differentiated astrocytes, and a higher amount and complexity of neurons. In the immune system, BMP4 and especially noggin promoted the proliferation of splenocytes, although the combination of both proteins exerted a more pronounced effect. *In vivo*, we found a general reduction in the expression of BMPs and noggin in the different phases of the experimental disease in the CNS. On the contrary, the expression of BMPs in the immune system was elevated upon EAE induction, reaching its maximum increase at the induction and inflammatory phases of the disease. Altogether point out a role of these proteins in the induction of the inflammatory response in EAE.
Conclusions: Our findings confirmed the role of BMP4 in astroglial commitment and found a positive effect on the differentiation and maturation of neural cells. Moreover, our results suggest that BMP signaling is involved in the regulation of the peripheral and probably in the local immune response. Thus, it seems to be relevant in the pathogenesis of EAE and could be a potential therapeutic target for MS.

Disclosure

- Herena Eixarch declares no competing financial interests.
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- Vanessa Gil declares no competing financial interests.
- Jose Antonio Del Rio declares no competing financial interests.
- Xavier 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 with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Pharmaceuticals and Almirall.

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P933

The genetic multiple sclerosis (MS) risk variant rs7665090-G enhances NF-κB signaling responses in astrocytes

G. Ponath, D. Pitt
Neurology, Yale University, New Haven, CT, United States

The NF-κB pathway has been strongly implicated by genome wide association studies as a central defect in MS pathology with more than 18% of genetic variants affecting genes involved in the NF-κB pathway. NF-κB regulates responses of many different cell types including astrocytes, where NF-κB signaling is critical for propagation of CNS inflammation. Therefore, genetic MS risk variants that affect the NF-κB pathway may lead to unchecked activation of astrocytes in response to inflammatory stimuli leading to excess production of cytokines, enhanced attraction of peripheral lymphocytes and impaired homeostatic and neuro-supportive functions.

We tested this hypothesis by modeling the impact of a common NF-κB-relevant genetic risk variant on astrocyte function using induced pluripotent stem cells (iPSCs). We obtained skin biopsies from MS patients homozygous for the rs7665090-G risk variant or the protective variant and generated iPSCs that we differentiated into astrocytes. Stimulation of astrocytes with the risk variant resulted in increased NF-κB signaling and secretion of TNF-α and IL-6 and reduced uptake of glutamate and lactate/glucose utilization ratios.

Thus, we demonstrate that the rs7665090-G MS risk variant enhances inflammatory responses of astrocytes and impairs glutamate homeostasis and energy supply to neurons. In MS, this might lead to a lower threshold for lesion formation and enhanced neurotoxicity. MS patients with this and other NF-κB-relevant risk variants might thus benefit from therapeutic blockade of NF-κB or NF-κB-activating cytokines.

Disclosure

Gerald Ponath: nothing to disclose
David Pitt: nothing to disclose

P934

Investigating the role of astrocytes' anti-excitotoxicity potential for neuronal damage formation in experimental autoimmune encephalomyelitis - an in vivo two-photon imaging approach

K.S. Rosiewicz[1], T. Crowley[1], M. Alisch[1], A. Margineanu[2], V. Siffrin[1]
[1]ECRC - Neuroimmunology Lab, Charité - Universitätsmedizin Berlin, [2]Advanced Light Microscopy, Max Delbrueck Center for Molecular Medicine, Berlin, Germany

Background and goals: Neuronal damage in autoimmune neuroinflammation is the correlate for long-term disability in patients suffering from Multiple Sclerosis (MS). Recent reports suggest that differences in disability accumulation might derive from genetic variations of genes involved in CNS glutamate homeostasis. We have recently demonstrated that neuronal damage formation was in part caused by excitotoxicity. Glutamate homeostasis is a major task of astrocytes, which have the capacity to remove excitotoxic substances from the extracellular space and are responsible for local confinement of transmitter release.
Methods and results: We investigated the role of astrocytes in established EAE lesions in respect to neuronal and myelin damage. We monitored the complex processes of the immune cell attack onto axons using two-photon laser scanning microscopy of living anaesthetized mice. We made use of fluorescence lifetime imaging microscopy (FLIM), which identifies the fluorescent decay rate of the fluorescence of a given fluophore. By that we improved the sensitivity of Ca2+ measurements in transgenic mice which express fluorescent Ca2+ indicators in the neuronal compartment. We used this technique to analyze the impact on axonal damage formation of different substances which were given during imaging on EAE lesions in living anaesthetized mice. *In vivo* imaging revealed that axonal Ca2+ elevations as sign of reversible neuronal and axonal damaged were influenced by inhibitors and modulators of the astrocytic glutamate receptors EAAT-1 and EAAT-2.
Conclusions: Live-imaging during disease has highlighted the overall role of astrocytes for damage processes in the inflamed CNS. These findings might open up new therapeutic targets to stop neurodegeneration and progressing disability in MS patients.

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Anca Margineanu: nothing to disclose

P935

The blood meningeal barrier orchestrates the immune response in multiple sclerosis

J. Alvarez[1,2], H. Kebir[2], L. Cheslow[1], S. Terouz[2], L. Bourbonniere[2], A. Prat[2]
[1]University of Pennsylvania, Philadelphia, PA, United States, [2]Université de Montréal, Montreal, QC, Canada

The central nervous system (CNS) barriers regulate the movement of leukocytes and immune mediators from the bloodstream into the CNS. Although CNS barriers function in distinct anatomical compartments, most studies to date have focused on changes in the blood-brain barrier (BBB) permeability and activation state during CNS inflammation. However, there is a growing body of evidence showing interactions between pathogenic T cells and the blood meningeal barrier (BMB) during the genesis of autoimmune CNS lesions in animal models of multiple sclerosis (MS). Furthermore, axonal loss and cortical pathology in MS correlate with the density of meningeal T cell and B cell infiltration, respectively. In order to determine how the BMB drives the development of neuroinflammatory responses, we established a novel human *in vitro* model of the BMB and BBB using primary cultures of CNS-derived endothelial cells. To gain a comprehensive understanding of the global differences between these two barriers during homeostasis and inflammation, we used deep RNA sequencing combined with in vitro and in situ immunofluorescent technologies. We found that

the BMB and BBB differ in their immunological profile, particularly with respect to their expression of cell adhesion molecules, chemokines and cytokines. In addition, anatomical components associated with barrier properties such as junctional proteins, extracellular matrix components and integrins are differentially expressed and influenced by the CNS microenvironment (astroglial stimuli). Therefore, we found that the phenotype of various human immune cell populations, including monocytes, T and B lymphocytes is distinctively affected upon transmigration across the BMB and the BBB. In particular, B cells and monocytes preferentially adhere to and migrate across the BMB. We also found that B cells formed aggregates upon contact with the BMB endothelium, a pattern that mirrors their distribution within the meningeal compartment during MS and EAE. Interestingly, B cells that had adhered to the meninges were characterized by an activated phenotype ($CD69^{hi}$, $CD40^{hi}$ and $Ninjurin\text{-}1^{hi}$), as compared to their BBB counterparts. Altogether, these findings demonstrate that the BMB and BBB differ in their barrier and immunological properties and that further studies of these CNS barrier sites will advance our understanding of the mechanisms underlying lesion formation in MS.

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Experimental models

P936

***In vivo* monitoring of acidosis and metabolic alterations in a model of multiple sclerosis**

D. De Battista[1], M. Bacigaluppi[1,2], L. Muzio[1,2], G. Comi[1,3], L. Chaabane[1]
[1]Institute of Experimental Neurology (INSPE), [2]Neuroimmunology Unit, [3]Department of Neurology, San Raffaele Scientific Institute, Milan, Italy

Metabolic alterations and acidosis are increasingly recognized as key players in neurodegeneration and neuroinflammation. Different MRI methods are available to characterize brain damage and MR-Spectroscopy (MRS) can also provide relevant biochemical information. In the present study, advanced MR methods were used to monitor both the metabolism and acidosis involvement in the experimental autoimmune encephalomyelitis (EAE) mouse and in a mouse model of focal cerebral ischemia induced by the middle cerebral artery occlusion (MCAO). Chronic EAE was induced in C57BL/6 mice (n=6) with the $MOG_{35\text{-}55}$ peptide. MR Spectrums were acquired in the cerebellum and in striatum of EAE and MCAO mice, respectively. The extracellular pH was obtained *in vivo* by measuring the chemical shift of an exogenous probe (IEPA, Soirem Research SL) sensitive to acidosis. As expected, cerebellum and striatum have a distinct metabolic profile in healthy mice but pH values were similar (pH=7.3±0.1). At the acute phase of EAE, alanine and lactate levels tend to increase (+61.8% and +20.9%, respectively) while glucose slightly decreased (-12.3%), which could be related to mitochondrial dysfunction that contributes to axonal loss in MS. This modulation of the energy metabolism occurred in concomitance with a decrease of NAA levels (-22.7%) an index of neuronal dysfunction, as expected in both models. In addition, in EAE mice the glutathione was significantly increased (+19.2%) probably to overcome the oxidative stress due to inflammation and mitochondrial dysfunction. Interestingly, lactate that was highly increased in MCAO mice remained low although tissue acidification was clearly found (pH=6.9±0.3). Interestingly, this acidification was in concomitance with NAA decrease as found in MCAO mice. Our results clearly suggest that acidosis is associated with neuronal dysfunction but not with lactate increase, which supports the concept that this metabolite is not a hallmark of acidosis during neuroinflammation and neurodegeneration but is related to hypoxia. To conclude, both markers of neuronal functionality (NAA) and oxidative stress (glutathione) appear to be relevant index for early brain damage in EAE. A longitudinal study to follow the alterations of both metabolism and pH during EAE progression should help to further characterized disease process.

Disclosure

The authors declare no competing financial interests.

P937

Signature of neurodegeneration due to primary cytodegeneration and adaptive immune responses

S. Nyamoya[1,2], J. Lanvermann[1], C. Dornblut[3], H. Morrison[3], M. Kipp[2]
[1]Institute of Neuroanatomy, Faculty of Medicine, RWTH Aachen University, Aachen, [2]Department of Anatomy II, Ludwig-Maximilians-University of Munich, Munich, [3]Leibniz Institute for Age Research, Fritz Lipmann Institute, Jena, Germany

CPI-17 (C-kinase-activated protein phosphatase-1 (PP1) inhibitor, 17kDa) is a cytoplasmic protein predominantly expressed in mature smooth muscle cells. CPI-17 acts as a phosphorylation-dependent inhibitor protein of smooth muscle myosin phosphatase. Myosin phosphatase inhibition increases myosin phosphorylation and in consequence smooth muscle contraction in the absence of increased intracellular Ca^{2+} concentrations. One factor regulating CPI-17 activity via phosphorylation is Protein kinase C (PKC). Since phosphorylation states are integral for oligodendrocyte proliferation and differentiation, in this project, we aimed at identifying new regulatory proteins involved in remyelination.

In a first step, genome-wide array analyses were performed to screen for potential candidate proteins regulating oligodendrocyte stability. We used the cuprizone model since in this model early oligodendrocyte apoptosis is paralleled by a selective and massive reduction of oligodendrocyte specific mRNA species. After 2 days of cuprizone intoxication, the expression of various proteins was profoundly decreased, among CPI-17. 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, focal lysophosphatidylcholine (LPC) injection into the brain or experimental autoimmune encephalomyelitis (EAE). CPI-17 expressing oligodendrocytes are as well lost in active and chronic Multiple sclerosis (MS) lesions. Furthermore, CPI-17 deficient animals

show impaired remyelination and augmented acute axonal damage after cuprizone-induced demyelination compared to wild type littermates.

In this study, we identified a novel regulator of oligodendrocyte differentiation. Future studies are now needed to understand how CPI-17 regulates remyelination.

Disclosure

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P938

Dysregulation of repressor element 1-silencing transcription factor in a mouse model of multiple sclerosis

V. Petrosino[1], S. Criscuolo[2], F. Buffolo[2], F. Cesca[2], N. Kerlero de Rosbo[1], F. Benfenati[2], A. Uccelli[1]
[1]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Italy, [2]Center for Synaptic Neuroscience, Istituto Italiano di Tecnologia, Genoa, Italy

The repressor element 1-silencing transcription factor (REST) regulates neurogenesis and neuronal identity through cell-specific gene repression. During neuronal differentiation REST levels are reduced and REST is quiescent in mature neurons, allowing expression of its target genes. Dysregulation of REST and its repercussion on the expression of its target genes have been implicated in several neurodegenerative disorders. However, the effect of REST dysregulation as a deleterious or protective mechanism is still being debated. We have addressed REST expression in chronic experimental autoimmune encephalomyelitis (EAE), the purported model for multiple sclerosis, a neurodegenerative disease characterized by inflammation leading to demyelination and axonal loss, induced in C57Bl/6J mice with myelin oligodendrocyte glycoprotein. Preliminary results indicate that REST mRNA and protein levels significantly increase in the spinal cord of EAE-affected mice compared to healthy controls 24 hours after disease onset. Analysis of mRNA expression of REST gene targets indicated that voltage-dependent Na+ channel Nav1.2 was significantly downregulated, confirming transcriptional repression by increased levels of REST and suggesting neuronal dysregulation at this early stage of EAE. Expression of brain-derived neurotrophic factor and synaptosomal-associated protein 25 was not affected. Through a time-course analysis of REST mRNA expression at specific EAE stages and in specific CNS areas, we confirmed that REST levels increased in the spinal cord at early disease phase,with a strong upregulation at disease peak, which decreased at the chronic stage. This was accompanied by concomitant downregulation of mRNA expression of REST target genes analyzed (Nav 1.2, somatostatin, synapsin, and NMDAR). Analysis of REST mRNA expression in different brain areas revealed a small upregulation in the striatum at disease peak, which, unexpectedly, was associated with upregulation of target genes at mRNA level. REST mRNA expression did not change in other brain areas. These data confirm that defects of REST expression occur throughout EAE in spinal cord and striatum. Our results suggest that neural cells respond to pathological stimuli modulating REST expression, identifying it as a potential molecular target in EAE for interfering with neuronal fate and rescue disease phenotype.

Disclosure

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P939

Resveratrol prevents the experimental autoimmune encephalomyelitis (EAE) in C57BL/J6 mouse model

O. Ciftci[1], C. Ozcan[2], A. Cetin[3], N. Basak[4], O. Kamisli[2]
[1]Department of Pharmacology, [2]Department of Neurology, Inonu University, Faculty of Medicine, [3]Department of Histology and Embriology, Inonu University, [4]Department of Pharmaceutical Toxicology, Inonu University, Faculty of Medicine, Malatya, Turkey

The aim of this study was determined the effects of resveratrol, on neuronal damage in brain tissue caused by Experimental allergic encephalomyelitis (EAE), an established model of multiple sclerosis in C57BL/J6 mice. Resveratrol is a natural phenol produced naturally by several plants (grapes, blueberries, raspberries and mulberries) in response to injury or when the plant is under attack by pathogens such as bacteria or fungi. Resveratrol has been reported to possess many pharmacological activities such as antioxidant, anti-inflammatory, anticancer, cardioprotective effects. To explore the therapeutic potential of reveratrol totally 40 C57BL/J6 mice were equally divided into four groups: (1) Control, (2) EAE, (3) resveratrol, and (4) resveratrol+EAE. 14 days after induction of EAE with (MOG_{35-55}) and pertussis toxin, the mice treated with resveratrol at the doses of 100 mg/kg/day for 7 days subcutaneously. To our results resveratrol treatment prevents the oxidative stress caused by EAE via a decrease in lipid peroxidations and increase in elements of the antioxidant defense systems in brain tissue. Also, EAE elevate the IL-17, express the pro-inflammatory cytokines, and caspase-3, show apoptosis, staining in EAE mice brain and increased the incidence of histopathological damage. However, immonohistochemical and histological changes were reversed with resveratrol. Moreover, elevated TNF-α and IL-1β levels, a result of EAE, were decreased and neurological deficits as clinical signs were reversed with resveratrol treatment in EAE mice, given resveratrol.

In conclusion, the current study demonstrated that resveratrol treatment effectively prevents oxidative, immunological and histological damage in the brain caused by EAE. It was thought that the beneficial effects of resveratrol are likely a result of its strong antioxidant and anti-inflammatory properties. Therefore, resveratrol may be clinically useful for the treatment of MS in the next years.

Disclosure

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P940

Cannabidiol mechanisms in the treatment of adoptively transferred EAE

C. González García[1], J.A. García-Merino[1], L. Campos Ruíz[1], I. Moreno Torres[1], R. García Hernández[1], M.J. Coronado Albí[2], A. García Grande[3], L. Rodríguez Esparragoza[1], A.J. Sánchez-López[1]

[1]Neuroimmunology, [2]Confocal Microscopy Unit, [3]Flow Citometry Unit, University Hospital Puerta de Hierro Research Institute, Majadahonda, Spain

Background: Cannabidiol (CBD), non-psychoactive cannabinoid, has been reported to bind cannabinoid receptors (CB1-CB2) with weak affinity, although its mechanisms of action are not clear. Previous results showed an improvement in clinical symptoms in adoptively transferred EAE (at-EAE) treated with CBD. This model avoids interferences of inflamed sites with encephalitogenic cell circulation and allows a better delineation of the effector phase of the disease.
Objectives: To analyze CBD in adoptively transferred EAE and to elucidate its mechanisms of action *in vitro*.
Methods: After at-EAE induction, clinical signs were evaluated in at-EAE+vehicle and at-EAE+CBD 50mg/kg/d. *In vitro,* expression of CB1, CB2 and GPR55 receptors was determined by confocal microscopy. Viability was studied by MTT assay in spleen reactive cells treated with CBD and/or CB1 or CB2 antagonists or GPR55 ligand (SR1, SR2 or lysophosphatidylinositol (LPI) respectively). Reactive species of oxygen (ROS) were determined by flow cytometry after pre-incubation with CBD. MRI of the brain was carried out at 7T.
Results: CB1, CB2 and GPR55 receptors were present in the encephalitogenic spleen cells. CBD culture decreased viability of these cells and this was not restored by pre-incubation with SR1, SR2 or LPI; furthermore, CBD treatment significantly elevated the level of total cellular ROS. Reduction in clinical signs correlated with a significant decrease of apparent diffusion coefficient values in the brain subiculum after CBD treatment.
Conclusions: Clinical signs and MRI findings after CBD treatment correlated with a reduced recruitment of inflammatory cells into the CNS. The decrease in infiltrating cells could be due to the diminished viability of encephalitogenic spleen cells found *in vitro* with CBD treatment, an effect related to ROS increase. The viability reduction of encephalitogenic cells, independent of CB1-CB2 and GPR55 receptors, may be one of the mechanisms through which this compound exerts its therapeutic action.

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P941

Viability and distribution of intrathecally transplanted neural stem cells in the acute and chronic disease phases of experimental autoimmune encephalomyelitis

A. Merlini[1,2], D. De Feo[1], F. Ruffini[1], G. Comi[2], G. Martino[1]

[1]Neuroimmunology Unit, San Raffaele Scientific Institute - Institute of Experimental Neurology, [2]Department of Neurology, San Raffaele Scientific Institute, Milan, Italy

Background: Intrathecal transplantation of adult neural stem/precursor cells (NPCs) ameliorates disease severity in experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis. We investigated whether NPCs transplanted in the acute or chronic phases of EAE displayed different behaviour in vivo.
Materials and methods: Adult NPCs were derived from the subventricular zone of 8-week old female C57Bl/6 mice. EAE was induced in syngeneic mice by subcutaneous immunization with myelin oligodendrocyte glycoprotein 35-55 peptide. One million GFP-labelled NPCs were transplanted intrathecally in the cisterna magna of EAE mice at peak of disease severity, ca 14 days post immunization (dpi), or in the chronic disease phase (80 dpi) or in healthy age-matched controls (HC). Each group comprised at least 4 animals.
Results: When transplanted in the acute EAE phase, at 1 day post transplantation (dpt), NPCs distributed within few millimetres from the injection site (2,46 ±0,90 mm in EAE; 2,78 ± 0,57 in HC), no further migration was observed at 7 and 60 dpt. At 1 dpt, 8,1% of transplanted NPCs survived in HC and 7,5% in EAE. At 7 dpt the number of surviving NPCs further decreased in both groups (HC: 2,6%; EAE: 4,6%) but at 60 dpt NPCs transplanted in EAE mice displayed increased survival (2,7%) when compared to HC (0,3%; $p< 0,05$). Some NPCs expressed the apoptotic marker activated caspase 3, with EAE mice showing a trend of reduced apoptosis at 1 dpt (HC: 3,2%; EAE: 1,5%) and at 7 dpt (HC: 3,8%; EAE: 1,4%; $p< 0,05$). Transplanted NPCs vastly disseminated in the subarachnoid spaces of the fourth ventricle or surrounding meninges, with a small quota of NPCs integrating in the parenchyma. At 60 dpt, 93,5 % of surviving NPCs retained their meningeal localization in the EAE group, while in the HC group 89,4% of the surviving NPCs were found in the parenchyma. Consistently, transplantation of NPCs in the chronic phase of EAE (80 dpi), when neuroinflammation has waned off, failed to retain NPC cells in the meninges when compared to transplantation of NPCs in the acute phase of EAE.
Conclusions: Neuroinflammation might influence long-term the viability, localization and therapeutic efficacy of transplanted NPCs in EAE. This finding has relevance for clinical translation of NPC by defining the better disease window for NPC transplantation.

Disclosure

Nothing to disclose in relation to the present study

P942

The role of plasma membrane lipid organization in demyelinating disease: using neurotoxic lipids to understand mechanisms of demyelination

L. D'Auria[1], M. Marshall[1], E. Ward[1], G. Scesa[1], C. Reiter[1], G. Li[2], R. van Breemen[2], E. Bongarzone[1]

[1]Anatomy and Cell Biology, [2]College of Pharmacy, University of Illinois at Chicago, Chicago, IL, United States

The Multiple Sclerosis (MS) is a complex and idiopathic disease whose research has been essentially focused on proteins to study

the mechanisms of toxicity. However, the myelin produced by the oligodendrocytes (OL) is mainly composed of lipids. The advent of new techniques evidenced that lipids can form membrane domains that have physiological functions in different cell lines. During OL differentiation, several lipids (e.g. the sphingolipids galactosylceramide and sphingomyelin) become particularly enriched in myelin sheaths. The high lipid enrichment in OL could also infer the existence and role(s) for lipid domains whose disorganization could elicit demyelination. This hypothesis is highly relevant in MS and other demyelinating diseases such as Krabbe disease (KD), a sphingolipidosis, where the neurotoxic lipid psychosine (galactosyl-sphingosine) could induce toxicity by a membrane-bound mechanism.

The goal of this study was then to determine whether perturbation of plasma membrane (PM) lipid architecture could lead to toxic mechanisms of demyelination.

By using cell models from basic plasmalemma to primary OL, we first determined the effect of the psychosine on the stability and dynamics of lipid domains and overall membrane integrity. Psychosine was found to induce the re-organization of sphingomyelin and gangliosides micrometric lipid subdomains. The PM mobility of sphingomyelin was restricted upon presence of psychosine. Two-photon microscopy of Laurdan demonstrated the presence of localized rigid psychosine-induced micrometric domains. This rigidity was associated with microvesiculation and PM shedding observed by microscopy and flow cytometry. Our results support a model where psychosine induces local restrictions in PM lipid mobility, increasing membrane curvature and favoring shedding which alters the local organization of associated signaling pathways. Similarly, the modulation of the endogenous lipid content from normal differentiating OL also presented a change in membrane rigidity leading to PM fragility. Altogether, this work is then relevant to understand how alteration of lipid membrane architecture lead to toxicity and demyelination. Decoding these lipid-based mechanisms represents a unique opportunity to provide breakthroughs for more efficient treatment in MS and in demyelinating-related diseases.

Disclosure

L. D´auria, M. Marshall, E. Ward, . Scesa, C. Reiter, G. Li, R. van Breemen have nothing to disclose
E. Bongarzone is a consultant for Lysosomal Therapeutics, Inc.

P943

In vivo modeling of the nascent Multiple Sclerosis lesion: Mechanisms of blood brain barrier permeability and demyelination

J. Linden, C.E. Flores, T. Vartanian
Weill Cornell Medical College, New York, NY, United States

Background: *Clostridium perfringens* epsilon toxin (ETX) has been proposed as a candidate environmental factor responsible for initiating nascent Multiple Sclerosis (MS) lesion formation. The nascent MS lesion in characterized by blood brain barrier (BBB) permeability, oligodendrocyte cell death, and microglia activation in the absence of immune cell infiltration. We have demonstrated that ETX specifically targets the BBB permeability and exclusively kills oligodendrocytes. In addition, we have demonstrated that mice treated with non-lethal dose of ETX develop focal BBB permeability and demyelinating lesions. However, the mechanisms involved in ETX induced BBB permeability and demyelination are poorly understood.
Goal: The goal of this study was to determine the mechanisms of ETX induced BBB permeability and oligodendrocyte cell death *in vivo*.
Methods: Mice were injected with non-lethal doses of ETX and sacrificed 24, 48, and 72 hours after treatment. Saline treated mice were used as controls. Harvested brains were cryo-sectioned and analyzed by fluorescent immunohistochemistry.
Results: ETX treated mice exhibited a significant increase of fibronectin and IgG in brain paranchmya compared to control mice, indicating increased BBB permeability. In addition, claudin-5 staining was disrupted in ETX treated mice. ETX treated mice also exhibited an increase in staining for activated microglia/macrophages compared to controls. Interestingly, astrocyte reactivity was lower in ETX treated mice. A possible slight disruption in claudin-11 staining was observed in ETX treated mice, suggesting alteration and retraction of myelin sheaths. Most changes were observed in the corpus callosum or perivascular white matter, areas prone to MS lesions in humans. Finally, there was a modest increase in cleaved caspase-3 staining in ETX mice, suggesting that BBB permeability and demyelination may be a result of ETX induced apoptosis.
Conclusions: Mice treated with ETX exhibit similar pathological changes observed in the newly forming MS lesion. This includes BBB permeability, microglia activation, possible myelin/oligodendrocyte disturbances, and activated caspase-3. Exposure of mice to ETX may be an acceptable model for studying the earliest stage of MS lesion development *in vivo*.

Disclosure

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P944

Altered expression of several fatty acid binding proteins during experimental autoimmune encephalomyelitis (EAE) in mice: Modulation by natural triterpenes

B. Gutierrez[1], I. Gallardo[1], M. Hernandez[1], R. Martin[1], A.M. Astudillo[1], J. Balsinde[1], N. Tellez[2], M. Nieto[3]
[1]IBGM-CSIC/UVa, [2]Neurología, Hospital Clinico Universitario, [3]IBGM-CSIC, Valladolid, Spain

Background: Fatty acid binding proteins (FABPs) comprise a family of proteins involved in the transport of long chain fatty acids. Since fatty acids may also function as signaling molecules, FABPs have been identified as key regulators of inflammatory pathways. Ligands of FABP-3, 4 and 5 include ω-6 and ω-9 fatty acids that may act as ligands for peroxisome proliferator-activating receptor-γ (PPARγ). Given that enhanced PPAR activity has been associated to experimental autoimmune encephalomyelitis (EAE), we hypothesized that an altered expression of FABP-3, 4 and 5 may be linked to EAE. In addition, the triterpene, oleanolic acid (OA) has been proven effective in controlling the inflammatory process in EAE, however its impact in regulating FABP expression has not been investigated.
Methods: C57/BL6 mice were MOG_{35-55}-inmunized and treated with OA (25 mg/kg/day, i.p) or saline. On day 21 cerebellum and

serum samples were obtained. FABP-3, 4, and 5 were quantified by using commercial ELISA kits. Cerebellum fatty acids were evaluated by gas chromatography-mass spectrometry.
Results: High levels of FABP-4 and 5 were detected in cerebellum from EAE mice (558.9±28.5 and 102.9±19.3 pg/mg tissue, respectively), compared to healthy mice (81.6.9±22 and 50.25±5.2 pg/mg tissue, respectively, $p< 0.05$). Treatment with OA strongly attenuated the increased expression levels of FABP-4 and 5 (175±68 and 55.12±7.9 pg/mg tissue, respectively) observed in the untreated-EAE mice. A similar pattern was observed in serum samples: FABP-4 expression levels were 78.8±14.1, 182±22.9 and 66.4±14.4 ng/ml, in control, EAE and OA-treated EAE mice, respectively, $p< 0.01$; and FABP-5 levels were 10.65±0.4, 20.78±2.9 and 14.54±3.8 ng/ml, in control, EAE and OA-treated EAE mice, respectively, $p< 0.05$. However, the expression levels of FABP3 in cerebellum were not affected during EAE development or OA-treatment. Additionally, cerebellum from EAE mice showed 1.98 times more arachidonic acid (ω-6) in diacylglycerol, and 2 times more oleic acid (ω-3) in diacylglycerol/triacylglycerol than cerebellum from both OA-treated EAE and control mice.
Conclusion: High expression of FABPs could represent an underlying disease mechanism in EAE mice. Then, OA by reducing FABP levels and the associated lipid remodeling could be preventing the development of EAE

Disclosure

Nothing to disclose

P945

Combination therapy with ozanimod and dimethyl fumarate is synergistic in a mouse model of experimental autoimmune encephalitis

K. Taylor, R.J. Peach, F.L. Scott
Receptos (a wholly owned subsidiary of Celgene), San Diego, CA, United States

Background: Despite the recent approval of several new agents with unique mechanisms of action for patients with Relapsing Multiple Sclerosis (RMS), there are still a significant proportion of patients that have continued disease activity despite treatment. This unmet need has created an opportunity for assessment of rational combination therapies in this patient population, a common strategy for other diseases including Type 2 diabetes and cancer.
Objective: This study assessed the potential benefit of combining ozanimod, which is in Phase 3 clinical development for RMS and is a selective modulator of sphingosine-1-phosphate 1 and 5 receptors ($S1P_{1R}$, $S1P_{5R}$), with dimethyl fumarate (DMF), proposed to modulate Nrf2, in a mouse model of Experimental Autoimmune Encephalitis (EAE).
Methods: Combination therapies were assessed in the MOG_{35-55} peptide-induced mouse model of EAE. Mice were treated either prophylactically at the time of immunization or therapeutically when first clinical signs of disease observed. Endpoints included paralysis score, CNS histopathology and lymphocyte function in *ex vivo* recall experiments.
Results: Therapeutically administered ozanimod[HW1] (0.6mg/kg PO QD) significantly reduced the End Clinical Score (Vehicle = 3.2 ± 0.25, Ozanimod = 2.1 ± 0.16, p=0.001), while DMF (15mg/kg PO BID) demonstrated no significant effect (DMF = 3.1 ± 0.26). In addition, splenocytes isolated from ozanimod-treated mice were devoid of IFN-g, TNF-a and IL-17A production, while splenocytes from DMF treated mice were fully competent. Histopathological analysis also demonstrated greater reductions in spinal cord inflammation in mice treated with ozanimod compared to DMF.

Interestingly, in combination, there was clear synergy [RC(2] between ozanimod and DMF when analyzing End Clinical Scores (Vehicle = 3.2 ± 0.25, Combination = 1.5 ± 0.23, $p< 0.0001$), Mean Maximal Score (Vehicle = 3.5 ± 0.16, ozanimod = 3.2 ± 0.09, DMF = 3.5 ± 0.14, Combination = 2.8 ± 0.17, p=0.001) and in assessments of demyelination within the spinal cord. Furthermore, we determined that the benefits of combining ozanimod with DMF were still observed when DMF was reduced from BID to QD dosing.
Conclusions: These data suggest there may be clinical benefit of combination therapy for ozanimod with DMF in RMS. This combination may also allow for reduced dosing frequency of DMF, which may overcome some of its tolerability and compliance issues.

Disclosure

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P946

Tolerization therapy reduces disease frequency and severity in mouse model of neuromyelitis optica

M.V. Jones[1], M. Levy[2]
[1]Neurology, [2]Johns Hopkins University, Baltimore, MD, United States

Background: We previously discovered that T cells from aquaporin-4 (AQP4) knockout mice immunized with the second extracellular loop of $AQP4_{135-153}$. These T cells do not cause disease in AQP4 knockout mice as these mice lack the AQP4 target. However, when adoptively transferred to wild-type mice, these AQP4-reactive T cells mount an inflammatory attack in the spinal cord and optic nerves very similar to human NMO disease. Thus, AQP4-reactive T cells alone are sufficient to recapitulate NMO in mice. We tested the ability to block AQP4-reactive T cells using a peptide tolerization strategy.
Design/Methods: Wildtype recipients of pathogenic AQP4-reactive T cells were treated with subcutaneous injections with a range of doses of $AQP4_{135-155}$ from 10 mM - 4 mg on days 1, 3 and 5 post-transfer and monitored for changes in weight and neurological behavior on the standard EAE scale. Pathological examination of spinal cord and optic nerve tissue included H&E, eriochrome for myelin and markers of inflammatory cells.
Results: All control mice developed neurological signs of transverse myelitis with an average EAE score of 2.5 on day 12. Mice treated with 10 mM $AQP4_{135-155}$ stratified equally into three groups: those who responded well with no evidence of disease or weight loss, those who developed disease but to a less severe degree with an average EAE score of 1.0, and those who did not respond to treatment and developed disease to a degree similar to

controls. Mice treated with higher doses of $AQP4_{135-155}$ at 1 mg and 4 mg died of anaphylaxis. Pathological examination showed inflammation in the spinal cord and optic nerve tissue in control mice; in mice treated effectively with 10 mM $AQP4_{135-155}$, the inflammation was markedly reduced.
Conclusions: In this animal model of NMO, tolerization therapy with subcutaneously injected $AQP4_{135-155}$ reduced the frequency and severity of NMO disease. Further studies are necessary to translate this approach to human NMO patients.

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P947

Mesenchymal stem cell therapy ameliorates long-term cognitive decline in a murine model of experimental autoimmune encephalomyelitis with relapsing-remitting course

C. Rosell-Valle[1], A.I. Gómez-Conde[2], R.D. Moreno-Fernández[1], M. Suardíaz[2], J. Ortega-Pinazo[2], C. Pedraza[1], O. Fernández[2], L.J. Santín[1], G. Estivill-Torrús[2]
[1]Instituto de Investigación Biomédica de Málaga (IBIMA), Universidad de Málaga, [2]Instituto de Investigación Biomédica de Málaga (IBIMA); Hospitales Universitarios Regional de Málaga y Virgen de la Victoria, Málaga, Spain

Cell therapy using mesenchymal stem cells is one of most recent current therapies for MS given their immunoregulatory properties and excellent potential to promote tissue repair. In addition of physical disability and neurodegeneration, MS associates with co-morbid behavioral, neuropsychiatric and cognitive decline. The study of cognitive impairment in experimental autoimmune encephalomyelitis (EAE), constitutes a very valuable tool to ultimately translate into clinical a better diagnosis and more effective MS treatment protocols.

We analyzed the behavioral profile of a murine model of EAE induced by myelin oligodendrocyte glycoprotein peptide MOG_{35-55} which developed a relapsing-remitting course. In the early neuroinflammatory phase of the disease, i.e. 19-21 days post immunization (dpi), EAE mice exhibited deficits in motor coordination/skill learning (Rotarod test), and spatial working memory (spontaneous alternation in Y-maze), as well as depressive symptoms (tail suspension test) and anxiety-like behavior (elevated plus-maze). EAE mice did not yet show object recognition memory impairments, suggesting that reference memory was not altered in this phase. However, from 33-35 dpi until late phases (49-52 dpi), independently of clinical score, EAE mice exhibited a memory decline showing lower discrimination index in the object recognition test. EAE late phase was also characterized by motor coordination and spatial working memory impairments as well as higher anxiety-like behavior. These data demonstrates a differential pattern of gradual cognitive dysfunctions during the relapsing-remitting EAE course that could help to understand the development of progressive cognitive decline in MS patients. In this scenery murine adipose tissue-derived mesenchymal stem cells (AMSCs) were obtained, cultured under standard conditions, and administered systemically to EAE mice to test therapy effectiveness on cognitive impairment. EAE-treatment was evaluated at long-term period (50 dpi) and showed that AMSCs infusion ameliorates locomotor coordination, working spatial memory (Y maze), episodic memory (object recognition test), anxiety (plus maze), depressive behavior (tail suspension test). In addition, behavioral profiles were confronted and correlated with hippocampal neurogenic response, neuronal immature/mature balance, and multiplex cytokine analysis.

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Genetics/Epigenetics and Pharmacogenetics

P948

Estrogen receptor-alpha regulates epigenetic changes on genomic regulatory regions: potential biomarkers in multiple sclerosis outcomes

M. Clerico[1], S. Cutrupi[1], A. Iannello[1], G. Ferrero[2], F. Cordero[2], S. Rolla[1], V. Annibali[3], M. De Bortoli[1], L. Durelli[1]
[1]Clinical and Biological Sciences, University of Torino, Orbassano, [2]Dept of Informatic, University of Torino, Torino, [3]Medical Affairs, Merck, Rome, Italy

Background: Estrogen immunomodulation is associated with a reduction of relapse rate among women with multiple sclerosis (MS) during the third trimester of pregnancy. Estrogen Receptor-alpha (ERa) may regulate the differentiation of T cell subtypes, particularly of T regulatory (Treg) and Th17 cells.
Goals: Identification and validation of cell-type-specific genomic regulatory regions able to influence the proportion of Treg / Th17 cells of MS patients during pregnancy.
Material and methods: Peripheral blood mononuclear cells (PBMC) from 13 pregnant women patients 8 pregnant (8 MS and 5 healthy) were collected during the 3rd trimester of pregnancy and post-partum. Cell-type-specific regulatory regions have been identified by data integrative analysis on FoxP3 and RORc loci, coding for lineage-determining transcription factor of Treg and Th17 cell differentiation. Epigenetic modifications and ERa binding enrichment were evaluated by chromatin immunoprecipitation assay. RORc and FoxP3 promoter and genomic regulatory regions have been selected by bioinformatic analysis. In vitro analyses on purified Th17 and Tregs treated with E2 were conducted.
Results: ERa binds on RORc and FoxP3 promoter and genomic regulatory regions. On the third trimester of pregnancy, we observed that on Treg cells H3K4me3 on FoxP3, gene activation marker, is enriched more than H3K27me3, gene silencing marker; the ratio of H3K4me3/ H3K27me3 changed, in a similar way, in the post-partum. In vitro, the E2 treatment, induces, on cell-type-specific regulatory regions of purified and polarized Th17 cells the enrichment of H3K27me3, gene silencing marker, on RORc and the enrichment of H3K4me3, gene activation marker, of FoxP3.
Conclusion: ERa binds to regulatory regions of Foxp3 and RORC, driving the balance of Treg/Th17. This effect of E2 is confirmed in vitro. This result in a larger population of pregnant and

non pregnant patients, could lead to the identification of new epigenomic biomarkers for monitoring disease outcomes and interferon treatment efficacy.

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P949

A next generation sequencing study in Italian multiplex families with multiple sclerosis

C. Guaschino[1], A. Zauli[2], F. Esposito[1], M. Sorosina[2], E. Mascia[2], A.M. Osiceanu[2], S. Santoro[2], D. Biancolini[3], S. Bonfiglio[3], D. Lazarevic[3], G. Tonon[3], V. Martinelli[4], G. Comi[4], F. Martinelli Boneschi[1]
[1]Department of Neurology and Laboratory of Human Genetics of Neurological Diseases, CNS Inflammatory Unit & INSPE, [2]Laboratory of Human Genetics of Neurological Diseases, CNS Inflammatory Unit & INSPE, [3]Center for Translational Genomics and Bioinformatics, [4]Department of Neurology, San Raffaele Scientific Institute, Milan, Italy

Introduction: While the role of common genetic variants is established from genome-wide association studies (GWAS) on sporadic cases of multiple sclerosis (MS), pointing to the existence of more than 100 non-HLA genetic loci, the heritability of the disease is still poorly captured. The aim of the study is to identify the role of rare variants involved in the predisposition to MS by analyzing an Italian cohort of large multiplex families.
Methods: Thirteen Italian families with ⩾ 3 affected relatives with at least 2 with a first-degree relationship (1 with 7, 1 with 5, 4 with 4, and 7 with 3 affected) have been recruited as part of a large multicentric Italian study. Whole exome sequencing (WES) on Illumina Platform (HiSeq 2500) with Agilent QXT V5 enrichment kit was performed. An internal pipeline based on BWA aligner and GATK UnifiedGenotyper (following GATK best practices) was used to perform variant calling on 37 relatives (27 cases and 10 controls) with a general coverage > 70x in all individuals. Functional variants with allelic frequency (AF) < 5% in the general population have been selected, and further screened in Italian cohorts of healthy subjects.
Results: Around 40.000 functional variants were found in affected relatives, of which 16.000 with rare frequency according to available software. Among them, 140 variants were present in all affected relatives of ⩾ half of families and 17 variants in 19 genes were detected in all relatives of all families. Analyses are ongoing to explore the frequency of these variants in the Italian healthy population and their segregation with the disease within families.
Conclusion: these data represent a potential pool of rare functional variants implicated in MS pathophysiology that should be further analyzed in larger datasets. The WES of other 35 subjects from multiplex families are ongoing in order to increase the sample size and to confirm these preliminary findings.

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P950

Identification and characterization of multiple sclerosis associated loci in the continental italian population

M. Sorosina[1], N. Barizzone[2,3], F. Clarelli[1], S. Anand[4], S. Lupoli[5], F. Esposito[1,6], E. Mangano[4], R. Bordoni[4], V. Martinelli[6], G. Comi[6], M. Leone[2], D. Cusi[5], N. Patsopoulos[7,8,9], P. De Jager[7,8,9], G. De Bellis[4], S. D'Alfonso[2,3], F. Martinelli Boneschi[1,6], PROGEMUS, PROGRESSO
[1]Laboratory of Human Genetics of Neurological Disorders, CNS Inflammatory Unit & INSPE, San Raffaele Scientific Institute, Milan, [2]Interdisciplinary Research Center of Autoimmune Diseases (IRCAD), [3]Department of Health Sciences, University of Eastern Piedmont Amedeo Avogadro, Novara, [4]National Research Council of Italy/Institute of Biomedical Technology, Segrate, [5]Department of Health Sciences, University of Milan, [6]Department of Neurology and Neurorehabilitation, San Raffaele Scientific Institute, Milan, Italy, [7]Ann Romney Center for Neurologic Diseases & Program in Translational Neuropsychiatric Genomics, Institute for the Neurosciences, Department of Neurology, Brigham and Women's Hospital, [8]Harvard Medical School, Boston, [9]Program for Medical and Population Genetics, Broad Institute, Cambridge, MA, United States

Multiple sclerosis (MS) is a complex disorder characterized by myelin damage and neurodegeneration. Until now 103 susceptibility genetic loci have been identified through genome-wide association studies (GWAS), however they involved samples from several different countries that could have a different genetic and environmental predisposition. The aim of the present project was to identify and characterise the most associated regions in the Italian population following a multi-step approach.

We started from 2 cohorts of Italian continental MS patients and healthy controls (HC): ITA_{GWAS} (750 MS, 1291 HC) with available imputed genome-wide genotypes and ITA_{iChip} (977 MS, 986 HC) with genotyping data in 184 immune regions. To boost the statistical power of the study, the top associated signals of association ($p< 0.005$) in the two Italian cohorts were meta-analysed with an imputation-based meta-analysed cohort of 20,512 cases and 19,145 HC of European ancestry from USA. A total of 16 loci of association were identified ($p< 5x10^{-7}$) and then tested for an association in a third Italian cohort (903 MS, 884 HC). This replication phase confirmed the association of two loci on chromosome 17 and chromosome 3, already known to be associated with the disease. To better characterize them we next sequenced them in an Italian cohort of 600 MS and 408 HC using a pooling approach and comparing high-risk MS patients and low-risk HC according to their genetic burden.

In the locus on chromosome 17 the sequencing analysis revealed the presence of 203 SNPs associated with disease (best signal $p= 1.11x10^{-23}$). We tested, based on their availability, the 203 SNPs for a cis-eQTL association using Braineac, Gtex Portal and SNPExpress databases. We found an association of several SNPs with the expression of EFCAB13 in brain tissues, while in more immunological tissues we observed that also TBKBP1 is regulated, with an opposite direction compared to brain.

A total of 12 signals were identified by the sequencing analysis in the intergenic locus on chromosome 3. No eQTL associations were found for any of those SNPs and their function needs to be better explored.

Concluding, we confirmed the loci on chromosomes 17 and 3 as highly associated also in the Italian population and we better characterised the origin of the signals using a next-generation sequencing approach. Moreover, we observed tissue-dependent regulatory functions, opening questions on the role of EFCAB13 and TBKBP1 in MS.

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P951

DNA methylation assessment using methylation-specific multiplex ligation dependent probe amplification in MS patients during relapses and remissions

M. Sokratous[1], E. Bellou[1,2], Z. Tsouris[1], A. Michalopoulou[1], D. Rikos[2], V. Siokas[1], V. Tsimourtou[2], T. Stamati[2], M. Dardioti[1], E. Sakalakis[2], G. Tsivgoulis[3], G. Hadjigeorgiou[1,2], E. Dardiotis[1,2]
[1]Neurogenetics Lab, [2]Department of Neurology, University General Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, [3]Second Department of Neurology, "Attikon" Hospital, School of Medicine, University of Athens, Athens, Greece

Background: DNA methylation is considered as an important factor in determining the function of immune cells and may predispose to certain autoimmune diseases including multiple sclerosis (MS). Suppressor of cytokine signaling 1 (SOCS1) is an inhibitor of cytokine signaling and a key regulator of autoimmune responses. Recent evidence suggest increased expression of SOCS1 in relapsing remitting MS. We conducted the present study to determine the methylation status of SOCS1 CpG islands in MS patients during relapses or remissions and in normal controls. We hypothesised that SOCS1 hypermethylation may be associated with disease activity.
Methods: Methylation-specific multiplex ligation dependent probe amplification (MS-MLPA), a multiple polymerase chain reaction (PCR) method, was used to determine the status of CpG islands in SOCS1 gene. We analysed DNA samples of 10 healthy controls and 47 MS patients, 29 of whom were on relapse and 18 on remission. PCR amplicons were separated by capillary electrophoresis via ABI PRISM 3730 Genetic Analyser and depicted by GeneMapper software version 5.0. Data analysis was conducted using Coffalyser.Net software.
Results: Two out of 18 (11.1%) of patients with relapse had hypermethylation and 2/18 (11.1%) had hypomethylation of SOCS1 gene while the rest 14/18 (77.8%) had normal methylation. Among patients on remission 3/29 (10.3%) had hypermethylation, 5/29 (17.2%) had hypomethylation and the rest 21/39 (72.4%) had normal methylation. Finally, 5/10 (50%) controls had SOCS1 gene hypermethylation while the rest 5/10 (50%) had normal methylation. Statistical analysis showed no significant difference in methylation patterns among patients in relapse, remission and healthy controls (p-value=0.08, 3x3, df=4). However, when methylation status was compared between MS patients and normal controls SOCS1 gene hypermethylation was overrepresented among normal controls (p-value=0.018, 2x2, df=1)

Conclusion: SOCS1 gene methylation status was significantly different between MS patients and controls, but not between MS patients in relapses and remissions.

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P952

Exome sequencing identifies a novel multiple sclerosis risk variant in the FKBP6 gene in a large dutch multiple sclerosis family

J.Y. Mescheriakova[1], J.M. Verkerk[2], A.G. Uitterlinden[2,3], C.M. van Duijn[3], R.Q. Hintzen[1]
[1]Department of Neurology, MS centre ErasMS, [2]Department of Internal Medicine, [3]Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands

Background: Multiple sclerosis (MS) is a complex disease. Segregation of MS in some families points to genetic contribution in MS etiology. Despite the discovery of many common genetic variants by genome-wide association studies (GWAS), a large portion of MS heritability still remains unexplained. This may be accounted for by rare genetic variants.
Objective: To identify rare variants contributing to MS risk by analyzing a large Dutch MS family with 11 affected individuals in several generations.
Methods: Genome-wide linkage screen was done to search for haplotype-sharing regions. Whole exome sequencing analysis was performed in selected family members with MS to identify novel coding variants in the haplotype-sharing regions and in the known MS risk genes identified by GWAS. The candidate variants were then genotyped in all family members and validated in a cohort of 554 MS patients and 3139 healthy controls.
Results: Significant linkage was obtained for the chromosomal region 7q11.22-q21.3 (LOD=2.75). In the sequencing data, this region was screened for variants with a minor allele frequency (MAF) < 1% and those with an altered protein function. A rare missense mutation in the FKBP6 gene was identified. This variant segregated with the disease in this family. In an independent cohort, this variant was more prevalent in MS patients with familial history of MS than in controls (OR=2.7, p=0.0059).
Conclusion: The rare missense variant in the FKBP6 gene that we found in this large MS family, was also more prevalent amongst MS patients with family history of MS and had a moderate effect on MS risk. The protein coded by this gene may function in immune-regulation and basic cellular processes involving protein folding and trafficking. How the newly identified variant acts to increase MS risk is not known and functionally studies are needed to clarify its role in MS.

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P953

Gene expression modulation induced by fingolimod in relapsing remitting multiple sclerosis

E. Mascia[1], F. Esposito[1,2], P. Provero[3,4], L. Ferrè[1,2], F. Clarelli[1], G. Sferruzza[1,2], C. Guaschino[1,2], M. Radaelli[2], L. Moiola[2], B. Colombo[2], V. Martinelli[2], G. Comi[1,2], F. Martinelli Boneschi[1,2]
[1]Laboratory of Human Genetics of Neurological Disorders, CNS Inflammatory Unit & INSPE, San Raffaele Scientific Institute, [2]Department of Neurology, San Raffaele Scientific Institute, [3]Center for Translational Genomics and BioInformatics, San Raffaele Scientific Institute, Milan, [4]University of Turin, Turin, Italy

Background: fingolimod (FTY) is an oral treatment recently approved for relapsing-remitting (RR) multiple sclerosis (MS). No gene expression experiments have been performed at whole genome level to assess the transcriptional changes induced by the treatment.
Aim: to investigate the molecular mechanisms underlying FTY action, by looking at transcriptional alterations induced by the treatment.
Methods: whole blood samples were collected at baseline (BL) and after 6 months of FTY treatment in RRMS patients. We excluded subjects with a clinical relapse or steroid treatment in the month before FTY, treated with interferon or cyclophosphamide in the 3 months before or previsouly treated with Natalizumab. The gene expression profiling was assessed using the Illumina® HumanHT-12v4.0 Expression BeadChips. Differentially expressed genes (DEGs) were identified using Limma software, including white blood cell and lymphocyte counts as covariates. As additional tool, we used the CellMix R package to deconvolute the expression data according to cell types. We then analyzed the obtained gene lists in terms of Gene Ontology enrichment.
Results: we enrolled 24 RRMS patients (F:M ratio 2.5), with a mean age at BL of 39.9±8.4 years, median EDSS 2.0 (range 1.0-4.5) and mean disease duration at BL of 10±7 years. At the primary analysis, we found 478 DEGs with FDR< 15%; the top ten were all downregulated, with the *CTLA4* being the more significantly modulated (log Fold-Change -2.399, p-value=0.00026). We than moved on to the deconvoluted data and selected 316 DEGs with a log Fold Change >1 and P-value< 0.01; out of them, 135 were up-regulated and 181 were down-regulated genes. When comparing DEGs list using the two tools, we observed a significant overlap for 51 down-regulated genes. Moreover, there was a substantial overlap between the pathways selected from both

experimental and deconvoluted data, confirming an enrichment in genes involved in lymphocyte activation (p-value=5.4E-10), lymphocyte differentiation (p-value=3.2E-05) and regulation of immune system process (p-value=4.1E-08).
Conclusions: FTY treatment appears to induce a significant downregulation of genes involved in lymphocyte activation and immune response. These data could be driven by FTY mechanism of action, although we took into account the effect on lymphocyte count at the analytical level. Additional experiments on sorted cells are ongoing, in order to better assess FTY effect at the cellular level.

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P954

Whole exome squencing in a chinese family with neuromyelitis optica spectrum disorder

Y. Chang[1], Q. Huang[2], Y. Wang[1], X. Sun[1], S. Yi[3], J. Bei[3], L. Peng[1], X. Hu[1], A. Kermode[4], W. Qiu[1]
[1]Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, [2]The Second Hospital of Zhaoqing, Zhaoqing, [3]SUN Yat-sen Universcity cancer center, Guangzhou, China, [4]University of Western Australia, Perth, WA, Australia

Background: Little is known about the underlying genetic basis of neuromyelitis optica spectrum disorder (NMOSD).
Objective: To identify the causative gene in a Chinese family with NMOSD.
Methods: Whole-exome sequencing was performed in 4 members of this family(2 with NMOSD, and 2 family controls), supplemented by independent *HLA-DP* genotyping.
Results: One mutation chr6:42902216,G>A within the *CNPY3* gene, which co-segregated with the NMOSD phenotype in this pedigree was identified. *CNPY3* gene encodes the protein which is associated with toll-like receptors function. It may involve in the NMOSD pathogenesis by changing the activity of TLRs. There was no HLA-DP allele co-segregated with the NMOSD phenotype found in this family.
Conclusions: *CNPY3* gene was implicated as a novel gene mutated in a Chinese family with NMOSD. Replication studies in other familial NMOSD cases and case-control studies are undergoing to verify the preliminary association.

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P955

TARDBP Ala382Thr mutation and C9ORF expansion in multiple sclerosis: a possible role in brain atrophy

L. Lorefice[1], G. Fenu[1], M.R. Murru[2], J. Frau[1], G. Coghe[1], S. Cuccu[2], D. Corongiu[2], F. Cabras[3], V. Sechi[3], M.A. Barracciu[3], E. Cocco[1], M.G. Marrosu[4]
[1]Multiple Sclerosis Centre, Department of Public Health and Clinical and Molecular Medicine, University of Cagliari, [2]Multiple Sclerosis Centre, ASL8-Department of Medical Sciences, University of Cagliari, Binaghi Hospital, ASL8-Cagliari, [3]Radiology Unit, Binaghi Hospital, ASL8- Cagliari, [4]Multiple Sclerosis Centre, Department of Medical Sciences, University of Cagliari, Cagliari, Italy

Background: Multiple sclerosis (MS) is a chronic multifactorial disease of the central nervous system, specifically characterized by inflammatory demyelination and primary neurodegeneration. Recently, it has been hypothesized a possible role for the TARDBPAla382Thr mutation and the C9ORF expansion in MS neurodegeneration,[1,2] considering their confirmed role in other neurodegenerative diseases.
The aim of this study was to explore if these mutations play a role in inducing or enhancing the brain atrophy in MS.
Methods: The study included a group of MS patients carrying the TARDBP Ala382Thr mutation and the C9orf72 expansion, genetically tested at the MS Centre of the University of Cagliari. Mutated MS patients were age, sex, disease course and EDSS-matched with MS patients without mutation, randomly selected from our genetic database. Recruited patients underwent a brain MRI. Volumes of whole brain (WB), white matter (WM) and grey matter (GM) were estimated with SIENAX.[3] The difference in WB, WM and GM volumes was assessed with independent samples t-test.
Results: The MS sample comprised 18 patients without mutation and 18 carrying it, of which 14 females for each group. Fifteen patients reported the TARDBP Ala382Thr mutation in heterozygous state and 3 the C9orf72 pathogenic expansion. Owing to the

effect of matching, demographic and clinical features (disease course and EDSS) were homogeneous in two groups. Mean age at the time of the brain MRI was 41.5 years (SD ± 11.8); relapsing course was reported for 15 patients in each group, and the mean EDSS score was 2.8 (SD ± 1.8). Disease duration was 15.2 years (SD ± 9.2) and 13.6 (SD ± 6.5) for patients with and without mutation, respectively. No difference in WB and GM volumes between two groups was reported. Lower WM volumes were resulted significantly associated with the presence of analysed mutations (687,81 ml ± 35 vs 710,92 ml ± 26.6; p 0.03).

Conclusion: Despite these mutations do not play a major role in MS pathogenesis, it is plausible they contribute in enhancing the brain atrophy. However, additional studies in other MS populations are needed to better know this issue.

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3. S. M. Smith, et al. NeuroImage, vol. 17, no. 1, pp. 479-489, 2002.

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MS risk alleles for *AHI-1* and *IL22RA* genes are associated with relapses in children and adults with MS

J. Graves[1], L. Barcellos[2], S. Simpson[3], A. Belman[4], J. Noble[5], R. Lin[3,6], A.-L. Ponsonby[7], T. Dwyer[7], L. Krupp[8], B. Taylor[3], E. Waubant[1], I. van der Mei[3]
[1]UCSF, San Francisco, [2]UC Berkeley, Berkeley, CA, United States, [3]Menzies Research Institute Tasmania, University of Tasmania, Hobart, TAS, Australia, [4]National Pediatric MS Center, Stonybrook, Stony Brook, NY, [5]Children's Hospital Oakland Research Institute, Oakland, CA, United States, [6]Guangxi Center for Disease Prevention and Control, Nanning, China, [7]Murdoch Children's Research Institute, Royal Children's Hospital, Parkville, VIC, Australia, [8]New York University Langone Medical Center, New York, NY, United States

Objective: We sought to determine whether established multiple sclerosis (MS) genetic susceptibility factors are associated with relapse rate in children and a replication cohort of adults with MS.
Methods: Genotyping was performed for 185 children with MS or clinically isolated syndrome with high risk for MS from two Pediatric MS Centers. They were prospectively followed for relapses. Fifty-two non-HLA MS susceptibility SNPs were both evaluated for association with relapse rate. Cox regression models adjusted for disease-modifying therapy (DMT) use, genetic markers of ancestry and sex. Replication of pediatric subject SNP results was performed using a second cohort of 141 adult MS subjects from the Southern Tasmanian Multiple Sclerosis Longitudinal Study.
Results: Over 622 patient-years of follow-up, 408 relapses were captured. Several non-HLA risk SNPs were associated with relapse hazard ($p< 0.05$) in the pediatric subjects. After adjustment for *HLA-DRB1*15:01*, sex, vitamin D level, and DMT, having two copies of risk allele for *AHI1* was associated with increased relapses in the pediatric subjects (HR 1.67, 95%CI 1.12-2.49, p=0.012) and this result replicated in the adult subjects (HR 1.81, 95% CI 1.07-3.08, p=0.028). The risk allele downstream of *IL22RA2* increased the hazard to relapse associated with low vitamin D in both children (HR 1.59, 95% CI 1.25,2.03, $p< 0.001$) and adults (HR 1.92, 95% CI 1.20,3.07, p=0.006).
Conclusions: Our results suggest genetic risk variants may also contribute to disease course. We further find genetic modification of vitamin D effects on relapse rate.

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P957

Chromosome conformation capture to discover candidate epigenetic markers of Multiple Sclerosis disease severity

D. Sangurdekar[1], T. Plavina[1], C. Singh[1], A. Enayetallah[1], M. Subramanyam[1], E. Hunter[2], A. Akoulitchev[2], J. Goyal[1]
[1]Biogen, Cambridge, MA, United States, [2]Oxford BioDynamics, Oxford, United Kingdom

Background: Multiple Sclerosis (MS) is a heterogeneous disease with diverse outcomes creating a need for better understanding of underlying pathophysiological mechanisms, and implementation of prognostic biomarkers to optimize treatment decisions. Growing evidence suggests an imperative role of epigenetic mechanisms in the development of autoimmune and neurodegenerative disorders, including MS.
Objectives: To identify an epigenetic signature associated with MS disease severity and progression.
Methods: Chromosomal Conformation Signature (CCS) profiling technology and platform (EpiSwitch™, Oxford BioDynamics) was used to profile whole blood from 16 MS subjects with varying disease severity (EDSS⩾5 and EDSS⩽2) and 7 healthy

controls. Markers initially discovered on an MS custom-designed CCS array platform were validated using PCR assays. Univariate and contingency table analysis was performed to select candidate markers associated with clinical and radiological MS disease characteristics.
Results: To build a discovery array, 747 genes associated with MS pathogenesis were annotated with chromosome conformation interactions predicted using the EpiSwitch™ *in silico* prediction software, resulting in 42,458 high-confidence CCS candidates. The array profiling generated 156 candidate markers from 96 unique genes that were then translated into the PCR assay used for marker verification in additional samples. As a result, 27 chromatin conformation markers from several genetic loci, including BSCL2, MICB and STAT4, were found to be associated with clinical and radiological characteristics in the tested discovery cohort of patients. A follow up study that comprises 60 MS patients with longitudinal sampling and diverse clinical characteristics has been initiated to further refine the signature.
Conclusions: Pilot study of MS patients with extreme clinical phenotypes using EpiSwitch™ chromatin conformation platform identified candidate hypotheses and markers that are being verified in a larger longitudinal cohort.

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P958

Genotype is predicting Multiple Sclerosis pathology in the cohort of the Netherlands Brain Bank

N.L. Fransen[1], M. Mason[2], B. Crusius[3], C. van Eden[1], M. Mizee[1], S. Luchetti[1], I. Huitinga[1]
[1]Neuroimmunology, [2]Neuroregeneration, Netherlands Institute for Neuroscience, [3]Immunogenetics, VU University Medical Center, Amsterdam, The Netherlands

Background: Clinical, radiological and neuropathological heterogeneity of Multiple Sclerosis (MS) suggests that different pathogenic mechanisms are involved in subgroups of MS patients. Single Nucleotide Polymorphisms (SNPs) show a relation with MRI outcome and disease severity in Genome Wide Association Studies (GWAS). We hypothesize that in subgroups of MS patients SNPs cause (in)activation of different pathogenic mechanisms, resulting in differences in pathological outcome, clinical disease course and response to immunomodulatory therapy.
Objective: identify SNPs that correlate with MS pathology in MS cohort of Netherlands Brain Bank (NBB).
Methods: 198 MS patients were included. From all archived tissue (n=3562) lesions were characterized with HLA-PLP immunohistochemistry. Lesion types were scored according to demyelination and microglia morphology. Reactive, active, chronic active, inactive and shadow plaques were distinguished in white matter and demyelination in cortical grey matter lesions. 104 SNPs were selected based on previous association with MRI measures or disease severity in GWAS and pathology in gene expression studies. DNA was isolated from leukocytes or cerebellum tissue. Competitive allele specific polymerase chain reaction (PCR) was performed for 104 SNPs. Statistical analysis of SNPs with total white matter lesion load, proportions of lesion types, cortical lesion presence and disease duration was performed in R.
Results: The most significant SNPs all showed a relation with proportion of reactive sites, indicating higher proportion of reactive microglia in normal appearing white matter; MIF (p=0,0001), MET (p=0,001), SKA1 (p=0,002) and AGBL4 (p=0,002). Analysis stratified by sex showed in males (n=66) most significant are MIF (p=0,0008) with proportion of reactive sites and RFK (p=0,0004) with proportion of active lesions. In females (n=103) most significant are SKA1 (p=0,001) with proportion of reactive sites, IGF2R (p=0,001) with total white matter lesion load.
Discussion: This exploratory study shows that in the NBB cohort SNPs are predicting pathological outcome of MS. This analysis suggests an important role for SNPs in predicting activation of microglia-macrophages. Validation of these SNPs in another post-mortem cohort of MS patients is needed. Further functional experiments on the effects of these SNPs on MS pathology will be conducted to better understand the different pathogenic mechanisms causing heterogeneity in MS.

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P959

Analysis of DNA methylation in post-mortem brain tissue from Multiple Sclerosis patients

M. Needhamsen[1], L. Kular[1], T. Kramarova[1], D. Gomez-Cabrero[2], E. Ewing[1,2], M.Z. Adzemovic[1], J. Tegnér[2], L. Brundin[1], M. Jagodic[1]
[1]Department of Clinical Neuroscience, Center for Molecular Medicine (CMM), [2]Department of Medicine, Unit of Computational Medicine, Center for Molecular Medicine, Karolinska Institute, Stockholm, Sweden

Background: The brain is a major target organ of autoimmune attacks in Multiple Sclerosis (MS). DNA methylation, also referred to as 5-methylcytosine (5mC), is a stable epigenetic mark in the form of a methyl group covalently bound to DNA, which is better preserved compared to for example RNA and proteins in postmortem autopsy brain tissue. Furthermore, DNA methylation reflects underlying genome activity (i.e. hypermethylation of promoters is typically associated with gene repression) and therefore comprises

a useful system for examining altered cellular mechanisms. Recently, an additional epigenetic mark, referred to as hydroxymethylation (or 5hmC), has gained particular attention due to high abundance in brain tissue. Noticeably, 5hmC displays a unique genomic distribution compared to 5mC, which suggest distinct functional roles of 5mC and 5hmC.

We aim to characterize 5mC and 5hmC in post-mortem brain tissue from MS patients and controls.

Methods and Results: Genomic DNA was extracted from snap frozen brain tissue blocks collected within 24h post-mortem and treated in parallel with oxidative bisulfite (oxBS) and BS for detection of 5mC and cumulative 5mC+5hmC levels, respectively, using the Infinium HumanMethylation450 BeadChip (450K) array, which covers 99% of RefSeq genes.

We have set up a bioinformatics analysis pipeline to quantify levels of 5mC and 5hmC from 450K array data. First, we filtered only specific probes with high detection value using the ChAMP Bioconductor package. Subsequently between array and within array normalization was applied prior to subtraction of oxBS from BS for quantification of 5hmC. Multidimensional scaling, principal component analysis and cluster analysis revealed a significant impact of tissue composition and brain regionality, which are necessary to be taken into account prior to further examining global and local difference in 5hmC and 5mC between MS patients and controls.

Conclusion: We have set up a method to address 5mC and 5hmC in post-mortem brain tissue. Preliminary data suggest that this enables identification of differential DNA methylation and altered pathways in MS brains.

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Genetic variants associated with intrathecal synthesis of IgG, IgM and IgA in multiple sclerosis

C. Gasperi[1], A. Krysta[1], G. Antony[2], A. Bayas[3], R. Gold[4], C. Heesen[5], T. Kümpfel[6], R.A. Linker[7], F. Paul[8,9,10], M. Stangel[11], B. Tackenberg[12], F. Then Bergh[13], H. Tumani[14], C. Warnke[15], F. Weber[16,17], W. Wick[18], H. Wiendl[19], U.K. Zettl[20], U. Ziemann[21,22], F. Zipp[23], D. Buck[1], B. Hemmer[1,24], on behalf of the German competence network of multiple sclerosis
[1]Department of Neurology, Klinikum rechts der Isar der TUM, Munich, [2]Central Information Office KKNMS, Philipps-University Marburg, Marburg, [3]Department of Neurology, Klinikum Augsburg, Augsburg, [4]Department of Neurology, Ruhr University Bochum, Bochum, [5]University Medical Centre Hamburg Eppendorf, Hamburg, [6]Institute of Clinical Neuroimmunology, Ludwig Maximilian University, Munich, [7]Department of Neurology, University Hospital Dresden, Dresden, [8]NeuroCure Clinical Research Center, Charité - Universitätsmedizin Berlin, [9]Department of Neurology, Charité - University Medicine Berlin, [10]Experimental and Clinical Research Center & Max-Delbrück Center Berlin, Berlin, [11]Department of Neurology, Hannover Medical School, Hannover, [12]Clinical Neuroimmunology Group, Department of Neurology, Philipps-University Marburg, Marburg, [13]Department of Neurology and Translational Center for Regenerative Medicine, University of Leipzig, Leipzig, [14]Department of Neurology and Translational Center for Regenerative Medicine, University of Ulm, Ulm, [15]Department of Neurology, Heinrich-Heine University, Düsseldorf, [16]Max Planck Institute of Psychiatry, Munich, [17]Neurological Clinic, Medical Park, Bad Camberg, Bad Camberg, [18]Department of Neurology, University Hospital Heidelberg, Heidelberg, [19]Department of Neurology, Klinik für Allgemeine Neurologie, University of Münster, Münster, [20]Department of Neurology, University of Rostock, Rostock, [21]Department of Neurology & Stroke, Eberhard Karls University Tübingen, [22]Hertie-Institute for Clinical Brain Research, Tübingen, [23]Department of Neurology, Focus Programm Translational Neurosciences (FTN) and Research Center for Immunotherapy (FZI), Rhine-Main Neuroscience Network (rmn2), Johannes Gutenberg University, Mainz, [24]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

Introduction: Intrathecal synthesis of immunoglobulins can often be observed in patients with multiple sclerosis (MS) and clinically isolated syndrome (CIS) and the amount of intrathecal immunoglobulin synthesis in an individual patient remains relatively stable over time. We could previously show an association between the IgG index and genetic variants located around the immunoglobulin heavy chain locus (IGHC) on chromosome 14 using a genome wide association study (GWAS). The variants corresponded to different allotypes that code for structurally distinct immunoglobulin heavy chains. The aim of this study was to confirm the previously described association by genotyping the single nucleotide polymorphism (SNP) rs74093865, which is in strong linkage disequilibrium (r^2 0.9) with the lead SNP rs10136766 from our previous study and to further investigate the effect of this genetic variant on intrathecal synthesis of IgA and IgM.

Methods: DNA samples from 785 MS or CIS patients with available data on intrathecal immunoglobulin synthesis, who were not part of our previous study, were obtained and genotyped for the rs74093865 using a TaqMan SNP genotyping assay . The association between rs74093865 and rank transformed IgG, IgM and IgA indices was tested using linear regression with adjustments made for sex, age, assay plate, time points of lumbar puncture and DNA sampling.

Results: rs74093865 was significantly associated with indices for IgG, IgM and IgA in patients with MS and CIS. In accordance

with our previous findings, the A allele, which corresponds to the IGHC Gm21* allotype, correlated with higher IgG index (p=2E-13). Interestingly, lower IgM and IgA indices were seen in patients carrying the A allele of rs74093865 (p=3E-7 and p=5E-4 for IgM and IgA indices, respectively).

Conclusion: The results of this study confirm the association of a genetic variant located around the immunoglobulin heavy chain locus with intrathecal immunoglobulin synthesis. Interestingly the Gm21* allotype seems to be associated with higher intrathecal IgG synthesis and lower intrathecal IgA and IgM synthesis.

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Excess of rare variants in risk genes for multiple sclerosis identified by DNA resequencing

E. Gil[1], N. Spataro[2], O. Fernández[3], A. Saiz[4], L. Ramió-Torrentà[5], F. Matesanz[6], S. Malhotra[1], A. Navarro[7], E. Bosch[2], X. Montalban[1], M. Comabella[1]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, [2]Department of Experimental and Health Sciences, Universitat Pompeu Fabra - Institute of Evolutionary Biology (CSIC-UPF), Barcelona, [3]Neuroscience, Instituto de Biomedicina de Málaga (IBIMA), Hospital Regional Universitario de Málaga, Málaga, [4]Neurology Department, Hospital Clinic and Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, [5]MS & Neuroimmunology Unit, Hospital Universitari de Girona Dr. Josep Trueta, Girona, [6]Department of Cell Biology and Immunology, Instituto de Parasitología y Biomedicina López Neyra, Granada, [7]Centre de Regulació Genòmica (CRG), Barcelona, Spain

Background: Genetic and environmental factors are known to influence the complex pathogenesis of multiple sclerosis (MS). Despite the identification of many risk common variants through genome-wide association studies (GWAS), much of the MS heritability remains unexplained. Rare variants (RV) with minor allele frequencies (MAF) < 1% could play an important role in explaining such missing heritability. Here, we performed targeted gene resequencing to identify RV affecting MS susceptibility in the following MS candidate risk genes: *FCRL1*, *RGS1*, *TIMMDC1*, *HHEX*, *CXCR5*, *LTBR*, *TSFM*, *GALC*, *TRAF3*, *STAT3*, *TNFSF14*, *IFI30*, *CD40* and *CYP24A1*.
Methods: All exons and regulatory regions of the selected genes (~140kb) were sequenced at high coverage (~85X) using the Illumina Hiseq technology after enrichment with a Nimblegen array in a total of 1,070 DNA samples, 524 from patients with relapse-onset MS and 546 from healthy donors. Raw data were first mapped to the human reference genome (hg19) using the BWA aligner and subsequently processed using a GATK pipeline. Variant discovery and functional annotation were performed with the Haplotype Caller tool of GATK and ANNOVAR, respectively. Enrichment for RV was assessed with collapsing statistical association methods using the Variant Tools package.
Results: We identified a total of 1,671 RV, which included 118 non-synonymous SNPs (89 predicted as damaging), 3 frameshifts, 4 stop-gains and 1 stop-loss. When considering all the discovered RV for each single gene, MS patients displayed an excess of RV in *RGS1* and *STAT3*. Both genes exhibited an excess of RV in their regulatory regions in MS patients, and *RGS1* particularly in its UTR3′ region. Additionally, an excess of RV was also observed in the coding regions of *TRAF3* in MS cases. However, only the RV enrichments observed for *RGS1* gene were significant after multiple testing correction.

Conclusions: In MS patients, RV cluster in specific fragments of some MS susceptibility genes. Further work is in progress to explore the functional role of the detected RV and contribute to a better understanding of the underlying genetic architecture and etiology of MS.

Disclosure

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Immunology

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MS patients show distinct CSF leukocyte profiles and cytokine intracellular production compared to other inflammatory and non inflammatory neurological diseases

C. Picon[1], S. Sainz de la Maza[2], E. Rodriguez-Martin[1], L. Costa-Frossard[2], Y. Aladro[3], S. Medina[1], M. Espiño[1], J.C. Alvarez-Cermeño[2], L.M. Villar[1]
[1]Immunology, [2]Neurology, Hospital Universitario Ramon y Cajal, [3]Neurology, Hospital Universitario de Getafe, Madrid, Spain

Introduction: Differences in leukocyte populations in the cerebrospinal fluid (CSF) between Multiple Sclerosis (MS) and other neurological pathologies have been reported. However is not fully elucidated which leucocytes subsets and cytokines producing cells are the major players on MS compared to other inflammatory (OIND) and non inflammatory (NIND) diseases of the central nervous system (CNS).
Objective: To explore immune intrathecal phenotypes that may help to identify MS patients from other diseases of the CNS and get insights on the physiopathology of the disease.
Patients and methods: 115 consecutive MS patients, 31 with other inflammatory diseases (IND) and 30 with non-inflammatory disease (NIND) were included in this study. We studied by flow cytometry the percentages and total cells counts of different lymphocyte and monocyte subsets present in CSF and the intracellular cytokine production (INF-γ, TNF-α, IL-22, IL-17) on CSF T cells.
Results: MS patients showed higher percentages and total cell counts of regulatory T cells ($p< 0.0001$), CD62L+CD4+ ($p=0.0011$) and B cells ($p< 0.0001$) than OIND and NIND patients. In addition, OIND group showed higher percentages and total cell counts of CD4 T cells producing IL-22 and IL-17 ($p< 0.0001$) than the other groups while MS patients had higher cell counts of CD4 and CD8 T cells producing TNF-α and INF-γ ($p< 0.0001$;$p< 0.0001$). Alternatively, NIND patients showed higher percentages of monocytes ($p=0.0002$), this increase was due to classical ($p=0.0024$) and alternative ($p< 0.0001$) subsets.
Conclusions: We have observed different leukocyte patterns in CSF of patients with MS and other inflammatory and non inflammatory neurological diseases. This contributes to elucidate the immunological mechanisms playing a role in MS.

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Infiltration of CD39 T cells in the CSF of relapsing-remitting multiple sclerosis patients

M. Belghith[1], K. Bahrini[2], M. Kchaou[3], N. Ben Ali[3], S. Blel[3], M.R. Barbouche[4]
[1]Immunology, Institut Pasteur, [2]Pasteur Institut, [3]Neurology, Charles Nicolle's Hospital, University hospital, [4]Immunology, Pasteur Institut, Tunis, Tunisia

Introduction/**Objective:** Multiple sclerosis is a chronic inflammatory disease of the central nervous system (CNS). It has been reported that effectors T cells involved in the pathogenesis of MS are mainly TH1 and TH17 populations. Indeed, they emerged as crucial players in CNS inflammation associated to disease. The purpose of this study is to characterize the phenotype of TCD4 subpopulation present in the cerebrospinal fluid (CSF) and to investigate biomarkers able to discriminate MS patients from patients with other neurological diseases.
Materiel and methods: We quantified the mRNA of INF-γ, IL-17, IL-10, IL-4, Foxp3 and CD39 in the CSF of 25 patients with relapsing remitting multiple sclerosis (RRMS), 20 patients with Neuro-Behçet disease (NBD) and 20 healthy controls. CD39 expression in the CSF was studied simultaneously with Foxp3 intracellular labeling by flow cytometry.
Results: Our findings show an increased level of INF-γ and IL-17 in the CSF of RRMS and NBD patients compared to controls ($p< 0.05$). Moreover, measurement of anti-inflammatory cytokines,

showed a significant increase of IL-10 in the CSF of NBD compared to other groups (p< 0,001). The evaluation of Foxp3 mRNA expression did not show a significant difference between the 3 groups. Thus, we studied another marker called CD39, which is defined as an ecto-enzyme that cleaves ATP to AMP. We demonstrated that CD39 is highly expressed in CSF of RRMS patients (p< 0,001). However, it is absent in the CSF from control group. Moreover, by cytometry the CD39 does not correlate with Foxp3 labeling in the CSF of RRMS patients.

Conclusion: To conclude, we show an increase of pro-inflammatory cytokines in the CSF particularly INF-γ and IL-17. Furthermore, a strong involvement of CD39+ cells seems to play a role in immunodysregulation in the CSF of RRMS patients.

Disclosure

Meriam Belghith: nothing to disclose"

P964

Anti-C1q antibodies are characteristically present in patients with relapsing-remitting MS but not in secondary progressive MS: implications for the role of complement activation in the pathogenesis of MS

S. Rentouli[1,2,3], C. Liaskos[2,3], G. Efthymiou[2,3,4], Z. Tsouris[3,4], V. Tsimourtou[4], G. Tsivgoulis[5], G.L. Norman[6], L.I. Sakkas[2], Z. Mamouris[1], D.P. Bogdanos[2,3], E. Dardiotis[4], G. Hadjigeorgiou[4]

[1]Department of Biochemistry and Biotechnology, School of Health Sciences, University of Thessaly, [2]Department of Rheumatology, University General Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, [3]Cellular Immunotherapy & Molecular Immunodiagnostics, Biomedical Section, Centre for Research and Technology-Hellas (CERTH)- Institute for Research and Technology-Thessaly (IRETETH), [4]Department of Neurology, University General Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, [5]Second Department of Neurology, "Attikon" Hospital, School of Medicine, University of Athens, Athens, Greece, [6]INOVA Diagnostics, San Diego, CA, United States

Introduction: Multiple sclerosis (MS) is a prototypic autoimmune demyelinating disease, the aetiology of which remains poorly understood. the role of complement activation in MS remains controversial though recent studies have suggested an important role for the C1q-C3 complement axis in synaptic alterations in the MS hippocampus. C1q has been reported as a target of autoantibodies in several autoimmune diseases but whether anti-C1q antibodies are present in patients with MS has not been studied in great detail.

Aim: To assess the diagnostic and clinical significance of anti-C1q antibodies in MS patients.

Material and methods: Serum samples from 129 patients with MS (102 RRMS and 27 SPMS, 39 male and 91 female, 42.4 ± 11.7 years) were tested for the presence of antibodies against C1q (IgG) by ELISA (INOVA).

Results: IgG anti-C1q were present in 21/129 (16.3%) MS patients. The presence of anti-C1q was statistically associated with the phenotype of the disease, as anti-C1q antibody positivity was associated with RRMS (20/102, 19.6%) rather than SPMS (1/27, 3.7%, p=0.04 x^2, p= 0.074, Fisher´s exact) and with sorter disease duration (8.8± 5.4 months vs 11.7± 7.5 months, p=0.046). The presence of anti-C1q was not associated with other clinical features including sex, age, EDSS score, number of relapses or type of treatment (interferon, first or second line treatment).

Conclusions: Anti-C1q antibodies are frequently detected in patients with MS. Their universal presence in patients with RRMS rather than SPMS may bear a pathophysiological meaning and requires further investigation.

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P965

Imbalances of highly inflammatory Th1/17 cell subsets are associated with early development of multiple sclerosis

J. van Langelaar[1], R.M. van der Vuurst de Vries[2], M. Janssen[1,2], A.F. Wierenga-Wolf[1], I.M. Spilt[1], G.P. van Nierop[2,3], J.Y. Mescheriakova[2], T.F. Runia[2], M.M. van Luijn[1], R.Q. Hintzen[1,2]

[1]Department of Immunology, [2]Department of Neurology, [3]Department of Viroscience, Erasmus MC, University Medical Center, MS Center ErasMS, Rotterdam, The Netherlands

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system mediated by local inflammatory T cells. Disease onset is often preceded by a clinically isolated syndrome (CIS), the earliest clinical presentation of MS. However, only half of the patients with an initial attack meet the standard MRI criteria at baseline or do not develop clinically definite MS at all. Hence, in-depth analyses of pro-inflammatory CD4+ T helper (Th) cells in early MS could lead to a better understanding and more accurate prediction of disease development. We performed a CIS prediction (n=30) and case-control (treatment-naive RRMS; n=40) study to explore differentiation and activation of blood Th cell subsets with distinct pro-inflammatory cytokine profiles using 12-colour flow cytometry. In fast CIS converters (developed clinically definite MS within 1 year), CXCR3+CCR6- ('Th1') and CXCR3+CCR6+ ('Th1/17'), but not CXCR3-CCR6+ ('Th17') cells showed lower frequencies and reduced proportions of effector memory cells compared to slow CIS converters (remained CIS for more than 5 years; p< 0.01). These reductions correlated with fatigue scores (r=0.56, p=0.002), which are predictive for CIS conversion (Runia et al., J Neurol Neurosurg Psychiatry 2015), and were also found in RRMS versus control blood (p< 0.01). In RRMS, Th1/17 cells were highly activated (HLA-DR+CD38+; p< 0.001), while this was the case for Th17 cells in CIS. After sorting and *in vitro* activation, Th1/17 cells prominently expressed

IFN-γ (33%) and GM-CSF (36%), which was much stronger than in Th1 (15% and 12%) and Th17 (3% and 16%) cells. Finally, the downregulation of CXCR3 on *in vitro*-activated Th cells, as well as the predominance of Th1 and Th1/17 memory cells within the total CD4+ T cell population in MS brain tissue (n=16) are possible explanations for the reduced Th1 and Th1/17 cell frequencies in early MS blood. These data indicate that conversion of activated Th17 into Th1/17 cells and their preferential migration with Th1 cells into the brain are key mechanisms underlying early MS development.

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P966

Paradoxical effects of TLR4 stimulation to B cells in multiple sclerosis

Y. Okada[1], T. Kondo[1,2,3], C. Fujii[3], Y. Hashi[1], H. Ochi[4], M. Nakagawa[5], T. Mizuno[3], S. Matsumoto[6], M. Urushitani[1], R. Takahashi[1]
[1]Department of Neurology, Kyoto University Graduate School of Medicine, [2]Department of Clinical Network and Collaborative Medicine, Kyoto University Hospital, [3]Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, kyoto, [4]Department of Neurology and Geriatric Medicine, Ehime University Graduate School of Medicine, Toon, [5]Department of Neurology, North Medical Center, Kyoto Prefectural University of Medicine, Kyoto, [6]Department of Neurology, Tazuke Kofukai Foundation, Medical Research Institute, Kitano Hospital, Osaka, Japan

Introduction: Exacerbation of Multiple sclerosis (MS) is thought to be triggered by infection. During infection B cells secrete proinflammatory and regulatory cytokines through toll-like receptors (TLR) and CD40 by activated T cells. Therefore, it is much of interest whether B cells derived from MS patients produce more proinflammatory and less regulatory cytokines during infection.
Methods: We enrolled 24 MS patients during remission and 16 during relapse and 21 Healthy subjects (HS). After isolating peripheral blood mononuclear cells, CD40 and TLR expression on B cells was measured by flow cytometry. The cells were cultured for 72h with lipopolysaccharide as TLR4 agonist and/or CD40 ligand. Cell stimulation cocktail (ebioscience) was added at 66h. Proinflammatory cytokines such as interleukin (IL)-6, lymphotoxin, tumor necrosis factor (TNF)-a and IL-10 were intracellularly stained and analyzed by flow cytometry.
Results and discussion: No significant difference among MS and HS was observed regarding proinflammatory cytokine production in response to TLR4 and/or CD40 stimulation with the exception of TNF-a-producing B cells upon TLR4 stimulation (Median: MS remission 10% vs. HS 5.8%, p= 0.012). The median frequency of TNF-a decreased to 3.6% during relapse (p= 0.055). The frequency of IL-10-producing B cells from MS patients decreased upon CD40 stimulation (HC 2.5% vs. MS remission 1.2% and MS relapse 1.3%, p= 0.017 and p= 0.013). Impaired IL-10 production upon stimulation by CD40 and TLR4 but not TLR4 alone was also observed in MS patients in remission (MS in remission 0.8% vs. HS 3.3%, p=0.001). The capacity of IL-10 production by B cells was partially but significantly recovered to 1.9% during relapse (p= 0.049). Six patients were analyzed both in remission and at relapse, and higher IL-10 production by B cells at relapse was confirmed (MS remission 1.0% vs. MS relapse 5.3%, p= 0.037). There was a linear association between IL-10 and TLR4 expression on B cells in HS (R= 0.79, p< 0.001). TLR4 expression on B cells was downregulated in MS remission, but elevated when relapsed.

In conclusion, Response to TLR4 stimulation skewed to inflammatory shift, i.e., less IL-10 production, in remission of MS. However, TLR4 expression was increased at relapse, resulting in increased IL-10 production. Together with decreased TNF-a production, TLR4 stimulation at relapse may have beneficial effect in MS.

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P967

T cell receptor repertoire of circulating and resident antigen-specific T cells of DR2+ patients affected by Multiple Sclerosis

G. Di Sante[1], A.K. Patanella[2], S. Rolla[1], A. Bianco[2], A. Piermattei[1], M. Valentini[1], G. Migliara[1], V. Annibali[3], F. Novelli[1], V. Nociti[2], F. Ria[1], M. Mirabella[2]
[1]Institute of Pathology - Catholic University, [2]Fondazione Policlinico Universitario Agostino Gemelli, [3]Medical Affairs Department - Merck, Rome, Italy

Background: The most important risk factors enhancing susceptibility for multiple sclerosis (MS) are HLA class II genes, in particular HLA DRB1*15 (DR2), implicated in the Antigen presentation to CD4+ T compartment. Autoreactive T cells have been isolated in the peripheral blood and cerebrospinal fluid (CSF) of MS patients. Numerous antigens have been investigated as potential target. In HLA-DR2+ subjects, an immunodominant T-cell epitope exists in the middle portion of myelin basic protein (MBP), corresponding to residues 85-99, that can be presented by DR2 and DQ6 to T-cell clones from MS patients.
Objective: In this study, we investigated the repertoire of T cells specific for MBP85-99 and MBP111-129 (subdominant epitope) in MS patients and in healthy donors (HD) in order to detect new disease biomarkers, which may facilitate MS management.
Materials and methods: We obtained the peripheral blood mononuclear cells (PBMCs) from a cohort of 82 MS patients (27 DR2+) and 13 HD (6 DR2+). In order to investigate the T cell receptor (TCR)-beta repertoire of T cells specific for the immunodominant

epitope MBP85-99 and the less immunogenic MBP111-129, we performed the immunoscope analysis (TRBV-TRBJ spectratyping). We analyzed TCR repertoire also in IL17A and IFNgamma-secreting magnetically sorted T cells (n=6) and, where possible, in resident T cells from CSF samples (n=20).
Results: We identified MBP85-99 specific 20 TCR expansions, focusing on 2 TRBV-TRBJ rearrangements: one shared by the 75% of MS DR2+ patients at the onset of disease and one present in 50% of clinically isolated syndrome (CIS) and MS patients. We also investigated the MBP111-129 response and found several specific TCR-beta chains not shared with the immunodominant epitope. One of the shared MBP85-99 specific TCR was expanded in IL17A secreting cells; interestingly, this TCR was detectable in the CSF-resident T cells. We sequenced the shared TRBV-TRBJ rearrangement to confirm the clonotypic nature of these T cells specific for MBP85-99 in MS patients, but not detectable in the CIS and healthy subjects.
Conclusions: These results suggest that the repertoire of TCR specific for MBP85-99 may be broader in CIS than in MS patients. Antigen-specific T cells may, therefore, present a potential future target for personalized MS therapies.

Disclosure

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P968

Intrathecal IgM synthesis: is really a prognostic factor?

J. Frau[1], G. Coghe[1], L. Lorefice[1], G. Fenu[1], M.A. Secci[2], L. Schirru[2], M.G. Marrosu[1], E. Cocco[1]
[1]University of Cagliari, [2]Centro Sclerosis Multipla, Ospedale Binaghi Cagliari, Cagliari, Italy

Background: Intrathecal IgM synthesis (ITMS) was found associated with poor MS prognosis in some studies performed in small samples of patients. (Villar 2002, 2003) In particular, it was associated to conversion in clinically definite MS after the first relapse, higher EDSS index, secondary progressive course, and higher number of relapses. The evaluation of ITMS in a pediatric group, using a different laboratory method, did not confirm this datum. (Stauch 2010)

The aim of our study was to evaluate the prognostic value of ITMS in a higher sample of Sardinian patients.
Methods: In the study were enrolled patients with MS (according to McDonald 2010). All of them were recruited from the MS Centre of the University of Cagliari from 2007 until to 2013 and underwent lumbar puncture (LP) for diagnostic purpose. For each patient were recorded demographic data, clinical course at LP, time to reach EDSS 3, 6, 8, 10, EDSS at last follow-up (2016), MS treatments until the last follow-up. The analysis of ITMS was performed by isoelettrofocusing and immunoblotting, using specific anti-human IgM antibodies, as descripted by Villar et al in 2011.
Fisher test was used to analyse the association of ITMS with clinical course, while with Kaplan-Meier was studied the time to reach EDSS 3 and 6.
Results: The enrolled subjects were 404, 390 relapsing-remitting (RR) and 14 primary progressive (PP); 314 patients started a MS treatment after the diagnosis. Out of the sample, 100 patients reached EDSS 3 (34 with and 66 without ITMS, p=0.7), 33 EDSS 6 (10 with and 23 without ITMS p=0.7), only 3 EDSS 8 and none EDSS 10. In 126 patients ITMS were found, in particular IgM were in 120 RR and 6 PP (p=0.38) subjects. It is to note that in 9 patients with ITMS the analysis of intrathecal IgG was negative.
Discussion: Our study did not confirm the prognostic value of IgM in terms of clinical course and time to reach the main EDSS milestones. It is to note that a high percentage of patients started very quickly after the diagnosis immunomodulating or immunosuppressive drugs, which could modify the course of the disease. Moreover, to explain the contrasting result, we could hypothesize a role of genetic factors, having MS Sardinian patients peculiar predisposing and protective HLA. We will study in the next future this important aspect. To our knowledge, our study has the higher sample size in literature, but our purpose is to increase the number of enrolled patients.

Disclosure

The authors have nothing to declare about this work

P969

Expression and induction of granulocyte-macrophage colony-stimulating factor in immune cells in multiple sclerosis

J. Aram, B. Gran, C.S. Constantinescu
Division of Clinical Neuroscience, University of Notiingham, Nottingham, United Kingdom

Background: Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) is a haematopoietic growth factor and an inflammatory cytokine produced by T cells and other immune cells. Recent evidence suggests that GM-CSF has an important role in MS pathogenesis. Our aim was to evaluate the expression of GM-CSF by different subtypes of peripheral blood mononuclear cells (PBMC) in MS patients and controls, and to determine the key factors regulating its expression.
Patients and methods: All patients were untreated RRMS. PBMCs were isolated and stimulated with anti-CD3+anti-CD28 for 5 days. Natural killer (NK) cells were isolated and cultured with different stimuli for 3 days. Cytokines from cell culture supernatants of stimulated PBMCs were measured with multiplex assay. Cells were phenotyped for lineage and intracellular cytokines, including GM-CSF, using flow cytometry.
Results: GM-CSF is expressed at significantly higher frequency by stimulated helper T (Th), cytotoxic T (Tc), and NK cells in untreated RRMS patients than healthy volunteers. There was a statistically significant increase in overall interferon-gamma (IFN-G) production in MS compared to healthy controls (MS n=10, controls n=10). Isolated and stimulated NK cells did not have different GM-CSF expression in MS patients and controls (MS n=7, controls n=5). Culture supernatants were shown to have significantly higher IL-2 and IL-12 in MS patients than controls (MS n=14, controls n=10), and blocking IL-2 significantly reduced GM-CSF expression.

Conclusion: Th (Th1 and Th17), NK, and Tc cells are all high producers of GM-CSF in MS, GM-CSF expression is reduced by blocking IL-2. The recent safety and tolerability results of a phase I trial of a monoclonal antibody in MS are encouraging. Therefore, GM-CSF is a potential therapeutic target in MS.

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P970

CD161 intermediate expression defines a neuropathogenic subset of CD8+ T cells in multiple sclerosis

B. Nicol[1,2], M. Salou[1,2], I. Vogel[1,2], A. Garcia[1,3], S. Nedellec[4], S. Wiertlewski[3,5], A. Boureille[3], L. Michel[1,3], S. Brouard[1,3], N. Degauque[1,3], A. Nicot[1], D.-A. Laplaud[1,3,5]
[1]INSERM U 1064, [2]Université de Nantes, [3]CHU de Nantes, [4]SFR François Bonamy, MicroPiCell, [5]INSERM 004, Nantes, France

Several lines of evidence suggest the involvement of IL-17-secreting $CD8^+$ T cells in Multiple Sclerosis (MS). In humans, these cells are characterized by the expression of CD161.The involvement of $CD8^+$ T cells with an intermediate expression of CD161 has not been described yet.

$CD8^+CD161^{int}$T cells from the blood and cerebrospinal fluid (CSF) of sex- and age-matched MS patients (n=50) and Healthy Volunteers (HV, n=30) were compared by flow cytometry. Their functional status was analyzed after *in vitro* activation in patients (n=16) and HV (n=14). Their ability to transmigrate through an *in vitro* blood-brain-barrier was studied. Their presence and phenotype were studied in CNS lesions and in the gut by immunofluorescence staining on post-mortem samples from MS patients (n=7). These cells were then injected in NOD-*scid* gamma (NSG) mice to study their function *in vivo*.

We observed a decreased frequency of $CD8^+CD161^{int}$ T cells in the blood and a specific enrichment in the CSF of MS patients compared to HV ($p< 0.05$). Circulating $CD8^+CD161^{int}$ T cells in MS patients have increased expression of several activation markers such as CD57/T-bet ($p=0.09$), DNAM-1 ($p< 0.05$) or a decreased expression of PD-1 ($p< 0.05$). After activation, these cells were able to secrete IFNγ, GZM-B, IL-17, IL-22 and GM-CSF, displaying a stronger Tc1-Tc17 phenotype compared to $CD8^+CD161^{neg}$ T cells. Hence the frequency of IL-22 and GM-CSF producing $CD8^+CD161^{int}$ T cells was increased in MS patients compared to HV ($p< 0,001$). Homing markers like CCR2, PSGL-1 and CD11a were overexpressed in MS patients' $CD8^+CD161^{int}$ T cells ($p< 0.05$, $p< 0.01$ and $p< 0.01$, respectively). Finally, among CD161 expressing cells, $CD8^+CD161^{int}$ were the most efficient to transmigrate through an *in vitro* blood-brain-barrier model ($p< 0,01$) explaining their higher proportion in the CNS of MS patients and ability to secrete IL-17 *in situ* compared to the blood ($p< 0.05$). This secretion was tissue specific and not observed in the gut of MS patients. In NSG mice, human $CD8^+CD161^{int}$T cells from MS patients and HV were correctly engrafted after 3 weeks post-injection.

This work demonstrates the involvement of a new population of $CD8^+$ T cells in MS pathophysiology with an activated phenotype and neuropathogenic properties. We are currently analyzing their behavior in an *in vivo* model of humanized Graft-Versus-Host disease in NSG mice. If confirmed, $CD8^+CD161^{int}$ T cells could be a potential therapeutic target in MS patients.

Disclosure

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P971

The intrathecal synthesis of BAFF inversely correlates with local IgG synthesis in multiple sclerosis at clinical onset

M. Puthenparampil, M. Silvia, L. Federle, E. Toffanin, S. Ruggero, F. Rinaldi, P. Gallo
Multiple Sclerosis Centre of Padua, Department of Neuroscience, University of Padua, Padua, Italy

Background: B-cells play a relevant role in multiple sclerosis (MS) pathology. BAFF (B cell activating factor of the TNF family) is a B-cell survival factor constitutively produced inside the CNS by astrocytes.
Objective: We studied the correlation between the intrathecal synthesis of BAFF and locally produced IgG in patients with clinically isolated syndromes (CIS) suggestive of MS or early relapse-onset MS (eRRMS) at clinical presentation.
Methods: Paired serum and CSF were obtained from 40 patients with CIS/eRRMS and 18 healthy controls (HC). Routine examination of CSF and serum included cell count and differentiation, CSF-IgG/serum-IgG ratio (Q_{IgG}), CSF-albumin /serum-albumin ratio (Q_{Alb}), calculation of intrathecal IgG synthesis by quantitative formulae (IgG Index, IgG Reiber Hyperbolic Function for IgG intrathecal synthesis fraction (IgGIF) and Local Production (IgGLoc)) and demonstration of IgG oligoclonal bands (IgGOB). BAFF was detected by means of a highly sensitive ELISA. BAFF ratio (CSF-BAFF/serum-BAFF, Q_{BAFF}) and Index (Q_{BAFF}/Q_{Alb}, BAFF-Index) were calculated. Patients were further classified in IgGOB+ and IgGOB-, on the base of IgGOB the detection in the CSF.
Results: Compared to both BOIgG- and HC, IgGOB+ presented lower CSF-BAFF concentration ($p< 0.05$) and BAFF Index ($p< 0.01$). No differences in standard CSF parameters and BAFF concentrations were disclosed between BOIgG- and HC, while BOIgG+ presented higher CSF-IgG concentration, QIgG, IgG Index, IgG Loc, IgGIF and Leucocyte counts compared to HC and BOIgG- (all *p-value* almost < 0.05). Finally, a significant inverse correlation between Q_{IgG} and Q_{BAFF} (r: -0.4, $p< 0.05$) and between BAFF index and IgGIF (r: -0.4, $p< 0.05$) or IgG Index (r: -0.3, $p=0.05$) was found only in IgGOB+.
Conclusions: The decreased intrathecal BAFF levels in IgGOB+ strongly suggest the absorption of this factor by the target cells and indicate that B-cells are early recruited in MS CNS. Whether locally produced BAFF contributes to FLS formation and/or to the chronic evolution of MS-related inflammation deserves further investigation.

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P972

Does natalizumab play a role in the natural killer cells activation against melanoma?

I. Gandoglia[1], A. Laroni[1], F. Ivaldi[1], P. Carrega[2], E. Armentani[1], G. Ferlazzo[3], G.L. Mancardi[1], N. Kerlero de Rosbo[1], A. Uccelli[1]
[1]University of Genoa, [2]Giannina Gaslini Institute, Genoa, [3]University of Messina, Messina, Italy

Natalizumab (NTZ) is a monoclonal antibody against the alfa4 subunit (CD49d) of integrin very late antigen-4 (VLA-4, α4/β1 integrin, CD49d/CD29), approved for relapsing-remitting multiple sclerosis (MS). NTZ inhibits lymphocyte trafficking into CNS by blocking the interaction between VLA-4, expressed on lymphocytes and its ligand, vascular cell adhesion protein-1 (VCAM-1 or CD106), expressed on brain endothelial cells. Natural Killer cells (NK) are lymphocytes of innate immune system expressing CD49d and they are able to provide an effective defence against tumour development. Some cases of melanoma are reported during NTZ treatment. We aim to assess if NTZ influences the cytotoxic function or migration of NK toward melanoma, impairing their ability to kill tumour cells.

The expression of CD49d is assessed by FACS analysis and it is confirmed both on freshly isolated NK and on activated bulk NK (expanded in vitro with IL-2 and phytohemagglutinin) obtained from healthy donors. FACS analysis demonstrates that melanoma cells express CD49d and its ligand, CD106. Upon a short incubation of NK with NTZ, a decrease of CD49d expression is observed. The cytotoxicity of NK, assessed by a CD107 assay, is not influenced by the exposure to NTZ during the time of degranulation assay (4 hours) or if melanoma and NK are separately incubated for 12 or 24 hours. The degranulation is reduced significantly after a 48-hrs incubation with NTZ indicating that NTZ can influence NK degranulation towards melanoma cells only after a prolonged period of incubation. We assessed the migration of NK toward melanoma using a migration chamber assay; we show that the number of migrating NK is dependent by the number of melanoma cells in lower chamber and that the exposure of NK and melanoma cells to NTZ affects the NK migration. In conclusion, our data show that blocking CD49d influences main NK functions by reducing the cytotoxicity of activated NK, and by modulating the cross-talk between NK and melanoma cells, impairing NK migration towards melanoma. These results suggest that the role of CD49d is not just involved in cellular adhesion and NK migration through an endothelial barrier but that it might also play a role in their main functions as activating signal.

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High yield primary microglial cultures for functional studies related to reparative or pathological processes relevant to neurodegeneration

A. Yu, S. Neil, J. Quandt
Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada

Microglia are the primary immune cells found within the brain or spinal cord, playing vital roles in neurotrophic support and modulating immune or inflammatory responses to pathogens or damage/stressors during disease. This study presents a novel protocol for culturing primary murine microglia with a high yield and purity from murine embryonic cortices.

We established glial cultures from murine embryonic cortices and aimed to boost microglial populations with granulocyte macrophage colony stimulating factor (GM-CSF) with or without interleukin-4 (IL-4). Primary microglia were confirmed as myeloid/non-dendritic with intermediate expression of CD45, CD11b positivity, CD11c negativity, with low expression of MHC class I and low/negligible expression of MHC class II, Iba-1 and the costimulatory markers CD80, CD86, and CD40. These characteristics are consistent with microglia isolated and freshly examined *ex vivo*. Phenotypical markers and cytokine expression were also analyzed following exposure to inflammatory mediators. CD86, CD39, CD40 and CD80 were all differentially regulated depending on the mediators applied. With the exception of CCL2, expression of several cytokines IL-6, IL-10, tumor necrosis factor alpha (TNF-a) and IL-1 were low in untreated microglia; Interferon gamma (IFN-g) had little effect yet exposure to lipopolysaccharide (LPS) enhanced expression of all but IL-1. Functional assessment of these cells was performed in a phagocytosis assay. Primary microglias are indeed capable of phagocytosis which is significantly altered by exposure to inflammatory mediators, and

notably is decreased following exposure to IFN-γ. In contrast, the murine microglial BV-2 cell line demonstrated high constitutive expression of CD86 and yielded markedly lower IL-10 and IL-6 cytokine secretion when treated with LPS or IFN-γ.

In conclusion, primary microglial cultures generated from embryonic cultures with GM-CSF possess phenotypical and functional characteristics of their naïve in vivo counterparts. With their potential to respond to inflammatory mediators without the initial bias observed in microglial cells lines they are a preferred alternative to cell lines for modeling both their inflammatory and immunomodulatory roles in development and disease.

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Adam Yu: Nothing to disclose
Sarah Neil: Nothing to disclose
Jacqueline Quandt: Nothing to disclose

P974

Study of age induced changes in CSF immune cell profiles shown by MS patients classified according to intrathecal IgM synthesis

L.M. Villar[1], C. Picon[1], S. Sainz de la Maza[2], E. Rodriguez-Martin[1], L. Costa-Frossard[2], I. Toboso[1], J.C. Alvarez-Cermeño[2]
[1]Immunology, [2]Neurology, Hospital Universitario Ramon y Cajal, Madrid, Spain

Background: Intrathecal synthesis of lipid specific oligoclonal IgM Bands (LS-OCMB) predict an aggressive Multiple Sclerosis (MS) course. Our aim was to elucidate the immune mechanisms associated with the presence of these antibodies in MS patients and their changes with age.
Material and methods: 124 consecutive patients diagnosed with MS were included in this study. CSF and serum samples were collected. We analyzed oligoclonal IgG and IgM in the CSF by isoelectrofocusing and immunoblotting and studied different leukocyte subsets in CSF by flow cytometry.
Results: 43 (35%) patients had LS-OCMB+ restricted to CSF and the remaining 81 were LS-OCMB-. When analyzing cell percentages in CSF we found that LS-OCMB+ patients showed increased values of CD19 cells ($p< 0.0001$) and on regulatory CD4 T cells ($p= 0.0009$). Conversely, LS-OCMB- patients showed increased percentages of monocytes ($p< 0.0001$), mainly due to CD14hiCD16-($p< 0.0001$) and CD14hiCD16+ ($p< 0.0001$) subsets. Also they had higher percentages of CD4 T cells producing IL-17 and IFN-gamma ($p=0.04$).

When studied absolute cell counts, we observed that LS-OCMB+ patients showed increased values in total B ($p< 0.0001$), CD4 ($p=0.0015$), CD8 ($p=0.0014$) populations. They also showed an increase of CD4 cells showing intracellular production of IFN-gamma ($p=0.0007$), TNF-alpha ($p=0.0004$). This association was also observed in CD8 cells.

No changes associated with age were found in leukocyte percentages and cells counts LSMB+ patients. Conversely LS-OCMB- ones showed and age associated decrease of total leukocyte counts ($r=-0.43$, $p< 0.0001$), decreasing total cell counts on CD4 ($p< 0.0001$), CD8 ($p=0,0009$) and B cells ($p< 0,0001$). Also the showed an age related decrease in B cell percentages ($r=-0.34$, $p=0.0020$) and an age-related increase of monocytes ($r=0.26$, $p=0.02$).

Conclusions: The presence of LS-OCM bands in MS is related to a high number of T cells producing inflammatory cytokines in CSF. Their absence associates with a lower number of B cells and an increased percentage of monocytes. These results suggest both groups of patients may have different disease mechanisms. Differences get more pronounced with age.

Disclosure

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P975

Modulation of Il27Ra expression by vitamin D

V. Beynon, C. Baecher-Allan, H. Weiner
Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Background: The pathophysiology of multiple sclerosis (MS) remains incompletely understood. An imbalance of proinflammatory and antiinflammatory immune signaling plays an important role. Deficiency or abnormal function of regulatory T cells have been reported in MS. A subpopulation of regulatory T-cells, T regulatory type 1 cells (Tr1) are induced by the cytokine IL27. An increase in serum IL27 has been shown to correlate with treatment response to IFNbeta. IL27 signals through a heterodimer comprised of the receptor IL27Ra and gp130. Given the role of IL27 signaling in immunomodulation and treatment response in MS, expression of IL27Ra on different T-cell subsets of MS patients and healthy controls (HC) was studied.
Methods: Peripheral blood mononuclear cells (PBMCs) from HC and MS patients were stained with anti-IL27Ra antibody as well as antibodies against certain cell-type specific surface markers. Magnetic bead isolated naïve CD4 T-cells were activated with anti-CD3/28 in the presence and absence of Vitamin D.
Results: Il27Ra surface expression was inversely correlated with serum Vitamin D levels in MS patients. Anti-CD3/28 activation of CD4 naïve T-cells led to increase in IL27Ra expression. Addition of Vitamin D to the culture inhibited the increase of IL27Ra expression.
Conclusions: Our findings suggest a possible link between IL27Ra and Vitamin D signaling.

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P976

EZH2 expression is up-regulated by multiple sclerosis therapies and expressed by effector memory and central memory T cells

S. Malhotra[1], M. Tintoré[1], M.L. Villar[2], J. Castilló[1], N. Fissolo[1], C. Matute-Blanch[1], C. Picón[2], E. Sarró[3], J. Río[4], X. Montalban[4], M. Comabella[4]

[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Dept & Epidemiology Dept, Vall d'Hebron University Hospital, Barcelona, [2]Department of Neurology & Immunology, Hospital Ramón y Cajal, Madrid, [3]Fisiopatologia Renal, VHIR-CIBBIM, [4]Multiple Sclerosis Centre of Catalonia Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, Spain

Background: EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) is a histone methyltransferase with putative roles in cell adhesion and migration via methylation of talin, a key regulatory molecule in cell migration. In the recent study conducted by our group, the expression of EZH2 and talin 1 (TLN1) was found to be significantly decreased in peripheral blood mononuclear cells (PBMC) from multiple sclerosis (MS) patients compared with healthy controls. In the present study, we aimed to further expand the role of EZH2 in MS by investigating the effect of MS therapies in EZH2 and TLN1 expression and characterizing the PBMC population that express EZH2.

Methods: EZH2 and TLN1 expression was measured by real time PCR in PBMC from 73 relapsing-remitting MS patients, of whom 14 patients were untreated and 59 patients treated with interferon-beta (IFNβ; n=17), copaxone (n=15), fingolimod (n=16), and natalizumab (n=11). In a subgroup of MS patients, EZH2 immunophenotyping and flow cytometry analysis was performed in PBMC from a subgroup of MS patients.

Results: Compared to untreated MS patients, EZH2 and TLN1 expression was significantly increased in PBMC by the effect of IFNβ (p=0.00005 and p=0.0003 respectively), copaxone (p=0.00005 and p=0.0009 respectively), and natalizumab (p=0.00008 for both). Fingolimod treatment significantly decreased TLN1 expression (p= 0.00005) but had no effect on EZH2 expression (p=0.64 vs. untreated patients). PBMC immunophenotyping revealed that EZH2 staining was mainly present in CD3+ T cells with effector memory (CD45RO+/CCR7-) and central memory (CD45RO+/CCR7+) phenotypes expressing VLA4.

Conclusions: The increased EZH2 and TLN1 expression in treated MS patients may be associated with a reduced T-lymphocyte trafficking into the central nervous system (CNS) by the effect of treatment. These findings are supported by immunophenotyping data showing preferential EZH2 expression in T cells with the potential to migrate to CNS. The differential effect of fingolimod on EZH2 and TLN1 expression may be related with its mechanism of action and requires further investigation.

Disclosure

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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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P977

Emerging role of extracellular vesicle-derived microRNAs/mRNAs in immune response of Multiple Sclerosis

S. Ritz, M. Meira, C. Sievers, F. Hoffmann, L. Kappos, T. Derfuss, R.L.P. Lindberg

Biomedicine and Neurology, Univerisity Hospital Basel, Basel, Switzerland

Background: MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression of >50% of protein-coding genes post-transcriptionally. MiRNAs are not only intracellular molecules, but they are also found in various body fluids, like serum, plasma and cerebrospinal fluid. Extracellular miRNAs can be stored inside extracellular vesicles (EVs), which make them stable and good candidates as biomarkers. However, very little is known about the functional importance of EVs and EV-derived miRNAs in immune response in MS.

Objectives: (1) To characterize EVs and their "cargo", including miRNAs, mRNAs and proteins, in MS compared with those in healthy volunteers (HVs). (2) To understand the functional significance of EVs in cell-to-cell communication of the immune system in MS.

Methods: ExoEasy kit (Qiagen) was evaluated for isolation of EVs from serum of MS patients and HVs. Nanoparticle Tracking Analysis (NTA) was used to estimate size distribution and to enumerate EVs. The Amnis® ImageStreamX Mark II imaging instrument and time-lapse confocal microscopy were used to visualize the uptake and intra- and intercellular traffic of EVs in immune cells. For functional studies, isolated EVs were added in culture to PBMCs/$CD4^+$T/$CD8^+$T cells to assess their effects on RNA/protein expression, cell proliferation and activation, regulatory T cell differentiation and apoptosis.

Results: ExoEasy kit was superior compared to the traditional, ultra-centrifugation technique. Flow cytometric and ImageStreamX analysis showed comparable amounts of EVs in MS patients (in remission) and HVs. The uptake of EVs by monocytes was evident by confocal microscopic analysis. Cellular studies indicated decreased proliferation and activation of stimulated CD4/CD8 cells by EVs. Notably, EVs modulated the polarization of Tregs. Our previous miRNA expression profiling of serum from various MS courses and HVs, revealed a set of differentially expressed miRNAs. The expression of these miRNAs and consequently their target mRNAs were also altered by EVs in our "in-vitro" cellular experiments.

Conclusions: Our results suggest a regulatory role of EVs in immune response in MS. We are currently analysing samples from MS patients in various disease stages (including in relapse) and

upon different treatments. Understanding of the role of EVs and their RNA/protein cargo will provide novel insights in immune regulation in MS. A discovery of novel indicators for various attributes of MS is anticipated.

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P978

Levels of shedding microvesicles in cerebrospinal fluid of Multiple Sclerosis patients distinguish different stages of disease course

T. Croese[1], M. Pisa[1], A. Finardi[1], M. Bastoni[1], V. Martinelli[2], G. Comi[2], R. Furlan[1]
[1]Institute of Experimental Neurology - San Raffaele Hospital, Milano, [2]San Raffaele Hospital, Milan, Italy

Introduction: Scientific and clinical interest in extracellular vesicles (EVs) has increased rapidly as evidence mounts that they may constitute a new signaling paradigm. Two broad categories of EVs, exosomes and shed microvesicles (sMVs), which differ in size distribution as well as protein and RNA profiles, have been described. sMVs are considered a new biomarker of pathological processes and they are related to microglia activation in vitro. The aim of this study was to compare the number of cerebrospinal fluid (CSF) derived sMVs released by microglia/macrophages between different forms and stages of Multiple Sclerosis (MS).
Methods: We collected CSF from 168 patients hospitalized at San Raffaele Hospital for neurological assessment of whom 138 were MS (47 clinically isolated syndrome - CIS; 83 relapsing remitting MS - RRMS of whom 11 with active MRI gadolinium enhancing lesions at MRI scan performed within one week from lumbar puncture; 8 secondary or primary progressive MS - SPMS/PPMS). We used as controls 30 CSF samples from patients with other neurological diseases (OND) (17 with cognitive impairments; 9 with migraine; 4 with neuropathies). CSF was directly stained with isolectin-B4 and then analyzed on a flow-cytometer.
Results: The mean number of sMVs in one milliliter of CSF in all groups was 1791. Considering subgroups separately: OND 379; CIS 1137; SPMS/PPMS 1430; non active RRMS 1776; active RRMS 3573. A Kruskal-Wallis test was performed in order to ascertain the difference between sMVs distribution in clinical subgroups ($X2= 65,5$; $p< 0,001$). Post-hoc Mann-Whitney tests were performed between all subgroups and we found significant differences between each other ($p< 0,02$) except for progressive MS and non active RRMS or CIS (non significant). A progressive increase of sMVs concentration in CSF was noticed with active MS showing the highest values than progressive MS, not active MS, CIS and controls who showed the lowest number of sMVs per ml (Jonckheere Terpstra $p< 0,001$; Spearman $0,623$ $p< 0,001$).
Conclusion: The number of sMVs was significantly different in the different stages of disease course. Moreover, all the patients affected by inflammatory disease showed higher microglia activation than patient with other neurological diseases. It should also be noticed that progressive MS displayed increased sign of microinflammation compared to the CIS subgroup.

Disclosure

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P979

Integrative transcriptomics and proteomics analysis reveals a potential role for serpina3n and s100A4 in the neurodegeneration process during experimental autoimmune encephalomyelitis

N. Fissolo[1], B. Miró[2], C. Matute-Blanch[1], S. Malhotra[1], Á. Sánchez[2], S. Issazadeh-Navikas[3], X. Montalban[1], M. Comabella[1]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, [2]Statistics & Bioinformatics Unit, Vall d'Hebron Research Institute, Barcelona, Spain, [3]Biotech Research and Innovation Centre (BRIC), University of Copenhagen, Copenhagen, Denmark

Background: This study expands upon previous research from our group in which the mechanisms of neurodegeneration were investigated in a time-course transcriptomic and proteomic integrative study in the animal model of MS, experimental autoimmune encephalomyelitis (EAE). Here, we aimed to identify the most relevant pathways derived from the integrative study involved in the neurodegenerative process.
Methods: C57BL/6 mice were immunized with MOG (EAE) or PBS (control). Animals were sacrificed at: 8, 16, 22, 29, 36, 50

and 90 days post immunization, and central nervous system (CNS) tissue was obtained. Gene expression profiling was determined in spinal cord by microarrays (Affymetrix Mouse ST Array 2.1.) and protein quantification was performed by mass spectrometry (Orbitrap Fusion Lumos). Genes and proteins with statistically significant differential expression were identified by R Bioconductor. Selected candidate genes and associated molecules were validated by RT-PCR in CNS samples. The contribution of selected candidates in the neurogenesis process was investigated in neural stem cells (NSC) differentiated into neurons whose gene expression profiles were determined also with microarrays at different differentiation stages. The STRING database was used to identify protein associations.

Results: A total of 1,763 genes and proteins present in both datasets (transcriptomic and proteomic) were used for the analysis. In a time-course series analysis of each dataset separately, and after integration of both datasets, serpinA3n and s100A4 were identified as the two candidates that showed the highest differences between the EAE and control groups. Compared to controls, expression levels for serpina3n and s100A4 were significantly increased in spinal cord tissue at all time points studied from day 16 onwards ($p< 0.05$). Proteins associated with serpina3n (Sfpi1 -transcription factor PU.1, and IL6), and with s100A4 (Anxa2 -annexin A2, Sugt1 -protein SGT1, and IL10RA) also showed increased expression levels in EAE vs. controls. These results were validated by RT-PCR. Finally, serpina3n and s100A4 expression were significantly increased during neurogenesis ($p=1.4 \times 10^{-7}$ and $p=2.5 \times 10^{-4}$).

Conclusions: The results from this study suggest that serpina3n and s100a4 pathways may be involved in the neurodegenerative process occurring in the CNS during EAE. Functional studies are currently underway to investigate how these findings may potentially translate to MS patients.

Disclosure

The authors have nothing to disclose around the present work

MS and infections

P980

Genetic association of HLA alleles with JC polyomavirus and cross-reactivity with BK polyomavirus

J. Huang[1], I. Lima Bomfim[1], A. Michel[2], J. Link[1], M. Khademi[1], C. Warnke[3], J. Hillert[1], L. Alfredsson[4], T. Waterboer[2], T. Olsson[1], I. Kockum[1]

[1]Department of Clinical Neuroscience, Karolinska Institutet, Solna, Sweden, [2]Infections and Cancer Epidemiology, The German Cancer Research Center (DKFZ), Heidelberg, [3]Department of Neurology, Heinrich-Heine-University, Duesseldorf, Germany, [4]Institute of Environmental Medicine, Karolinska Institutet, and Centre for Occupational and Environmental Medicine, Stockholm County Council, Solna, Sweden

JC polyomavirus (JCV) infections are commonly latent and asymptomatic with a seroprevalance rate between 40-90%. When immunosuppressed, such as during treatment of multiple sclerosis (MS) patients with natalizumab, JCV reactivation may cause progressive multifocal leukoencephalopathy, an often fatal disease caused by lytic infections predominantly of oligodendrocytes. Previous studies have shown genetic associations between the human leukocyte antigen (HLA) and JCV seropositivity namely *HLA-DRB1*15* and *HLA-DQB1*06:03*. The aim of this study is to further investigate the role of HLA and JCV serostatus and consider the genetically similar BK polyomavirus (BKV).

MS cases (n=6872) and matched healthy controls (n=5780) were sampled from several Swedish MS case-control studies. Anti-JCV antibodies for both virus capsid protein (VP1) and large T-antigen (TAg) along with anti-BKV VP1 antibodies were measured using a Luminex multiplex serology assay. HLA allele variants were imputed from previous single nucleotide polymorphism genotypes using HLA*IMP:02. JCV serostatus was determined by reference to available second-generation STRATIFY JCV values and analyzed by combined VP1/TAg epitopes or separately.

JCV seroprevalence was 73.0% and 76.1% among MS cases and controls, respectively. *HLA-DRB1*15:01* showed a strong negative association with JCV serostatus in both MS cases (Odds Ratio(OR)=0.64, Probability(P)=1×10^{-10}) and controls (OR=0.63, P=2×10^{-10}). Additionally, *HLA-DQB1*06:03* showed a positive association in MS cases (OR=1.30, P=0.005) and controls (OR=1.34, P=0.003). TAg-based JCV serostatus showed no significant association with *HLA-DRB1*15:01* and *HLA-DQB1*06:03*. VP1-based BKV serostatus showed a strong positive association with TAg-based JCV serostatus (OR=1.27, P=2×10^{-74}) but a similar association was not seen with VP1-based JCV serostatus.

Strong association was seen for *HLA-DRB1*15:01* and *HLA-DQB1*06:03* haplotypes with additional associations for *HLA-DQA1*05*, *HLA-DRB3*01*, and *HLA-DPB*02*. Overall HLA associations in this study supports findings from previous studies. Epitope-stratified analysis indicates major HLA associations likely originate from the viral capsid protein, known as the most immunogenic surface protein of JCV. Lastly, association between TAg-based JCV serostatus and VP1-based BKV serostatus also suggests a possible cross-reactivity between antibodies.

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P981

EBV infection affects the processing of myelin oligodendrocyte glycoprotein peptides in B cells - Implications for multiple sclerosis

E. Morandi[1], S.A. Jagessar[2], B.A. t`Hart[2], B. Gran[1]
[1]Clinical Neurology research group, Division of Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom, [2]Immunobiology Department, Biomedical Primate Research Centre (BPRC), Rijswijk, The Netherlands

Multiple Sclerosis (MS) is a neurodegenerative disease with an immune-mediated pathogenesis in which Epstein Barr Virus (EBV) is a risk factor. Our hypothesis is that EBV infection renders B cells potent antigen presenting cells (APC) for autoreactive T cells, through influences on intracellular proteolysis and post-translational modifications of self antigens. The aim of this study is to assess the effect of EBV infection in B cells on processing of myelin oligodendrocyte glycoprotein (MOG).

We investigated the processing of MOG through SDS PAGE gel analysis in the presence or absence of cathepsin inhibitors and we determined the proteolytic activity of Cathepsin G by activity assay. We also studied the effect of autophagy and citrullination on the processing of the immunodominant peptides MOG_{35-55} and MOG_{1-20}. In addition, we measured the expression of peptidylarginine deiminase 2 (PAD_2) by RT-PCR and LC3ii, an autophagy marker, by Western Blotting, in EBV infected and uninfected cells.

We found that EBV infection increases the activity of Cathepsin G, leading to increased degradation of MOG_{35-55} and MOG_{1-20} by B cells. However, infection also rescues recombinant extracellular human MOG from total degradation. Moreover, inhibition of Cathepsin G or citrullination of Arginine (Arg) in position 4 and 46 or increased autophagy activity abrogated the degradation of MOG peptides (destructive processing).

We propose a model in which EBV infection induces autophagy in B cells and a high concentration of Ca^{2+} in autophagosomes facilitates the activation of PAD, which mediates citrullination of Arg residues in putative F-LIR motifs (Arg4 and Arg46) that mediate association of rhMOG (peptides) with autophagosomes. Citrullinated MOG_{35-55} and MOG_{1-20} are protected from degradation and can be presented to autoreactive T cells on MHC. This mechanism could facilitate presentation of a disease-relevant myelin autoantigen that may be involved in MS induction and progression.

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P982

Widespread epstein-barr virus reactivation and cytotoxic activity in the brain of a multiple sclerosis patient with lethal relapse after natalizumab withdrawal

B. Serafini[1], E. Scorsi[1], B. Rosicarelli[1], V. Rigau[2], E. Thouvenot[3], F. Aloisi[1]
[1]Department of Cell biology and Neurosciences, Istituto Superiore di Sanità, Rome, Italy, [2]Department of Pathology, Hôpital Gui de Chauliac, CHRU de Montpellier, [3]Service de Neurologie, Hôpital Carémeau, CHU de Nîmes, Université Montpellier 1, Montpellier, France

Natalizumab (NTZ), a humanized monoclonal antibody directed against alpha4 integrin, is a very effective treatment for patients with highly active multiple sclerosis (MS), but rebound of MS disease activity after NTZ discontinuation has emerged. Because NTZ interferes with CNS immune surveillance and our previous studies suggest that a deregulated EBV infection could be the main stimulus for cytotoxic lymphocyte recruitment and activation in the MS brain, in this study we verified the hypothesis that severe MS rebound after NTZ discontinuation might result from devastating immune-mediated inflammation stimulated by uncontrolled EBV expansion and reactivation in CNS-infiltrating B cells.

We have analysed post-mortem brain tissue from a 50-year-old male MS patient who developed a fatal relapse 3 months after NTZ withdrawal, with numerous new active lesions on MRI, CSF lymphocytosis but no evidence of JCV infection (Rigau et al. Neurology 2012;79:2214). Sections cut from 4 brain tissue blocks (2 from the cerebral hemispheres and 2 from the brain stem) were analysed using immunohistochemistry and in situ hybridization. Chronic inactive (n=3), chronic active (n=3) and actively demyelinating white matter lesions (n=3) with different degrees of perivascular and parenchymal lymphocytic infiltration (mainly CD20+ B cells, CD138+ plasma cells and CD8+ T cells) were analyzed.

Cells expressing markers of EBV latent infection (EBER, LMP2A) were detected in most perivascular infiltrates in all lesions analyzed. Cells expressing proteins associated with the immediate early (BZLF1) and early (BFRF1) phases of the EBV lytic cycle were more frequent in chronic active and actively demyelinating lesions. Cells expressing the structural viral proteins p160 and gp350/220 were also detected in all lesions analyzed, being strikingly more numerous in actively demyelinating lesions. CD8+ T cells represented 70-80% of total infiltrating CD3+ T cells; the percentage of CD8+ cells co-expressing granzyme B ranged between 5% and 50% in chronic inactive and actively demyelinating lesions, respectively.

These findings suggest that massive entry of EBV infected cells in the CNS after NTZ withdrawal, or previous intracerebral EBV spreading during NTZ treatment, may have triggered a highly destructive, cytotoxic immune response causing lethal MS rebound after NTZ discontinuation.

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P983

Epstein-Barr virus immune response in multiple sclerosis patients and their family members

J.Y. Mescheriakova[1], G.P. van Nierop[2], J. Klaasse[2], S.M. Scherbeijn[2], G.M. Verjans[2], A.A. Baltissen-van der Eijk[2], R.Q. Hintzen[1]
[1]Department of Neurology, MS centre ErasMS, [2]Department of Viroscience, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

Background and Objective: Multiple sclerosis sometimes clusters in families where several individuals are affected and other family members are at higher risk of MS. Little is known about the shared microenvironment in these MS families, including infections with Epstein-Barr virus (EBV). More specifically, EBV nuclear antigen-1 (EBNA-1) specific IgG levels are associated with increased risk of developing MS. The aim of our study was to determine the immune response to EBV in patients, their healthy siblings and unrelated spouses.
Methods: Sera of patients and their family members were used to measure IgG levels against EBNA-1 and Varicella Zoster Virus (VZV) as control. In samples negative for EBNA-1 we measured anti-VCA IgG to ascertain EBV serostatus. Well validated chemiluminescent assays (Liaison XL, Diasorin) were used to determine IgG levels according to the manufacturers' instructions. IgG titers were ^{10}log transformed and non-parametric tests were used in the statistical analyses.
Results: 305 MS patients, 198 non-affected full-siblings and 174 unrelated healthy spouse controls were enrolled in this study. MS patients were younger and more often females compared to siblings and spouses. There were no differences in the VZV seroprevalence rates between the groups. EBV seroprevalence was slightly higher in MS patients than in spouse controls but not significant (99.3% vs 97.7%, p=0.19). Significantly more MS patients (303/305, 99.3%) than their siblings (182/198, 91.9%) were EBV seropositive (OR 13.3, 95% CI 3.03-58.6, $p=1.2*10^{-5}$).There was a gradient in EBNA-1 specific IgG levels, with being the highest in MS patients > siblings > spouse controls ($p< 0.0001$). MS patients also showed an elevated IgG response against VZV compared to non-MS ($p< 0.0001$). Furthermore, after correction for multiple testing there were no difference in EBNA-1 and VZV IgG levels between females and males in all study groups.
Conclusions: Although raised within the same family microenvironment, MS patients differ from their siblings in their increased IgG response to EBNA-1. However, compared to unrelated controls also siblings show an elevated EBNA-1 IgG response. Likely, the shared genetic background is responsible for this finding.

Disclosure

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P984

Secretion of autoantibodies by autoreactive B cells is supported by anti-viral T cells

N. Sanderson[1], M. Zimmermann[1], L. Eilinger[1], R. Lindberg[2], L. Kappos[2], T. Derfuss[2]
[1]University Basel, [2]University Hospital Basel, Basel, Switzerland

A central question of B cell autoimmunity is how autoreactive B cells escape the mechanisms that normally ensure their destruction or tolerisation. In order to develop into an antibody-secreting effector cell, a B cell must bind its cognate antigen, and then receive "T cell help", i.e., positive signals from a T cell that recognises its own cognate peptide displayed on the major histocompatibility molecules on the B cell´s surface. Because autoreactive T cells are efficiently deleted in the thymus, such T cell help is denied to B cells that recognise self antigens, and such B cells are eliminated by apoptosis. This checkpoint depends on the specificity of antigen capture by B cells, which in solution is very high. However, when the antigen is captured from the membrane of another cell, other non-cognate membrane antigens can be co-captured simultaneously. We investigated this phenomenon using B cells specific for the self antigen myelin oligodendrocyte glycoprotein (MOG) and cells expressing both MOG and influenza haemagglutinin (HA). Using live and fixed cell microscopy, flow cytometry, T cell proliferation assays and various measures of antibody production, we observed that MOG-specific B cells capture large amounts of MOG and small amounts of HA, and can subsequently gain T cell help "fraudulently" from HA-specific T cells, enabling the B cells to secrete anti-MOG antibodies. This co-captured-antigen-dependent antibody secretion is approximately ten-fold less than that mediated by cognate antigen, but nonetheless clearly different from the situation without T cell help, when no antibody secretion can be detected. B cells exposed to cognate antigen expressed in cell membranes are much more strongly activated than those exposed to the same antigen in solution, with higher levels of CD69 and CD25. We propose that antigen co-capture from cell membranes can explain the provocation of autoimmune responses during viral infections.

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P985

Widespread brain atrophy following PML secondary to Nataluzimab therapy

S. Kumari, G. Mazibrada
Neurology, Queen Elizabeth Hospital, Birmingham, United Kingdom

Objective: To report a case of severe brain atrophy in a 34-year-old Caucasian gentleman post infection with progressive multifocal leukoencephalopathy (PML).
Background: Progressive multifocal leukoencephalopathy is a rare but serious infection associated with immunosuppressive agents such as Nataluzimab (Tysabri). Poor survival indicators include older age, higher EDSS prior to infection and widespread involvement seen on MRI. Current treatment protocols are experimental with little supportive evidence. PML is caused by a neurotropic polyoma virus called John Cunningham virus (JC virus), which infects oligodendrocytes, astrocytes and neurons causing lysis. Very little is known about subsequent widespread atrophy from PML. However the JC virus has been demonstrated to cause

cerebellar atrophy as a result of granular cell degeneration in the cerebellum and therefore may cause global atrophy when multiple lobes are involved.

Methods / Results: A 34-year-old Caucasian gentleman, with known relapsing remitting multiple sclerosis (EDSS 3.5 before Tysabri) and established on treatment with Tysabri for three years (EDSS 0) presented with a one month history of progressive neurological symptoms. MRI brain showed widespread multi-lobar changes with involvement of the brain stem and basal ganglia strongly suggestive of PML, further confirmed with the presence of JC virus on cerebrospinal fluid analysis.

He was admitted and received plasmapheresis, cidofovir, mirtazapine, mefloquine, granulocyte colony stimulation factor, maroviroc as well as a levetiracetam and sodium valproate. He deteriorated and ultimately required sedation for myoclonic status epilepticus. He continued with treatment and stabilised but has been left with permanent neurological deficits (EDSS 6).

Sequential MRI brain imaging has shown improvement in the signal change from PML but a gradual and significant loss of the cerebral cortical volume globally (see images).

Conclusions: This case highlights that gross brain atrophy may develop in severe, cases of multi-lobar PML. Additionally it demonstrates a possible approach to treating life threatening PML.

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Environmental risk factors

P986

Selective and transient effect of vitamin D_3 supplementation on antibody responses against Epstein-Barr virus nuclear antigen 1 in relapsing-remitting multiple sclerosis

E. Røsjø[1,2], A. Lossius[2,3], N. Abdelmagid[4], J.C. Lindstrøm[2,5], M.T. Kampman[6], L. Jørgensen[7,8], P. Sundström[9], T. Olsson[4], L.H. Steffensen[6,10], Ø. Torkildsen[11,12], T. Holmøy[1,2]

[1]Department of Neurology, Akershus University Hospital, Lørenskog, [2]Institute of Clinical Medicine, Univeristy of Oslo, [3]Department of Immunology and Transfusion Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway, [4]Department of Clinical Neuroscience, Neuroimmunology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [5]Helse Øst Health Services Research Centre, Akershus University Hospital, Lørenskog, [6]Department of Neurology, University Hospital of North Norway, [7]Department of Health and Care Science, University of Tromsø, [8]Department of Clinical Therapeutic Services, University Hospital of North Norway, Tromsø, Norway, [9]Department of Pharmacology and Clinical Neuroscience, Section of Neurology, Umeå University, Umeå, Sweden, [10]Department of Clinical Medicine, University of Tromsø, Tromsø, [11]KG Jebsen MS Research Centre, Department of Clinical Medicine, University of Bergen, [12]Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway

Background: Elevated serum antibody levels against Epstein-Barr virus (EBV) and a poor vitamin D status have both been identified as potential risk factors for multiple sclerosis (MS). An interaction between these factors is plausible due to the effect of vitamin D on humoral immune responses.

Objectives: To examine effects of high-dose oral vitamin D_3 supplementation on antibody levels against EBV nuclear antigen 1 (EBNA1) in patients with relapsing-remitting MS (RRMS).

Methods: Serum 25-hydroxyvitamin D_3 (25(OH)D) and immunoglobulin G antibody levels against EBNA1 (whole protein and amino acid 385-420 fragment), EBV viral-capsid antigen (VCA), cytomegalovirus (CMV), and varicella zoster virus (VZV) were measured in 68 RRMS patients enrolled in a 96-week randomised double-blinded placebo-controlled clinical trial of oral vitamin D_3 supplementation (20,000 IU/week) (NCT00785473). Samples were obtained at baseline, week 48 and at study conclusion, and no restrictions were set on the use of disease modifying treatments. The main results were analysed by use of a mixed model approach and verified by use of Mann-Whitney tests.

Results: The mean 25(OH)D level more than doubled in the vitamin D group from the initiation to the conclusion of the study with end of study levels being significantly higher than in the placebo group (123.2 versus 61.8 nmol/L, $p< 0.001$). Compared to the placebo group, both anti-EBNA1 protein and fragment antibody levels decreased in the vitamin D group from baseline to week 48 ($p=0.038$ and $p=0.004$, respectively), but not from baseline to week 96. Vitamin D_3 supplementation did not affect antibodies against VCA, CMV or VZV when matched to placebo.

Conclusions: The results indicate that high-dose oral vitamin D_3 supplementation may selectively and transiently affect humoral immune responses against the latent EBV antigen EBNA1 in RRMS.

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Baseline vitamin D levels and multiple sclerosis activity in relapsing-remitting patients treated with fingolimod

L. Ferrè[1,2], G. Sferruzza[1,2], E. Mascia[1], F. Clarelli[1], G. Dalla Costa[2], M. Radaelli[2], F. Sangalli[2], A. Nuara[2,3], C. Guaschino[1,2], M.A. Rocca[2,4], M. Filippi[2,4], F. Martinelli Boneschi[1,2], G. Comi[1,2], V. Martinelli[2], F. Esposito[1,2]

[1]Laboratory of Human Genetics of Neurological Disorders, CNS Inflammatory Unit & INSPE, San Raffaele Scientific Institute, [2]Department of Neurology, San Raffaele Scientific Institute, [3]Experimental Neurophysiology Unit, San Raffaele Scientific Institute, [4]Neuroimaging Research Unit, INSPE, San Raffaele Scientific Institute, Milan, Italy

Background: Several studies highlighted the role of 25-hydroxy-vitamin D (VitD) in modulating multiple sclerosis (MS) inflammatory activity. Moreover, higher VitD levels were associated to a better outcome during interferon-beta (IFNb) therapy.
Aim: To investigate the correlation between VitD levels and disease activity under fingolimod (FTY) treatment.
Methods: Relapsing remitting (RR) MS patients who started FTY at San Raffaele (Milan), with VitD serum level at baseline were prospectively followed for 2 years. VitD levels were adjusted for month of blood collection, age and sex. A linear regression analysis was performed considering the annualized relapse rate, the number of new/enlarging T2 lesions and gadolinum enhancing (Gd+) lesions at brain MRI scans performed under FTY, and the NEDA (non-evidence of disease activity) status as outcomes. Categorical analyses using VitD values retrieved from literature were also carried out.
Results: 235 RRMS patients were enrolled. Female:male ratio was 2.3:1, mean age at FTY start was 38.4±9.6 and mean disease duration was 9.9±7.1. Baseline VitD was on average 61.36 nmol/l (10.11-215.1): 95 patients had VitD< 50 nmol/l (Category-1), 83 subjects had values of 50-74.9 nmol/l (Category-2), 35 patients had values of 75-99.9 nmol/l (Category-3) and 22 subjects had VitD≥100 nmol/l (Category-4). No linear association was found between baseline VitD levels and the tested clinical outcomes. However, we observed that patients with the higher VitD levels (Category-4) had a lower mean number of new/enlarging T2 lesions at MRI scans performed at baseline, 1 and 2-year compared to Category-1 (p-value=0.008, 0.037 and 0.005 respectively). Similar results were found also when comparing Category-4 to Category-2, where patients had a higher number of new/enlarging T2 lesions at 1 and 2-year MRI (p-value=0.024 and 0.015) and also a higher number of Gd+ lesions at 2-year (p-value=0.04).
Conclusions: In the tested cohort, the mean baseline VitD levels didn't seem to significantly modulate the clinical and MRI activity under FTY over 2-year follow-up, probably because FTY had already a significant efficacy with 48% of patients being NEDA in our cohort. However, patients with baseline VitD levels in the higher range had lower MRI activity at baseline and during the 2-year follow-up, confirming previous data on IFNb treated patients. Further data are needed to better investigate the effect of Vitamin D in MS patients treated with FTY.

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P988

Association between body mass index and clinical outcome in neuromyelitis optica spectrum disorder

M. Choi, J.M. Seok, Y.S. Kim, K.H. Lee, B.J. Kim, J.-H. Min
Neurology, Samsung Medical Centre, Sungkyunkwan University School of Medicine, seoul, Republic of Korea

Background: Neuromyelitis optica (NMO) is a demyelinating and autoimmune disorder of CNS with a disease-specific antibody against CNS water channel, aquaporin 4 (AQP4). Among various environmental factors, obesity is associated with the immunological regulation in autoimmune disorders, such as multiple sclerosis and systemic lupus erythematosus. Still, there is no study for obesity in NMO. Herein, we aimed to investigate the association between BMI and disease activity / disability in NMO spectrum disorder (NMOSD).
Method: We retrospectively reviewed data of consecutive 79 patients, who were diagnosed as NMOSD with anti-AQP4 antibody (anti-AQP4). After excluding 4 patients with incomplete records, body mass index (BMI) was calculated as body weight (kg) divided into square of height (m); patients were divided into the two groups; the normal BMI group (BMI < 25kg/m^2) (N=58) and the overweight group (BMI≥25kg/m^2) (N=17). We analyzed clinical findings such as the Expanded Disability Status Scale (EDSS) score, progression index (PI, EDSS/year), and annual relapse rate (ARR).
Results: A total of 75 patients (mean age, 48.0±13.7 years; F:M =67:8) were included in the study. At the last visit, all patients were during remission and the disease duration was 7.04±5.95 years. BMI was 22.89±3.99 kg/m^2; 41 patients had a normal BMI (< 25 kg/m^2), 17 were overweight (25-29.9 kg/m^2), and 17 were obese (≥30 kg/m^2). Between the three groups, there is no

difference of EDSS, PI and ARR (all, p>0.05). In addition, BMI at the last visit were not correlated with final EDSS, PI, and ARR, after adjusting for age, sex, the use of steroid and immunosuppressive agents (all, p >0.05).
Conclusion: In this study, there was no association between BMI and disease activity / disability in patients with NMOSD. Further large-cohort prospective studies with the measurement of inflammatory markers will help to elucidate the immunological effect of obesity in NMOSD.

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Misong Choi: nothing to disclose

P989

Residual disability after multiple sclerosis relapses: the role of smoking

J.I. Rojas, J. Miguez, L. Patrucco, D. Giunta, E. Cristiano
Centro de esclerosis múltiple de Buenos Aires, CEMBA, Buenos Aires, Argentina

Recovery from multiple sclerosis (MS) relapses is variable and the factors influencing residual disability (RD) after a relapse are still to be elucidated. The objective was to assess RD after the first MS relapse and it´s association with previous history of active smoking after accounting for the effects of demographics and clinical variables.
Methods: Patients were selected from the longitudinal cohort of an MS center of Buenos Aires, Argentina. Patients were required to have an initial diagnosis of relapsing-remitting MS and a minimum of 1 year of prospective follow-up that included yearly brain MRI and biannual clinical visits. RD after the first relapse was calculated by the Expanded Disability Status Scale after at least 6 months of the relapse appearence. Patients were asked about smoking status and, if they were smokers, number of cigarette smoked per day at their first relapse. Patients were grouped as being non-smokers, ex-smokers or current smokers. 'Ever-smoking' was defined as at least 20 packs of cigarettes or 12 oz (360 g) of tobacco in a lifetime, or at least one cigarette per day or one cigar a week for 1 year. A multivariable analysis for factors influencing RD was performed including age, gender, oligoclonal bands, relapse severity, monosymptomatic/polysymptomatic relapse, steroid treatment fo the relapse, lesión load on MRI and smoking status as the main variable.
Results: a total of 183 patients were included, 121 (66%) females, mean age at disease onset 34.5 ± 7.8 years, mean time follow up 4.5 ± 1.2 years. 76 (41.1%) of the patients were ever smokers at the time of disease onset. RD after 1 year was observed in 87 (47%) of the patients (36% in never smokers and 64% in ever smokers). Higher risk of RD was associated with ever smoker status (p< 0.001) accounting for influence of demographics and the clinical variables mentioned.
Conclusion: smoking status was significantly associated with RD after the first relapse. Measures in order to reduce tobacco exposure are, therefore, essential since the beginning of the disease.

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J. Miguez, D. Giunta declares no conflict of interest

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Epigenomic changes in monocytes from RRMS patients with high body mass index and related preclinical animal models

P. Casaccia[1], K. Castro[1], M. Petracca[1], Y. Zhu[1], M. Gacias[1], C.T. Watson[1], P. Kosa[2], T. Sikder[1], J. Zhang[1], P. Naik[1], Y. Bencosme[1], S. Phelps[1], M. Kiebisch[3], A. Sharp[1], B. Bielekova[2], M. Inglese[1], I. Katz Sand[1]
[1]Icahn School of Medicine at Mount Sinai, New York, NY, [2]National Institute of Neurological Disease and Stroke, National Institute of Health, Bethesda, MD, [3]Berg Health Inc, Framingham, MA, United States

Epidemiological studies have highlighted the importance of Body Mass Index (BMI) on Multiple Sclerosis (MS) incidence. However it remains to be determined whether and how a high BMI (⩾25) may potentially influence disease course. In this study we first analyzed (i.e. discovery cohort) RRMS patients with a BMI ⩾25 (high BMI n=26) and low BMI < 25(n =29) for disease severity based on clinical disability and imaging, as well as immunophenotype in cross-section. While the EDSS did not reveal any statistically significant difference in clinical disability, the MRI metrics highlighted higher T1 lesion volume and lower gray matter volume in high BMI subjects compared to low BMI. Immune profiling of high BMI RRMS patients in the discovery cohort, revealed a positive correlation with peripheral monocyte counts, which was confirmed in an independent cohort of RRMS patients recruited at NIH (high BMI n=51; low BMI n=41). To gain an insight into potential mechanisms for this correlation we performed unbiased epigenomic and metabolomic profiling. When comparing data from high and low BMI RRMS patients, we detected hypermethylated gene ontology categories related to negative regulation of cell migration and hypomethylated gene ontology categories related to functional activation and migration of monocytes in the high BMI group. Those findings were also detected in a preclinical model of MS in mice fed a high fat diet, which had greater monocytic infiltration in the spinal cord and more severe clinical outcome than controls. Additionally, metabolomic profiling of plasma samples from RRMS patients with low and high BMI revealed differences in specific lipid mediators. Specifically, we measured decreased levels of endogenous PPAR-gamma agonists, which have been reported to modulate the transcriptome and function of monocytes. Exposure of human monocytes to increasing concentrations of these metabolites partially recapitulated the DNA methylation changes detected in patients with low and high BMI. The current model under investigation suggests that metabolic changes might modulate DNA methylation in monocytes and promote their pro-inflammatory phenotype, which promotes a cytotoxic phenotype that potentially contributes to a more severe central nervous system tissue destruction in MS. The clinical impact of these findings will require longitudinal assessment of MS disease course and careful phenotyping.

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P991

Increasing area level deprivation in England impacts age of progression and wheelchair use in multiple sclerosis

B. Mitchell, J. Raffel, R. Nicholas
Imperial College London, London, United Kingdom

Introduction: The United Kingdom (UK) multiple sclerosis (MS) tissue bank is a country-wide prospective donor scheme offering detailed clinical information with well characterised tissue samples for use in research. In a local population in South-East Wales it has been shown that area deprivation has an impact on the disease course in MS. We investigated this phenomenon in an English population-based national cohort.
Methods: Data were collected on the UK MS Tissue bank population in whom we had full lifetime address history, and full details of their MS milestones: relapse rate in the first two years, and age of onset, progression, wheelchair use and death. Neighbourhood socioeconomic status (SES) was categorised using the English Index of Multiple Deprivations (IMD) based upon the small geographical areas in which they lived over their lifetime ("lower layer super output areas" - encompassing approximately 1,500 people). Data were analysed using multi-variate analysis.
Results: A full address history and MS milestone history was available in 174 subjects. The average age of onset was 31.7 years, age of progression 44.4 years, age of wheelchair use 51.5 years and age of death 63.3 years. The average number of relapses in the first two years was 2.2. A multi-variate analysis demonstrated that a higher average area deprivation prior to progression, based on all prior addresses of the subject, were associated with an earlier age of progression (p=0.011). A higher average area deprivation prior to wheelchair use again was associated with earlier age of requiring wheelchair use (p=0.037). There was no association between these MS milestones and average area deprivation scores, based on all subsequent addresses of the subject after reaching these two milestones.
Conclusion: This study argues that there is an impact of deprivation on the time to achieving MS disease milestones. This research supports the hypothesis that lower socio economic status is associated with health inequalities in MS outcomes.

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Vitamin D metabolic pathway alterations and risk of multiple sclerosis in patients with clinically isolated syndromes

A. Farina[1], G. Dalla Costa[1], M.J. Messina[1], L. Moiola[1], B. Colombo[1], R. Furlan[1], A. Rubinacci[1], A. Mena-Bravo[2], G. Comi[1], V. Martinelli[1]
[1]San Raffaele Hospital, Milan, Italy, [2]University of Cordoba, Cordoba, Spain

Introduction: vitamin D, a key environmental risk factor of MS, is predominantly influenced by ultraviolet B exposure from sunlight, but recent evidence suggests that also genetics and epigenetics are important determinants. The aim of the current study was to assess the presence of vitamin D pathway alterations related to MS risk.
Methods: patients admitted at our hospital between 2000 and 2013 for a clinically isolated syndrome (CIS) have been included. We evaluated baseline serum 25(OH)D and vitamin D metabolites levels as well as clinical, brain MRI and CSF data. Cox proportional models have been used to study the association between vitamin D metabolites and MS risk, and K-means clustering algorithms have been used to assess the presence of different vitamin D metabolism patterns.
Results: 120 CIS patients have been included in the study, and during follow-up (mean 7.71 years) 53.3 % of them developed the disease. Low levels of 25(OH)D or 1,25(OH)2D were significantly associated with a higher MS risk [HR 2.57 (CI, 1.19-5.56) and 2.56 (0.91-5.88)]. Among patients with medium or high levels of 25(OH)D two clusters have been identified, where the cluster with a significantly lower production of active and inactive metabolites (low CYP27 activity) had a significantly higher risk of MS (HR 3.85, CI 1.02-10).

Conclusions high 25(OH)D levels are associated with a lower MS risk, but 25(OH)D levels are not representative in the single patient of the final active form of vitamin D. In fact, 1,25(OH)2D is influenced by the activity of catabolic enzymes (CYP24) and activating enzymes (CYP271b), which could be altered in MS.

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Neurobiology

P993

Immunoglobulin M oligoclonal bands in monosymptomatic optic neuritis: relation to clinical and paraclinical findings

J.L. Frederiksen[1,2], L.M. Villar[3]
[1]Dept. of Neurology, Rigshospitalet Glostrup, [2]University of Copenhagen, Copenhagen, Denmark, [3]Institute Ramón y Cajal for Biomedical Research, Department of Immunology, Ramón y Cajal University Hospital,, Madrid, Spain

Introduction: Acute monosymptomatic optic neuritis (AMON) is an inflammatory condition of the optic nerve presumably of autoimmune origin. More than 50 % develop multiple sclerosis (MS). AMON patients were chosen to achieve a homogenous patient group in which complete diagnostic work up was performed within one month from onset. We investigated the presence of Immunoglobulin M (IgM) oligoclonal bands (OB) in the CSF in AMON to determine whether this finding is associated with demographic findings and results of clinical and paraclinical findings suggestive of MS. In addition if the presence of IgMOB in the CSF predicted the development of MS.
Methods: We performed a prospective study of IgMOB in the CSF analysed with the standardized method used in Madrid in 95

adult Danish patients (73 women, 22 men) referred to Glostrup University Hospital with AMON, median age 32 (range 18 to 62) years. Associations between IgMOB and age, gender, results of brain MRI at 3.0 Tesla and routinely measured biomarkers in the CSF in patients with AON were assessed.
Results: IgMOB was present in 13/95 (14%) patients in AON. The two group of patients did not differ with regards to age and gender. IgGOB were present in all but 1 patient with IgMOB. There frequency of finding of elevated leucocyte count in the CSF, elevated IgG index and presence of IgGOB in the CSF was as expected from the literature. No significant association was found between brain MRI (with and without contrast enhancement), which may be due to a low frequency of IgMOB. Of 95 patients 36 developed MS during follow up. Six of these had igMOB in the CSF. The presence of IgMOB did not increase the risk of developing MS at short term.
Conclusions: The study showed a low sensitivity of IgMOB in AMON, but a clear association between presence of IgMOB and presence of IgGOB in the CSF. The results of routinely measured biomarkers in the CSF and brain MRI without and with Gadolinium DTPA were as expected in the 95 consecutively referred patients with AMON. The presence of IgMOB did not increase the short term risk of developing MS. In an ongoing study we will analyse patients from Madrid fulfilling the same inclusion criteria to increase the statistical power and perform a follow up of the whole group to examine whether IgMOB in the CSF predict development of MS on the long term.

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Cellular mechanisms of Cavβ3 subunit regulation of neuroinflammation

S.K. Williams[1], R. Fairless[1], E. Sanesteban Beceiro[1], A. Belkacemi[2], K. Pichi[1], V. Flockerzi[2], R. Diem[1]
[1]Neurology, University Clinic Heidelberg, Heidelberg, [2]Pharmacology and Toxicology, University of the Saarland, Homburg, Germany

Calcium influx into neurons has been suggested to mediate neurodegeneration under autoimmune inflammatory conditions, such as multiple sclerosis. In previous work, we have demonstrated that calcium accumulation mediates neuronal degeneration in a model of optic neuritis, primarily through the N-type voltage-dependent calcium channels (Cavs), as demonstrated by manganese-enhanced MRI and *in vivo* calcium imaging. To further address the role of the N-type Cav, we induced experimental autoimmune encephalomyelitis (EAE) in mice deficient for either the pore-forming subunit Cav2.2 or the regulatory subunit Cavβ3. Mice lacking Cav2.2 had reduced disease severity compared to wild-types in agreement with our experiments targeting N-type Cav with ω-conotoxin which resulted in both reduced inflammatory infiltration and axonal damage. However, mice lacking Cavβ3 had enhanced disease progression, suggesting that under autoimmune inflammatory conditions, Cavβ3 may play a role independent of its function as a Cav subunit.

In order to determine how Cavβ3 might influence the course of EAE, we investigated both neuronal and T cell compartments. Firstly, we assessed the extent of neurodegeneration by quantifying retinal ganglion cell (RGC) survival during EAE in both wild-type and Cavβ3 mice. Secondly, we determined whether the Cavβ3 subunit renders neurons more susceptible to degeneration by investigating the sensitivity of isolated Cavβ3-deficient cortical and hippocampal neurons in comparison to wild-type-derived neurons to Cav-dependent and independent toxic insults. Additionally, since Cavβ3 has been shown to influence T cell activation, we have also investigated T cell phenotypes following induction of EAE by FACS analysis, and their ability to infiltrate the central nervous system (CNS).

Although we saw increased RGC degeneration in Cavβ3 knock-out mice, consistent with the elevated EAE disease scores, isolated Cavβ3 deficient neurons were not intrinsically compromised in their survival. Instead, they were less susceptible to glutamate excitotoxicity, consistent with the role of Cavβ3 as a Cav subunit, as was confirmed by calcium imaging. Although T cell phenotypes were not altered in either healthy or diseased animals between wild-type and Cavβ3 deficient mice, Cavβ3 knockouts had significantly elevated T cell infiltrates. Thus, we hypothesize that the increased neurodegeneration in Cavβ3 deficient mice is due to increased access of T cells into the CNS.

Disclosure

The authors have nothing to disclose. This study was supported by the German Research Foundation (FOR2289).

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Alpha B-crystallin, a marker of oligodendrocyte stress, is upregulated within the optic nerve head during development of autoimmune optic neuritis

A. Stojic, J. Bojcevski, S.K. Williams, R. Diem, R. Fairless
Neurology, University Clinic Heidelberg, Heidelberg, Germany

Background: Autoimmune optic neuritis (AON), induced by immunisation of Brown Norway rats with myelin oligodendocyte glycoprotein (MOG), has been shown to mimic many pathological aspects of multiple sclerosis (MS). Previously, we showed that prior to inflammatory demyelination and axonal loss within the optic nerves, neurodegeneration of retinal ganglion cells and ultrastructural changes in their still myelinated axons could be observed. This occurred in parallel with microglial activation, particularly in the optic nerve head (ONH). These responses are similar to those reported in preactive MS lesions, where clusters of activated microglia appear in the absence of demyelination or leukocyte infiltration, and are accompanied by increased expression of the heat shock protein alpha B-crystallin (cryαb) in oligodendrocytes. Due to these similarities, we wished to determine if cryαb is similarly upregulated during the onset of AON.
Results: Although apoptosis of oligodendrocytes could not be detected prior to the onset of inflammatory demyelination, increased levels of cryαb in optic nerve lysates and its expression in oligodendrocytes was observed already during the induction phase of AON, particularly in the ONH area. Since we have previously shown this area to be partially permeable to blood-derived factors such as autoantibodies, we wished to determine whether the deposition of autoantibodies alone could induce oligodendrocyte stress in this area. To address this, sera was transferred from MOG-immunised animals into naïve recipients, and

cryαb expression was assessed. Anti-MOG antibody levels were detectable in the sera of recipient rats for up to 5 days post-serum transfer (although at considerably lower levels than in actively immunised animals), and its deposition was also observed within the ONH. Although major signs of optic nerve pathology (such as inflammatory demyelination) were not seen in recipient animals, the presence of oligodendrocyte stress, observed by increased presence of cryαB, could be detected in the area of the ONH in a similar manner to that observed in the induction phase of AON.

Conclusion: Cryαb upregulation is an early event during AON, being expressed mainly by oligodendrocytes and particularly in the vicinity of the ONH. Investigation of recipients following sera transfer from MOG-immunised rats suggest that this is, at least in part, mediated by the entry of circulating anti-MOG antibodies through the partially permeable ONH.

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Glutathione S-transferase polymorphisms associated with disease severity in multiple sclerosis (MS) increase neuronal vulnerability to oxidative stress

G. Ponath, D. Pitt
Neurology-School of Medicine, Yale University, New Haven, CT, United States

MS is an inflammatory demyelinating disease of the central nervous system (CNS) whose clinical outcome varies greatly between patients. Although the disease process is driven by inflammation, the lesion load is a poor predictor for clinical disability. The biological basis for differences in clinical outcomes is not understood. Glutathione S-transferases (GSTs) are part of the cellular defense against damage induced by free radicals, peroxides, and toxins. Polymorphisms of GSTs have been associated with Parkinson's and Alzheimer's disease and disease severity in MS patients, suggesting that neurodegeneration is driven in part by the genetically determined efficacy of GSTs to remove toxic products of oxidative stress.

We obtained skin biopsies from MS patients with a combination of GST deletions/variants, GSTM1*0/GSTP1*Ile^{105}/GSTT1*0, that have been shown to be associated with increased long-term disability, and with protective variants. Fibroblasts were reprogrammed into induced pluripotent stem cells and differentiated into neural cells. Depletion of glutathione through cystine/glutamate exchange in immature neurons with the GST risk deletions/variants resulted in increased reactive oxygen species, lipid peroxidation and cell death compared to neurons with the protective variants. Similarly, GST risk variants were associated with increased oxidative stress and cell death in mature neurons that were exposed to peroxynitrite or co-cultured in transwell plates with classically activated macrophages.

Thus, we demonstrate that specific GST deletions/variants that predict increased long-term disability in MS patients are associated with increased neuronal vulnerability to oxidative stress. Our findings substantiate the role of GST in neurodegeneration in MS and may ultimately lead to the development of treatments that are tailored to MS patients with GST-related variants.

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Search of therapies that favour remyelination based on genomic-signatures of neural stem cells

C. Costa, R. Nurtdiov, S. Malhotra, H. Pohl, X. Montalban, M. Comabella
Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, Spain

Background: It has recently become evident that the adult mammalian brain contains a population of multipotent neural stem cells (NSCs) that may give rise to myelinating oligodendrocytes (OG). It is known that remyelination occurs in patients with multiple sclerosis (MS), the prototype demyelinating disease, though it often fails or is incomplete. In this setting, therapies that favour endogenous oligodendrogenesis may become attractive neuroprotective strategies for MS patients. In this study, we aimed to identify chemical compounds that enhance oligodendrogenesis based on genomic signatures of NSCs differentiated into OG.

Methods: NSCs isolated from the subventricular zone of mice were differentiated into OG progenitor cells (OPCs), pre-myelinating OG, and mature myelinating OG. Cell cultures were characterized with immunostainings (Olig2/NG2/O4/O1/MBP/PLP/GFAP/DXC), and the gene expression profiling was determined at different stages of cell differentiation with microarrays. Gene expression signatures characteristic of OG differentiation were matched with the expression profiles obtained from small compounds using the Connectivity Map, a public database of genome-wide expression profiles derived from the treatment of cell lines with FDA-approved drugs.

Results: A gene expression signature that included 17 genes was considered informative from the differentiation steps of NSCs to OG and matched with the gene expression profiles generated by small compounds using the Connectivity Map. From an initial list of 32 chemical compounds, 5 were selected for further *in vitro* testing and added to NSCs and OPCs cultures for 3 days to evaluate their ability to favour differentiation from NSCs into mature myelinating OG. After cell culture characterization by real time PCR using specific TaqMan probes for Olig2, NG2, PDGF, MBP and PLP, and by immunostaining with the abovementioned markers, selected chemical compounds were found to induce changes in cell differentiation from NSCs to OPCs and from OPCs into mature myelinating OG. An *in vivo* validation of selected compounds in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), is currently underway.

Conclusions: This genomic signature-based approach using screening of drug libraries in mouse NSCs allowed the identification of chemical compounds that favour oligodendrogenesis *in vitro*. If validated *in vivo* in EAE, these compounds may have the potential to enhance remyelination in MS patients.

Disclosure

C. Costa, R. Nurtdinov, S. Malhotra, H. Pohl 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.
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Progressive MS

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Cervical spinal cord atrophy is an early marker of progressive MS onset

B. Zeydan[1], X. Gu[1], M.B. Keegan[1], B.G. Weinshenker[1], D. Pelletier[2], C.J. Azevedo[2], C. Lebrun-Frenay[3], A. Siva[4], D.T. Okuda[5], K. Kantarci[6], O.H. Kantarci[1]
[1]Neurology, Mayo Clinic College of Medicine, Rochester, MN, [2]Neurology, Multiple Sclerosis Center, University of Southern California, Keck School of Medicine, Los Angeles, CA, United States, [3]Neurology, Hopital Pasteur, Nice, France, [4]Neurology, Istanbul University, Cerrahpasa School of Medicine, Istanbul, Turkey, [5]Neurology and Neurotherapeutics, Clinical Center for Multiple Sclerosis, University of Texas Southwestern Medical Center, Dallas, TX, [6]Radiology, Mayo Clinic College of Medicine, Rochester, MN, United States

Background: Spinal cord atrophy, in the absence of profound clinical deficits, may serve as a marker of progressive MS onset. In this study, the cervical average segmental area (CASA) within a year of onset of bout-onset progressive MS (BOPMS) was compared to relapsing remitting MS (RRMS) and radiologically isolated syndrome (RIS) subjects.
Methods: Two raters independently calculated CASA values in 49 RIS and 56 MS (age and sex matched 31 RRMS and 25 BOPMS) patients. The MRIs analyzed were acquired as part of routine clinical studies. For every measurement, the intra-rater and intra-rater variability was minimized by twice replicated measurements per rater with excellent agreement ($p < 0.05$). The mid-sagittal-T2-weighted image from end of C2 to end of C7 vertebra was used to measure C-spine length, correcting for spine curvature. Spinal cord segmental area (mm2) of axial T2-weighted images between C2-C7 landmarks was multiplied by slice thickness and the resulting volume (mm3) was divided by C-spine length (mm) to calculate CASA (mm2). The variance was assessed by F-test.

The three patient groups were compared with appropriate T-test.
Results: Due to taller height, men had larger C2-C7 spinal cord volumes than women ($p=0.001$), similar to non-MS controls in other studies, but CASA was not different between men and women ($p=0.487$). There was no correlation between age at cervical MRI and CASA in RIS ($p=0.196$) or in MS ($p=0.151$). CASA was larger in RIS (mean±SD; 82.5±23.5) than in MS (mean±SD; 75.8±13.5) ($p=0.004$). CASA in RRMS (mean±SD; 79.7±16.2) compared to RIS was not significantly different ($p=0.204$). CASA was significantly lower at the onset of BOPMS (mean±SD; 72.1±9.2) compared to age matched RRMS ($p=0.031$). The greatest difference in CASA was observed in RIS versus BOPMS ($p < 0.001$).

Conclusion: Cervical average segmental area is easy to obtain from routine clinical scans. A lower number at the time of conversion to progressive MS highlights a more prominent spinal cord injury associated with a radiologically progressive phenotype before the establishment of a clinically progressive disease course.

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Effect of pregnancy on disease course in progressive MS: a case-control study

I. Kister[1], T. Spelman[2], P. Duquette[3], M. Girard[3], M. Trojano[4], G. Izquierdo[5], R. Bergamaschi[6], P. Grammond[7], E. Pucci[8], F. Grand'Maison[9], R. Hupperts[10], G. Iuliano[11], F. Granella[12],

C. Oreja-Guevara[13], V. Jokubaitis[2], H. Butzkueven[2], MSBase Investigators

[1]New York University School of Medicine, New York, NY, United States, [2]Department of Medicine and Melbourne Brain Centre, Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia, [3]CHUM - Hopital Notre Dame, Montreal, QC, Canada, [4]Department of Basic Medical Sciences, Neurosciences, and Sense Organs, University of Bari, Bari, Italy, [5]Hospital Universitario Virgen Macarena, Seville, Spain, [6]National Neurological Institute, Mondino, Italy, [7]Center de Réadaptation Déficience Physique Chaudière-Appalache, Charny, QC, Canada, [8]Neurology Unit, ASUR Marche - AV3, Macerata, Italy, [9]Neuro Rive-Sud, Hôpital Charles LeMoyne, Longueuil, QC, Canada, [10]Maaslandziekenhuis, Sittard, The Netherlands, [11]Ospedali Riuniti di Salerno, Salerno, [12]Department of Neuroscience, University of Parma, Parma, Italy, [13]University Hospital San Carlos, Madrid, Spain

Background: Relapse rates during pregnancy and post-partum period have been studied extensively, but we lack data on impact of pregnancy on progressive phase of MS. Such data is important from biologic standpoint as well as for purposes of counseling women with progressive MS, who are interested in becoming pregnant.

Objectives: To compare post-partum disability progression and relapse rate in women with progressive MS and propensity-score matched patients without pregnancy during follow-up.

Methods: We identified all women in the MSBase Registry with progressive MS at the time of pregnancy; a live birth; ⩾1 EDSS within 24 months prior to pregnancy; ⩾2 years post-delivery follow-up. Patients were matched 1:2 on age, disease duration, disease subtype, disability (EDSS) and proportion of time on DMT with women who did not become pregnant during follow up. Baseline was defined as time of delivery for women who were pregnant and as date of contemporaneous EDSS assessment at which they satisfied the inclusion criteria for non-pregnant patients. Hazard ration of disability progression was calculated using marginal Cox model; $p < 0.05$ was considered significant.

Results: Pregnancy was recorded for 55 women in the MSBase with secondary-progressive (N=49) or primary-progressive (N=6) MS at the time of conception. Mean age (interquartile range) at baseline was 31.6 (28.4, 34.7) years; disease duration - 7.8 (4.5, 13.3) years; EDSS - 2.5 (1.5, 5). These patients were successfully propensity-score matched 1:2 with women with secondary progressive (N=100) or primary-progressive (N=10) MS, but no pregnancy. Hazard ration (HR) for time to three-month confirmed disability progression was lower among women who become pregnant compared to those who did not (incidence/100 person-years was 10.62 (95% CI, 7.76, 14.53) for pregnant group v. 17.97 (14.56, 22.17) for non-pregnant group; HR 0.67 (0.47, 0.97); p=0.036). Relapse rates, calculated in 6 months intervals for 24 months after baseline, were similar in both groups, though there was a trend toward higher relapse rate among pregnant group in the first 6 months post-baseline (delivery) (p=0.15).

Conclusions: Women who became pregnant during progressive phase had lower hazard of disability progression as compared to those who did not become pregnant. Whether this is due to neuro-protective effect of pregnancy will require additional studies.

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Non-gaussian diffusion MRI allows early characterization of tissue disruption in PPMS

M. Petracca[1], C. Saiote[1], L. Fleysher[1], M. Fabian[1], J. Howard[2], C. Farrell[1], A. Miller[1], F. Lublin[1], M. Inglese[1]
[1]Icahn School of Medicine at Mount Sinai, [2]New York University Langone Medical Center, New York, NY, United States

Background: Primary-progressive MS (PPMS) is characterized by progression of disability from disease onset without occurrence of relapses, and is associated with diffuse damage in normal appearing brain tissue. Diffusional kurtosis imaging (DKI) is a sensitive indicator of tissue damage and provides pathologically specific information on microstructural changes.
Objectives: To characterize the extent of microstructural pathologic changes in a PPMS cohort over a short-term follow-up period (1 year), and to explore their relationship with clinical disability.
Methods: We recruited 26 patients (14 F) with PPMS, mean age 50.92±10.30 years, median Expanded Disability Status Scale (EDSS) 4.0 (range 1.5-6.0), mean 9-Hole Peg Test (9HPT) 33.89±15.33 seconds and 25-foot walking test (25FWT) 7.34±2.16 seconds, Paced Auditory Serial Addition Test (PASAT-3") -0.30±0.92 and 20 controls (11 F), mean age 51.05±9.80 years. The 3T magnetic resonance imaging (MRI) protocol included T2-weighted Turbo-Spin-Echo; b) T1-weighted 3D Fast-Field-Echo; c) twice-refocused spin echo for DKI at both time points.

DKI was processed using Diffusional Kurtosis Estimator and FSL software to obtain fractional anisotropy (FA), mean diffusivity (MD), mean kurtosis (MK), axonal diffusion (DA), axial and radial diffusion of the extra-axonal space (Dax, Drad), axonal water fraction (AWF) and tortuosity; for all the DKI metrics, maps were derived and compared between groups using a Tract-based Spatial Statistics (TBSS). Voxelwise non-parametric paired t-tests were used to measure changes from baseline to follow-up, linear correlations between DKI and clinical metrics were tested with non-parametric permutation inference.
Results: TBSS at baseline showed a widespread pattern of changes in FA, MD, MK, AWF and tortuosity in MS subjects in comparison with controls and a more restricted decrease in DA and Dax. At one year, the widespread MK decrease was confirmed and a significant decrease in AWF, mainly localized in the corpus callosum (CC), was detected. AWF changes in the splenium of the CC and antherior thalamic radiation were correlated with follow-up EDSS and Multiple Sclerosis Functional Composite (MSFC) respectively (TFCE, $p < 0.05$ corrected for voxelwise multiple comparisons for all tests).
Conclusions: DKI derived metrics are sensitive to short-term microstructural changes in PPMS and their change over time correlates with clinical disability.

Disclosure

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Complement activation and anaphylatoxin receptor upregulation in chronic active grey matter lesions of progressive multiple sclerosis

R. Evans[1], L. Watkins[1], J. Neal[2], S. Loveless[2], M. Rees[1], P. Morgan[2], O. Howell[1,3]
[1]Swansea University Medical School, Swansea University, Swansea, [2]Cardiff University Medical School, Cardiff University, Cardiff, [3]Division of Brain Sciences, Imperial College London, London, United Kingdom

Introduction: Multiple sclerosis lesions of the grey matter are different to lesions of the white matter. As yet, the pathomechanisms of cortical grey matter (GM) lesion development and neurodegeneration have not been recognised but a role for the innate immune system, including activated microglia and the complement cascade, appears important.
Aims: We characterised complement expression and microglial activation in a post-mortem cohort of progressive MS to better understand their role in cortical GM pathology.
Methods: Twenty two cases of progressive MS (18 secondary progressive, 13 female, median age at death 50yrs (range 38-66yrs)) and 6 controls (1 female, median age at death 77yrs (range 35- 88yrs)) were provided by the UK MS Society tissue bank. Tissue lysates of micro-dissected GM lesion and normal appearing GM were prepared for blotting experiments, whilst two blocks of cortical GM per case were sectioned for immunostaining and quantitative analysis.
Results: Complement recognition fragment C1q, central complement activation product C3b and terminal complement complex expression were elevated in MS GM lesion lysates (n=7) by 3.4-,

2.9- and 4.2-fold respectively, in comparison to matched normal appearing GM. Protein expression findings were mirrored by an increased number of C1q, C3b and C9neo immunostained cells in GM lesions in comparison to normal appearing and control GM, demonstrating that complement is expressed and activated to completion in MS cortical GM lesions. Microglia were identified based on the expression of IBA-1, CD68 and HLA-D, and the numbers of HLA-D, complement anaphylatoxin C3a and C5a receptor (R) positive cells were quantified. The number of activated (HLA-D+) microglia were significantly increased in GM lesion centre and lesion edge in subpial and deep GM lesions (all p values < 0.05), whilst the number of microglia able to respond to the anaphylatoxins C3a and C5a (C3aR+ and C5aR+ cells) were significantly increased in the same GM lesions ($p< 0.05$).
Conclusions: Our findings of increased complement expression, activation and receptor expression support an important role for complement signalling and microglial activation in the ongoing pathology of MS cortical GM lesions.

Disclosure

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Cortical lesion load correlates with periventricular NAWM damage severity in PPMS

M. Pardini[1], L. Fleysher[2], C. Farrell[3], M. Fabian[3], A. Miller[3], D. Chard[4,5], F. Lublin[3], M. Inglese[2,3,6]
[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy, [2]Department of Radiology, [3]Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [4]Queen Square MS Centre, University College of London, UCL Institute of Neurology, [5]National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre, London, United Kingdom, [6]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Icahn School of Medicine at Mount Sinai, New York, NY, United States

Background and Objectives: In subjects with relapse-onset MS it has been recently shown that a more severe periventricular white matter lesion burden is associated with a more marked thinning of the cortical ribbon, possibly pointing to a common pathogenetic mechanism between these two facets of MS pathology. Starting from this observation, we decided to explore if in subjects with primary progressive multiple sclerosis (PPMS) cortical lesion load is associated with the severity of periventricular normal appearing white matter (NAWM) damage, as assessed with diffusion weighted imaging (DWI).
Methods: Twenty-three subjects with PPMS and nineteen healthy controls were included in the study. T1 volumetric, PD/T2, phase-sensitive inversion recovery (PSIR) and DWI images were acquired at 3T for all subjects. WM lesions were identified on PD/T2 sequences and were then co-registered to diffusion data. Mean diffusivity (MD) NAWM maps were created excluding WM lesions and a 2 mm-thick peri-lesional rim. Skeletonized NAWM MD maps were then computed using the TBSS pipeline. In each skeletonized NAWM MD map those supra-tentorial voxels with a distance from the lateral ventricles between 2 and 6 mm were included in the periventricular NAWM mask while those voxels of skeletonized WM with a distance from the lateral ventricles higher than 6 mm were included in the deep NAWM mask. Mean MD values were computed separately for these two masks for each subject. Lastly, cortical lesions volumes were assessed on PSIR images.
Results: As expected skeletonized NAWM was abnormal in PPMS compared to HC. In the PPMS group, a significant correlation ($r=0.69$ $p=0.001$) was observed between skeletonized periventricular NAWM MD values and cortical lesion load with a greater cortical lesion burden being associated with more abnormal periventricular NAWM MD. Conversely, there was no correlation ($p=0.18$) between cortical lesion load and deep NAWM MD values. The same pattern of correlations was observed if juxtacortical lesions load was used instead of total cortical lesion load.
Discussion: Our data suggest that a common factor play a role in the development of both cortical lesion and periventricular NAWM damage in subjects with PPMS. The proximity of cerebrospinal fluid (CSF) to both the cerebral cortex and periventricular NAWM and the role played by CSF in cortical lesion formation seem to imply that CSF-mediated soluble are also involved in modulating NAWM damage in PPMS.

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P1003

Predicting which patients with multiple sclerosis will develop a progressive course using patient information and clinically obtained brain volumes

J.M. Honce[1], K.V. Nair[2], S.H. Sillau[3], B. Vollmer[3], T. Vollmer[3], E. Alvarez[3]

[1]Radiology, [2]Pharmacy, [3]Neurology, University of Colorado Denver, Aurora, CO, United States

Background: Patients with progressive multiple sclerosis (MS) tend to be older, male, have smaller brain volumes, and respond poorly to current treatments. Brain atrophy is increasingly being evaluated in measuring drug effectiveness and incorporated into NEDA4. We hypothesize that brain volumes can also inform the risk of developing a progressive course in MS. Our objective was to use clinically obtained brain volume and disease information to predict patients that develop a progressive course.

Methods: This is a cross-sectional evaluation of patients at the Rocky Mountain MS Clinic at the University of Colorado who had a 3D T1 MRI and completed patient reported outcomes including the Patient Determined Disease Steps (PDDS) as a disability measure within 12 months. Whole brain volume and bilateral thalamic volumes were obtained using NeuroQuant software and normalized to intracranial volume to obtain brain parenchymal fraction (BPF) and thalamic volume fraction (TVF). Disease information such as age, gender, and type of MS were extracted from electronic medical records. Relative risk regressions were performed for progressive MS with BPF and TVF as the main explanatory variables, in separate models, adjusted for age.

Results: 166 patients were evaluated, 151 with relapsing remitting MS and 15 patients with progressive MS. Patients with progressive MS were older (57.3 versus 47.3 years, p=0.0019), more likely to be male (40% versus 12.6%, p=0.0126), and more disabled (median PDDS of 4 versus 1, p< 0.0001) than relapsing remitting MS patients. Progressive patients had smaller BPF (0.730 vs 0.768, p=0.0001)(range 0.6691-0.7894) and TVF (0.0082 vs .0092, p=0.0020)(range 0.0063-0.0099). Increased BPF and TVF decreased the probability of progressive MS. An increase of 0.01 in BPF, controlled for age, decreased the risk of progressive MS by an estimated 19.64% (p=0.0217) with a receiver operating characteristic (ROC) area of 0.803 (0.690-0.916). An increase of 0.001 in TVF, controlled for age, decreased the risk of progressive MS by an estimated 43.58% (p=0.0262) with a ROC area of 0.789 (0.668-0.910).

Conclusion: Patients with progressive MS were older, more likely to be male, more disabled, and had smaller brain volumes than patients with relapsing remitting MS as previously described. However, here we begin to examine the risk of brain atrophy on developing a progressive disease course. Further work is required to confirm these relationships.

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P1004

A descriptive study on recruitment effort for a phase I clinical trial of subcutaneous alemtuzumab in patients with progressive MS: the SCALA trial

B. Rodríguez-Acevedo[1], C. Nios[1], S. Soler[1], J. Castilló[1], À. Vidal-Jordana[1], L. Midaglia[1], M. Tintoré[1], I. Galán[1], G. Arrambide[1], M. Zuluaga[1], J. Sastre-Garriga[1], J. Río[1], M. Comabella[1], A. Mora[2], S. Vergara[1], M. Arqué[2], L. Ramió-Torrentà[3], R. Robles[3], J. Batlle[4], X. Montalban[1]

[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Dept & Epidemiology Dept, Vall d'Hebron University Hospital, [2]Sanofi Genzyme, Barcelona, [3]MS & Neuroimmunology Unit, Hospital Universitari de Girona Dr. Josep Trueta, Girona, [4]Servei de Neurologia, Hospital Santa Tecla, Tarragona, Spain

Background: The number of patient candidates pre-screened for eligibility are usually absent from clinical trial reports. This information may be useful, not only as an indicator of whether trial participants were representative of all eligible patients, but also to inform estimates of the amount of resources that sponsors and investigators need to invest in recruitment.

Objectives: To describe the outcomes of the pre-screening period of a single-centre phase I clinical trial.

Material and methods: This was a retrospective case series study of patients registered as potential candidates for inclusion in a phase I, randomized, open-label, clinical trial on alemtuzumab 12mg SC or IV (SCALA; NCT02583594). The recruitment goal was to enrol 24 patients with progressive MS from December 2015 to April 2016. The data were collected using a recruitment management system specifically developed at the site for research studies.

Results: A total of 173 progressive MS patients were identified in the hospital database as potential candidates for this study. Based on examination of their records, it was determined that 75 (43,4%) did not fulfill the entry criteria or were otherwise not suitable in the opinion of the investigators. The remaining 98 patients were verbally asked to participate; 23 patients (23,4%) declined participation at this stage. The remaining 75 patients were provided with the informed consent form. Of these 75 patients, 46 were not enrolled in the study; the most common reason (68%) for not enrolling was patient decision. A total of 29 (16,8%) of the original 173 patients identified were enrolled into the study. The median number of contacts between patients and members of the investigator's team was 3 (range 1 to 13) from first approach to final decision.

Conclusion: Our study illustrates the primary challenges in recruiting progressive MS patients for clinical trials. A thorough assessment of the resources required should be conducted in advance, both by sponsors and investigators. Further research may lead to enhanced efficiency in the recruitment and pre-screening of patients in clinical trials.

Disclosure

The clinical trial related to this study has been financed by Sanofi

P1005

Cytokine levels in interstitial brain fluid in progressive multiple sclerosis measured via intracerebral microdialysis

J. Bergman[1], A. Dring[1], A. Wuolikainen[1], J. Gilthorpe[1], T. Bergenheim[1], A. Svenningsson[1,2]
[1]Umeå University, Dept of Clinical Neuroscience, Umeå, [2]Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

Background: The pathophysiology of progressive MS (PMS) remains elusive. Conventional immune modulating therapies do not significantly alter the progressive course of the disease. Other disease mechanisms are therefore likely to be involved during this phase of MS.
Objective: To analyse the presence of a large panel of cytokines derived directly from the interstitial fluid in the periventricular area of PMS patients with the use of cerebral microdialysis.
Method: During the course of a phase 1b trial of intrathecally administered rituximab in PMS (NCT01719159) a ventricular catheter was connected to an Ommaya reservoir for drug delivery. In ten of these patients an additional microdialysis catheter with a 100 kD pore size was introduced in the periventricular area and perfused for seven days with a dextran-containing dialysis fluid. The dialysate was collected six times every day with 2 - 6 hours' interval. Cytokine content in the dialysate was analysed via a Luminex-based multiplex system analysing 19 different cytokines, chemokines and angiogenesis factors.
Results: Several potential immune active substances were identified in the microdialysis fluid from PMS periventricular white matter. The levels in brain were clearly higher then the levels measured from a reference catheter placed in subcutaneous tissue. Significant levels of IL1RA, IFN-gamma, IP10, MCP1, IL-6, IL-8, MIP1a, MIP1b and VEGF were detected in the brains of PMS patients, which all were otherwise completely devoid of active focal inflammatory activity as measured by MRI.
Conclusion: This study demonstrates the occurrence of several cytokines and chemokines mainly belonging to the innate immune system in the target organ of patients with PMS. Although it cannot be ruled out that these immune mediators also are a part of the normal central nervous system, our data indicate an ongoing inflammatory process as part of the pathophysiology of PMS.

Disclosure

JB has nothing to declare
AD has nothing to declare
AW has nothing to declare
JG has nothing to declare
TB has nothing to declare
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Imaging

P1006

Comparison of structural T1-weighted sequences: MPRAGE to MP2RAGE

D. Pareto[1], J. Alonso[1], M. Alberich[1], J. Río[2], X. Lladó[3], À. Rovira[1]
[1]Radiology, [2]Neurology and Neuroimmunology and Multiple Sclerosis of Catalonia, University Hospital Vall d'Hebron, Barcelona, [3]Computer architecture and technology, University of Girona, Girona, Spain

Background: Technical developments are bringing new sequences available. MP2RAGE was developed with the aim of removing the sensitivity to the B1 transmit and receive field inhomogeneities, improving the contrast of deep grey matter and automatic segmentation.
Objective: To compare the performance of MP2RAGE and MPRAGE in: a) segmentation of subcortical grey matter regions, in healthy controls (HC); b) estimation of brain parenchymal fraction (BPF) in HC and multiple sclerosis (MS) patients; and c) quantification of lesion volume (LV) in MS patients.
Material and methods: Both sequences were acquired in 9 healthy controls and 29 MS patients in a 3.0T system (Trio, Siemens). Subcortical grey matter volumes and BPF were estimated with FIRST and Sienax respectively, both tools from the FSL library. The LV was obtained with the Lesion Estimation Toolbox (LST). The agreement between measurements was assessed by calculating the Intraclass Correlation Coefficient (ICC), and differences were assessed by a paired t-test analysis.
Results: Agreement in HC of FIRST volumes was almost perfect (ICC>0.81) for all structures except for the right (R) pallidum (ICC=0.63) and the left (L) amygdala (ICC=0.79). Regarding the BPF, agreement in was substantial almost perfect (ICC=0.95). Finally, LV estimation based on the two sequences was almost perfect too (ICC=0.97). Differences between both measurements were significant for the three parameters analysed: subcortical grey in the R and L thalamus ($p=0.046$; $p=0.025$), L and R caudate ($p=0.050$; $p=0.045$), L putamen ($p=0.004$) and R hippocampus ($p=0.027$); the BPF ($p< 0.001$) and the LV ($p=0.022$).
Conclusions: Agreement in parameters quantified from MPRAGE and MP2RAGE images was quite high. Nevertheless, results suggest that combining measurements obtained from the different sequences requires further studies.

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X. Lladó has nothing to disclose
A. Rovira serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, has received speaker

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P1007

Lesion filling more strongly affects estimation of grey than white matter volumes in a large patient sample depending on hyperintense lesion load

D. Pinter[1], M. Khalil[1], P. Greiner[1], D. Moser[1], E. Pirker[1], A. Pichler[1], G. Bachmaier[2], S. Ropele[1], S. Fuchs[1], F. Fazekas[1], C. Enzinger[1,3]

[1]Neurology, [2]Institute for Medical Informatics, Statistics and Documentation, [3]Radiology, Medical University Graz, Graz, Austria

MRI-based brain volume measurements may be affected by MS lesions which can distort the segmentation process of specific tissue classes. Lesion filling (LF) has been applied to improve automatic segmentation-based brain volume estimation. However, in clinical practice it is time-consuming and technically demanding. We therefore examined to what extent different amounts of white matter (WM) changes affect such volume estimations and thus distort group comparisons between healthy controls (HC) and MS patients or different MS subgroups in a large patient sample. 180 patients with early RR-MS (mean age= 35.9, SD=9.7; 63% female; EDSS median= 1) and 65 healthy controls (HC; mean age=31.0, SD=8.9; 51% female) underwent brain MRI at 3T. Hyperintense T2-FLAIR lesion load (T2-LL) was assessed by a semi-automated region growing algorithm subsequent to lesion identification by an experienced rater and normalized by intracranial volume. T2 lesion maps were then registered to 3D-T1-weighted sequences. Lesion filling according to T2 lesion maps was performed using the respective FSL tool. A segmentation-based algorithm (SIENAX) served to obtain brain volume measurements with and without LF using the T1 sequences. We stratified patients by the extent of WM changes into four groups defined by T2-LL quartiles.

T2-LL ranged from 1.45 cm^3 to 127.61 cm^3. Normalized brain volume, total grey matter (GM), and cortical GM volume were significantly lower in the total MS groups compared to HC with and without LF. Within-group comparisons further demonstrated that brain, GM and cortical GM volumes were significantly overestimated without LF, and these within-group differences were mainly driven by patients with high T2-LL (3rd / 4th quartiles). Within the 4th quartile, mean GM overestimation without LF reached 6 cm^3(0.8%). LF did not change WM volume (WM underestimation without vs with LF 0.65 cm^3 across all MS groups) and cerebrospinal fluid volume estimation to a significant extent.

For large patient groups brain volume estimation with SIENAX showed robust differences between MS patients and HC, even without LF. The misclassification of brain and GM volumes varied considerably with T2-LL, with higher deviation with larger T2-LL. While these results are not unexpected, they emphasise the need for LF, in particular when smaller cohorts of MS patients or individuals with high T2-LL are studied. However, LF for group comparisons in large clinical cohorts seems negligible.

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P1008

Initial cross-sectional MR spectroscopy analysis of a cohort of secondary progressive MS patients enrolled in the MS-SMART trial

D. Plantone[1], B. Solanky[1], D. Miller[1], S. Pavitt[2], G. Giovannoni[3], C. Gandini Wheeler-Kingshott[1,4,5], F. De Angelis[1], A. Doshi[1], C. Weir[6], R. Parker[6], N. Stallard[7], C. Hawkins[8], B. Sharrack[9], G. Cranswick[10], S. Chandran[11], J. Chataway[1], for the MS-SMART trialists

[1]Queen Square Multiple Sclerosis Centre, NMR Research Unit, Department of Neuroinflammation, UCL Institute of Neurology, University College London, London, [2]Leeds Institute of Health Sciences, University of Leeds, Leeds, [3]Department of Neurology, Barts and The London NHS Trust, The Royal London Hospital, London, United Kingdom, [4]Brain MRI 3T Research Center, C. Mondino National Neurological Institute, [5]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy, [6]Edinburgh Clinical Trials Unit, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, [7]Statistics and Epidemiology, Division of Health Sciences, Warwick Medical School, University of Warwick, Warwick, [8]Keele University Medical School, Royal Stoke University Hospital, Stoke-on-Trent, [9]Department of Neurology, Royal Hallamshire Hospital, Sheffield, [10]Edinburgh Clinical Trials Unit, University of Edinburgh, [11]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom

Background: Proton MR spectroscopy (MRS) is able to detect and quantify different metabolites in the central nervous system, and has been widely studied in multiple sclerosis (MS). These include: N-acetyl aspartate (NAA) and N-acetylaspartylglutamate (NAAG) (both markers of neuronal integrity); myoinositol (mI, a marker of glial proliferation); glutamate and glutamine (Glx, representing a mixture of aminoacids acting as excitatory and inhibitory neurotransmitters); creatine and phosphocreatinine (Cr+PCr, suggested marker of gliosis); and glycerophosphocholine+phosphocholine (GPC+PCh, markers of membrane phospholipids, highly suggestive of ongoing inflammation when elevated). Normalization of metabolite levels to Cr+PCr has several advantages, including the reduced influence of inhomogeneities and relaxation parameters.
Aim: To examine metabolite concentrations using MRS, in 120 secondary progressive MS (SPMS) patients, and to correlate them with clinical and demographic measures.
Method: 120 SPMS patients, enrolled in the MS-SMART trial (NCT01910259) were studied at baseline by 1H-MRS. The mean values of GPC+PCh/Cr+PCr; NAA+NAAG/Cr+PCr; Glx / Cr+PCr; mI/Cr were calculating by considering one single voxel of normal appearing white matter (NAWM) in each hemisphere. Kendall's tau-b coefficients were used to test the correlations

between the variables. Two sample t-tests were performed to test for differences between gender groups and EDSS band.
Results: There were no significant associations between any of the metabolites studied and: age, EDSS, total disease duration, SPMS duration and time since diagnosis. NAA+NAAG/Cr+PCr was significantly higher in females ($p = 0.02$) and mI/Cr was significantly higher in males ($p < 0.01$).
Conclusion: Our initial cross-sectional results show that the metabolic processes underlying the progression of the disease may differ between males and females, and ultimately could affect clinical course.

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P1009

Neurite orientation dispersion and density imaging (NODDI) of the spinal cord in relapsing remitting multiple sclerosis

F. Tona[1], N. Cawley[1], F. Grussu[1], F. Prados[1,2], S. Ourselin[2], L. Kipp[3], C.A. Gandini Wheeler-Kingshott[1,4,5], O. Ciccarelli[1]
[1]NMR Research Unit, Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, University College London, Institute of Neurology, [2]Translational Imaging Group, CMIC, University College London, London, United Kingdom, [3]Stanford Multiple Sclerosis Center, Department of Neurology and Neurological Sciences, Stanford University, Palo Alto, CA, United States, [4]Brain MRI 3T Research Center, C. Mondino National Neurological Institute, [5]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

Background: Neurite orientation dispersion and density imaging (NODDI) is a novel diffusion-weighted (DW) magnetic resonance imaging (MRI) technique able to map neurite morphology in vivo and to provide more specific markers of tissue integrity than standard diffusion tensor imaging (DTI).
Aim: The aims were to (i) apply NODDI to assess differences in spinal cord microstructure between relapsing-remitting MS (RRMS) patients and healthy controls (HC) and (ii) investigate associations between MRI measures and disability.
Methods: 26 RRMS patients (mean age 40.2 years (±7.3), mean disease duration 8.8 years (±6.6), median expanded disability scale (EDSS) 2.5 (1.0-6.5), 21 female) and 19 HC (mean age 37.1 years (±12.6), 12 female) were recruited and underwent a spinal cord protocol on a 3T Philips scanner, which included multi-shell DW imaging and conventional volumetric MRI. Disability was assessed with standard clinical scales (EDSS, timed 25-foot walk test, 9-hole peg test, ashworth spasticity scale, vibration threshold, grip strength). DW-MRI data were analyzed to obtain maps of NODDI isotropic volume fraction (isoVF), orientation dispersion index (ODI), neurite density index (NDI) and DTI fractional anisotropy (FA). From these maps, mean values were extracted within manual segmentations of grey matter (GM), total white matter (WM) and dorsal, lateral and ventral WM columns. Multivariable linear regression models corrected for age, gender and spinal volume were applied to compare MRI measures between the two groups and to explore association between MRI and clinical variables.
Results: 23/26 patients showed lesions in the cervical cord. RRMS showed reduced NDI in GM ($p=0.016$) and dorsal ($p=0.008$), lateral ($p=0.007$) and ventral ($p=0.046$) WM when compared to HC. Similarly, FA was reduced in GM ($p=0.006$) and all WM columns compared to HC (ventral $p=0.046$; lateral $p=0.034$ and dorsal $p=0.03$). In patients, reduced NDI values in the dorsal WM were associated to measures of vibration perception ($p=0.016$); no association was found between FA and clinical measures.
Conclusion: These results suggest that there is reduced density of axons in WM and dendrites in GM in the RRMS spinal cord, which can be detected in vivo with NODDI. The relationship between reduced neurite density in the dorsal WM, which mediates sensory function, and worse vibratory function, suggests that NODDI may pick up subtle changes that are clinically relevant and that cannot be seen with DTI.

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P1010

Objectively measured daily activity is associated with corticospinal pathway abnormalities in patients with MS

N. Solà-Valls[1,2], E. Martínez-Heras[2], E. Solana[2], M. Sepúlveda[1,2], A. Prats-Galino[3], Y. Blanco[1,2], A. Saiz[1,2], S. Llufriu[1,2]
[1]Neuroimmunology and Multiple Sclerosis Unit, Hospital Clinic, [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), [3]Faculty of Medicine, Universitat de Barcelona, Barcelona, Spain

Background: Damage of the corticospinal tract (CST) has been associated with disability. However, the neural correlation of walking dysfunction in multiple sclerosis (MS), a key factor for disability, is poorly known.
Objective: To evaluate the changes in microstructural integrity of CST, cortical thickness of CST-related areas and volume of brainstem and spinal cord in patients with MS and their association with objectively measured daily activity (DA).
Methods: 35 MS patients and 19 healthy volunteers (HV) underwent a 3 Tesla MRI with diffusion tensor imaging (DTI) and 3D-structural sequences. Probabilistic tractography from brainstem to cortical regions relevant for ambulation was used to reconstruct CST and obtain DTI indices (fractional anisotropy, mean diffusivity, radial diffusivity and axial diffusivity). Also, cortical thicknesses of CST-related areas, cerebellar cortex, brainstem and C1-C3 spinal cord (SC) volumes were analysed. All subjects wore a triaxial accelerometer for seven days to measure DA in counts per day and completed the international physical activity questionnaire (IPAQ). The Expanded Disability Status Scale score (EDSS) was obtained in patients.
Results: MS patients had a median EDSS (range) of 2.0 (0-6.0) and a mean disease duration (SD) of 9.9 (8.6) years. MS and HV did not differ in gender, age, body mass index or IPAQ. Average DA (counts/day) was significantly lower in patients (MS mean [SD]=495,290 [188,030] vs. HV mean [SD]=630,832 [199,377]; p=0.02). MS patients differed from HV in all DTI indices of CST, bilateral superior parietal thickness, left cerebellar cortex, brainstem and SC volume ($p< 0.05$). In patients, average DA correlated with bilateral cerebellar cortical volume (left: r=0.59, $p< 0.001$, right: r=0.60, $p< 0.001$) and brainstem volume (r=0.45, p=0.02). We did not find significant associations between DA and CST DTI indices, cortical thicknesses or SC volume.
Conclusion: Structural integrity of cerebellar cortex and brainstem seem relevant to maintain daily activity in patients with MS.

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P1011

Effect of ocrelizumab on magnetic resonance imaging markers of neurodegeneration in patients with relapsing multiple sclerosis: analysis of the Phase III, double-blind, double-dummy, interferon beta-1a-controlled OPERA I and OPERA II studies

D.L. Arnold[1,2], A. Bar-Or[1], G. Comi[3], H.-P. Hartung[4], S.L. Hauser[5], L. Kappos[6], F. Lublin[7], K. Selmaj[8], A. Traboulsee[9], G. Klingelschmitt[10], D. Masterman[11], P. Chin[11], H. Garren[10], J. Wolinsky[12]
[1]McGill University, [2]NeuroRx Research, Montreal, QC, Canada, [3]University Vita-Salute San Raffaele, Milan, Italy, [4]Heinrich-Heine University Düsseldorf, Düsseldorf, Germany, [5]University of California, San Francisco, CA, United States, [6]University Hospital Basel, Basel, Switzerland, [7]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [8]Medical University of Lodz, Lodz, Poland, [9]University of British Columbia, Vancouver, BC, Canada, [10]F. Hoffmann La-Roche Ltd., Basel, Switzerland, [11]Genentech, Inc., South San Francisco, CA, [12]University of Texas Health Science Center at Houston, Houston, TX, United States

Background: Ocrelizumab (OCR) is a humanised monoclonal antibody that selectively targets $CD20^+$ B cells. The pathogenesis of multiple sclerosis (MS), including neurodegeneration, is thought to be influenced by B cells. Volumetric magnetic resonance imaging (MRI) measurements can be used to assess neurodegeneration.
Objective: To evaluate the effect of OCR vs interferon beta-1a (IFNβ-1a) on brain MRI markers of neurodegeneration in patients with relapsing MS enrolled in two identical Phase III, randomised, double-blind, double-dummy trials (OPERA I and OPERA II).
Methods: In OPERA I and OPERA II, patients were randomised (1:1) to receive OCR 600mg via intravenous infusion every 24 weeks or subcutaneous IFNβ-1a 44μg three-times weekly over 96 weeks. MRI endpoints thought to be related to neurodegeneration included the change in whole brain volume, change in cortical grey matter volume and change in cerebral white matter volume.
Results: Compared with IFNβ-1a, OCR reduced the rate of whole brain volume loss from baseline to Week 96 by 23.5% ($p< 0.0001$) and 23.8% (p=0.0001), and from Week 24 to Week 96 by 22.8% (p=0.0042) and 14.9% (p=0.0900) in OPERA I and OPERA II, respectively. OCR-treated patients showed a smaller mean percentage of cortical grey matter volume loss compared with IFNβ-1a from baseline to Week 96, with a mean difference of 0.273% (p=0.0005) in OPERA I and 0.516% ($p< 0.0001$) in OPERA II. In OPERA I, OCR-treated patients also showed a smaller mean percentage volume loss of cerebral white matter compared with IFNβ-1a from baseline to Week 96, with a mean difference of 0.261% (p=0.0024); in OPERA II, there was no difference (p=0.2748) in cerebral white matter volume loss in

patients treated with OCR compared with IFNβ-1a from baseline to Week 96.

Conclusion: The rate of neurodegeneration as measured by whole brain, cortical grey and cerebral white matter volume loss on MRI was reduced by OCR compared with IFNβ-1a in patients with relapsing MS over 96 weeks.

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Disclosure

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Gaelle Klingelschmitt is an employee of F. Hoffmann-La Roche Ltd.

Donna Masterman is an employee and/or shareholder of Genentech, Inc.

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P1012

Consistency of longitudinal brain volume loss assessment in MS using SIENA/FSL

R. Opfer[1,2], P. Suppa[2], L. Spies[2], C. Egger[1], S. Schippling[1]

[1]Neuroimmunology and Multiple Sclerosis Research, Department of Neurology, University Hospital Zurich and University of Zurich, Zurich, Switzerland, [2]jung diagnostics GmbH, Hamburg, Germany

Background: SIENA/FSL is a widely used method to measure brain volume loss (BVL). When more than two MRI scans are available there are different ways of calculating the total BVL. BVL can be calculated directly by comparing only the baseline with the latest MRI scan (direct method). Alternatively, BVL is calculated by taking all intermediate MRI scans into account (indirect method).

Objectives: To determine the consistency of SIENA by comparing the direct with the
indirect method and to establish a 95% confidence interval for a single BVL measurement with SIENA.

Methods: Two independent, longitudinal single scanner cohorts were used. The first cohort consisted of 38 MS patients who received at least three consecutive MRI examinations (20 patient received 3, 13 patients 4, and 5 patients 5 MRI examinations). MRI acquisition was performed on a single 3T Philips scanner using the same 3D MPRAGE protocol (mean ± std age 33 ± 7 years, disease duration 3.6 ± 5.8 years, EDSS 1.5 ± 1.1). The second cohort was taken from the Open Access Series of Imaging Studies (OASIS). 56 (34 healthy and 22 demented individuals) from the longitudinal study were included who received at least three MRI examinations (43 patient received 3, 9 patients 4, and 4 patients 5 MRI examinations, mean age 75.5 ± 7.3 years). BVL was computed with the direct and with the indirect method using

SIENA. For each patient the error was defined as the difference between the direct and the indirect method (in %). We compared the distribution of the error between the two cohorts. From the distribution of the error we derived the 95% confidence interval for a single BVL measurement with SIENA.
Results: For the Philips cohort the mean error (±std) was 0.01 ± 0.17%. The median of the absolute error was 0.08%; the 90th percentile was 0.30%. For the OASIS cohort the corresponding results were 0.02 ± 0.26%, median 0.09%, and 90th percentile 0.31%. For the Philips cohort we obtained 95% confidence interval ± 0.24% and for the OASIS cohort ± 0.36%.
Conclusion: In case more than two consecutive MRI examinations are available the direct and the indirect method yield very consistent results (< 0.02% deviation). For both cohorts the median error between direct and indirect method was smaller than 0.09%. The error distribution of the two cohorts was similar, suggesting that the consistency error is independent of disease characteristics, age distribution and the applied MR scanner.

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P1013

Cognitive decline in multiple sclerosis is associated with structural network disruption - a single-subject network approach

C.M. Rimkus[1,2], M.M. Schoonheim[3], M.D. Steenwijk[1,4], M. Wattjes[1], J. Killestein[5], C.C. Leite[2], F. Barkhof[1], B.M. Tijms[6]
[1]Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands, [2]Department of Radiology, University of Sao Paulo, Faculty of Medicine, Sao Paulo-SP, Brazil, [3]Department of Anatomy and Neurosciences, [4]Physics and Medical Technology, [5]Department of Neurology, MS Centrum, [6]Alzheimer Center and Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands

Introduction: Recent studies have shown alterations in coordinated patterns of grey matter morphology in multiple sclerosis (MS) suggesting disconnection of structural networks. However, it remains unknown how these abnormalities relate to cognitive impairment in individual patients, as such studies used a group level approach. Here, we represent structural networks as nodes (GM structures) and edges (co-variation between structures), in order to study structural network abnormalities in MS and their relationship with cognitive decline.
Methods: A total of 148 MS patients (99 female, mean age 41.5 ± 8.5, mean EDSS 2.9 ± 1.6) (122 cognitively preserved (CP), and 26 cognitively impaired (CI)) and 33 matched healthy controls (HC) were included in the study. Single-subject GM graphs were constructed from 3DT1-weighted MRI scans, based on GM morphological similarity. Network properties (size, degree, connectivity density, clustering coefficient (*C*), path-length (*L*), normalized clustering (γ) and normalized path-length (λ)) were compared between groups and correlated with scores of cognitive functioning (normalized by age, educational level, gender, normalized GM volume and T2 lesion volumes). Predictors that explained the most variance in average cognition and cognitive functioning within 7 domains were identified with stepwise regression models.
Results: All MS groups showed lower connectivity density, compared to HC. The CI group also showed decreased size, degree, *C* and a tendency to lower λ, compared to HC and CP. Lower *C* and λ were selected as significant predictors of worse cognitive functioning. Lower λ was associated with more impaired executive functioning (b=70.2; p=.011); lower C was associated with slower information processing speed (b=42.5; p=.039) and more impaired working memory (b=10.9; p=.045) and attention (b=10.8; p=.004).
Conclusion: Our study shows that MS patients have less connections than controls, which was more prominent in the CI group. As a result, the CI subjects also showed lower clustering, path-length and lambda values, which is indicative of a more random topology. Lower values of C and λ were associated with a more severe cognitive impairment. These findings suggest that MS is associated with structural network disconnection, and a more pronounced loss of connections, observed in CI subjects, might deviate the network topology towards a more random topology.

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P1014

Inhomogeneous magnetization transfer (ihMT): application for multiple sclerosis (MS)

E. Van Obberghen[1], O. Girard[1], A. Le Troter[1], E. Soulier[1], P. Viout[1], M. Guye[1], G. Varma[2], D.C. Alsop[2], J.P. Ranjeva[1], J. Pelletier[1,3], G. Duhamel[1]
[1]CRMBM/CEMEREM/CNRS, Aix-Marseille Université, Marseille, France, [2]Department of Radiology, BIDMC, Harvard Medical School, Boston, MA, United States, [3]Pôle de Neurosciences Cliniques, Service de Neurologie, APHM, Hôpital de la Timone, Marseille, France

Background: Multiple sclerosis (MS) is an autoimmune inflammatory disease that causes demyelination of the central nervous system. Non-conventional MRI techniques (e.g. Magnetization Transfer) help in characterizing this pathology, which is not only a focal disorder affecting white matter (WM), but it also affects the gray matter (GM) and is responsible for a diffuse progression as in the "normal-appearing WM". Unfortunately, none of the

current MR techniques is really specific to myelin and factors occurring in MS such as inflammation, gliosis, axonal injury, demyelination and remyelination, all participate to the MR signal, hence preventing accurate assessment of the myelin status.
Objectives: Our study aimed at evaluating the sensitivity for MS disease of a new MR contrast, namely « inhomogeneous magnetization transfer » (ihMT), which has shown unique apparent specificity for myelin in normal subject studies.
Methods: Thirty-two patients (27 diagnosed with relapsing-remitting MS (RR), 5 with primary progressive MS (PP)), and 13 sex- and age-matched control subjects were scanned at 1.5T. The protocol included anatomical and ihMT sequences. Quantitative analyses of the ihMT ratios (ihMTR) were performed in different brain areas for the 3 groups (PP, RR, controls) and values were compared to regular MT ratios.
Results: IHMTR/MTR values measured in occipital (OWM), frontal (FWM) and temporal (TWM) lobes of WM were found significantly lower in patients (RR and PP) than that of controls, hence demonstrating that ihMT is sensitive to MS. Of particular interest, significant differences were found in ihMTR in OWM and TWM between PP and RR patients, whereas in contrast, no differences were found for MTR values.
Conclusions: Our preliminary results suggest that ihMT is sensitive to MS disease and that its specificity for myelin might be a precious asset for discriminating between pathological states and monitoring demyelination and remyelination in MS patients. Further studies are needed to confirm and extend these conclusions.

Disclosure

nothing to disclose

P1015

Automated segmentation of FLAIR lesion volume and number: validation and comparison to manual inter-rater variability

C. Egger[1], R. Opfer[1,2], C. Wang[3], T. Kepp[2], L. Spies[2], M.P. Sormani[4], M. Barnett[3], S. Schippling[1]
[1]Neuroimmunology and Multiple Sclerosis Research, Department of Neurology, University Hospital Zurich and University of Zurich, Zurich, Switzerland, [2]jung diagnostics GmbH, Hamburg, Germany, [3]Sydney Neuroimaging Analysis Centre, Brain and Mind Centre, University of Sydney, Sydney, NSW, Australia, [4]Biostatistics Unit, Department of Health Sciences, University of Genoa, Genoa, Italy

Introduction: Magnetic resonance imaging (MRI) has become key in the diagnosis and disease monitoring of patients with multiple sclerosis (MS). Both T2 lesion load and Gadolinium (Gd) enhancing T1 lesions represent important endpoints in MS clinical trials by serving as a surrogate of clinical disease activity and disability worsening. Due to methodological constraints, T2 lesion quantification is mostly performed manually or semi-automated in a time consuming fashion, although strong efforts have been made to allow automated quantitative lesion segmentation. In 2012, Schmidt and co-workers published an algorithm to be applied on fluid-attenuated inversion recovery (FLAIR) sequences. The aim of this study was to apply the Schmidt algorithm on FLAIR data on an independent data set and compare automated to manual T2 lesion segmentation by independent, experienced raters.
Methods: Fifty MRI data sets that were acquired on a 3.0T GE scanner (Discovery MR750, GE Healthcare, Great Britain) using an 8ch head coil were analysed. T2-lesion load (total lesion volume and total lesion number) was determined using three versions of an automated segmentation algorithm (LGA and LPA based on either SPM8 or SPM12) first described by Schmidt et al. (2012). Manual segmentation was performed by three independent raters. Inter-rater correlation coefficients (ICC) and dice coefficients (DC) were calculated for all possible pairwise comparisons.
Results: We found a strong correlation between manual and automated lesion segmentation based on LGA SPM8, regarding lesion volume (ICC = 0.958 and DC=0.6) that was comparable to the inter-rater correlation (ICC=0.97 and DC=0.66). Correlation between the two other algorithms (LPA SPM8 and SPM12) and manual raters was weaker but still satisfying (ICC=0.927 and DC= 0.53 for LGA SPM12 and ICC=0.949 and DC=0.57 for LPA SPM12). Variability of both manual as well as automated segmentation was significantly higher regarding lesion numbers.
Conclusion: Automated lesion volume quantification can be applied reliably on FLAIR data sets using the algorithm of Schmidt et al. and shows good agreement with manual segmentation.

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P1016

Composite corticospinal tract MRI measure improves prediction of motor disability progression in clinically isolated syndrome

G. Bommarito[1], M. Pardini[1], A. Bellini[1,2], L. Roccatagliata[3], C. Solaro[4], E. Capello[1], A. Laroni[1], G.L. Mancardi[1], A. Uccelli[1], M. Inglese[5]
[1]Department of Neurology, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova and IRCCS AOU San Martino-IST, [2]UOC Fisica Medica e Sanitaria, [3]Department of Neuroradiology, IRCCS AOU San Martino - IST, [4]Neurology Unit, Department Head and Neck, ASL3 Genovese, Genova, Italy, [5]Department of Neuroscience; Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, United States

Prediction of disability progression and response to treatments is still challenging for patients with Multiple Sclerosis (MS). The use of a multimodal MRI approach could help filling up the gap

between radiological features and measures of clinical outcome and improving disability prediction, even at early stages of the disease. The aim of this study was to investigate whether the combination of multiple instead of single or conventional MRI measures would better correlate with motor disability in patients with Clinically Isolated Syndrome (CIS).

Twenty-one subjects with CIS (11 females; mean age 40±12 years, median EDSS 1,5, range: 0-2.5) and fourteen healthy controls (7 females; mean age 25±1,7 years) were prospectively enrolled. All CIS patients were enrolled within 3 months from the clinical presentation. All subjects underwent a brain MRI scan at 1.5T, with the following protocol: T2-weighted, 3D-T1-weighted FSPGR, Diffusion Tensor Imaging. Gray matter volume (GMV), white matter volume (WMV) and brain parenchimal fraction (BPF) were obtained from lesion filled T1-weighted images. The masks of the left and right corticospinal tract (CST) included in the JHU tractography atlas were translated from atlas space to native diffusion space using a non-linear transformation. CST volume and fractional anisotropy (FA) were computed for both healthy controls and CIS subjects. Z scores were calculated for both FA and volume measures for all CIS subjects based on controls data and combined to obtain a composite score. EDSS scores were assessed in patients at baseline and at 12-month follow-up. Patients were stratified according to pyramidal functional score equal to (group 1) or greater than 0 (group 2) for both time points.

Group 1 patients had a higher composite measure and corticospinal volume than Group 2 patients at baseline (p=0.007 and p=0.010, respectively); however, only the combined values differed significantly between the two groups at 12 months (p=0.03). No differences were found for BPF, WMV and GMV.

The combination of multiple MRI measures applied to corticospinal tract was more efficient in explaining motor impairment at baseline and in predicting pyramidal functional score at 12 month, even in minimally disabled patients.

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P1017

Nucleus-specific abnormal thalamic resting state functional connectivity in multiple sclerosis

F. Lin[1], R. Zivadinov[1,2], J. Hagemeier[1], B. Weinstock-Guttman[3], S. Gandhi[1], D. Jakimovski[1], H.E. Hulst[4], R.H.B. Benedict[3], N. Bergsland[1,5], M.G. Dwyer[1]
[1]Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, [2]MR Imaging Clinical and Translational Research Center, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, [3]Jacobs Multiple Sclerosis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY, United States, [4]VU University Medical Center, Amsterdam, Department of Anatomy and Neurosciences, Amsterdam, The Netherlands, [5]IRCCS "S.Maria Nascente", Don Gnocchi Foundation, Milan, Italy

Background: The thalamus is affected early in multiple sclerosis (MS), and along with substantial atrophy, significant alterations in structural and functional connectivity with other brain regions have been observed. However, previous studies have looked at the thalamus as a whole, despite its heterogeneous composition of multiple, functionally distinct nuclei. Focusing individually on alterations in functional connectivity of these specific nuclei may therefore better elucidate their specific role in MS pathology and disability.
Objectives: To explore abnormalities in individual thalamic nuclei resting state (RS) functional connectivity (FC) patterns in MS patients.
Methods: Using predefined atlas-based thalamic nuclei maps (anterior, posterior, medial, and lateral), we examined individual nucleus FC in 64 MS patients and 26 age- and sex-matched healthy controls. Whole-brain voxelwise statistical maps were quantified for within-group FC and between-group differences for each nucleus for each hemisphere. Data processing was carried out using AFNI and FSL. Cluster-level correction was performed for multiple comparisons (minimum Z>2.3; cluster significance: $p < 0.05$, corrected).
Results: FC was significantly altered in MS for the anterior, posterior, and medial thalamic nuclei, with different and anatomically meaningful changes for each nucleus. Compared with controls, MS patients showed decreased FC between the left medial nucleus and the left parietal areas of the default mode network ($p< 0.046$). The left posterior nucleus showed decreased FC with areas of the left parietal attentional network ($p< 0.045$). MS patients also show decreased right medial thalamic FC with the bilateral caudates ($p< 0.015$) and the left cerebellum ($p< 0.045$). Interestingly, MS patients showed increased anterior nucleus FC with the anterior cingulate cortex ($p< 0.041$). Statistically significant FC alterations were not seen for the lateral nucleus.
Conclusions: Thalamic functional impairment in MS appears nucleus-specific. Future study of the thalamus should take its heterogeneous nature into account, and should investigate nucleus-specific clinical and cognitive correlates of altered FC.

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P1018

Age at disease onset influences gray matter and white matter damage in adult multiple sclerosis patients

L. Vacchi[1], M.A. Rocca[2], B. Colombo[3], M. Rodegher[3], L. Moiola[3], A. Ghezzi[4], G. Comi[3], A. Falini[5], M. Filippi[2]
[1]Ospedale San Raffaele - Vita-Salute San Raffaele UniversityDepartment of Neurology and INSPE, [2]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, [3]Department of Neurology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, [4]MS Center, Ospedale di Gallarate, Gallarate, [5]Department of Neuroradiology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Background: Age of MS onset may influence clinical status (level and time to reach fixed disability) during adulthood. Maturational effects and different pathophysiological mechanisms could contribute to explain clinical differences between pediatric and adult MS onset.
Aims. Here, we explored brain gray matter (GM) atrophy and white matter (WM) microstructural abnormalities in adult patients according to their age of MS onset.
Methods.:3D T1-weighted and DT MRI scans were acquired from 58 pediatric-onset (PO), 58 age-matched (AOA), 58 disease duration-matched (AODD) adult-onset MS patients, and 58 healthy controls (HC) at 3 Tesla. Whole-brain voxel-wise methods were used to define the regional distribution of damage in the brain GM and WM, using tract-based spatial statistics (TBSS) and voxel-based morphometry (VBM). Between-group comparisons were adjusted for age or disease duration, as appropriate. Correlations with age at onset were performed.
Results: Compared to HC, MS patients had the expected patterns of regional GM and WM alterations. Compared to POMS, AOA patients showed a reduced FA in the main bilateral supratentorial WM tracts. Compared to AODD, POMS had a reduced FA in the previous WM tracts. Compared to POMS, AOA patients had a widespread pattern of regional GM atrophy, whereas AODD patients had atrophy of the right fusiform gyrus. POMS patients showed atrophy of the right superior temporal gyrus (STG) in comparison to AODD. Right STG and left putamen atrophy correlated with older age at onset in PO-MS patients.
Conclusions: Compared to AOA, POMS patients have less extensive GM and NAWM involvement, suggesting that neurodegenerative and inflammatory-demyelinating processes could be less pronounced. However, with increasing disease duration, an accelerated NAWM change seems to occur in POMS, which suggests an impaired reserve of structural plasticity over the long term.
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P1019

Spatial and temporal characteristics of magnetisation transfer ratio changes in different corticothalamic systems in multiple sclerosis

S.H. van de Pavert[1], M. Pardini[1,2], A. Eshaghi[1], F. Prados[1,3], Ö. Yaldizli[1,4], V. Sethi[1], S. Ourselin[3,5], C.A. Gandini Wheeler-Kingshott[1,6,7], D.H. Miller[1,8], O. Ciccarelli[1], D.T. Chard[1,8]
[1]Queen Square MS Centre, NMR Research Unit, Department of Neuroinflammation, UCL Institute of Neurology, University College London, London, United Kingdom, [2]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova and IRCCS AOU San Martino-IST, Genoa, Italy, [3]Translational Imaging Group, Centre for Medical Image Computing, Department of Physics and Bioengineering, University College London, London, United Kingdom, [4]Department of Neurology, University Hospital Basel, Basel, Switzerland, [5]Dementia Research Centre,

UCL Institute of Neurology, University College London, London, United Kingdom, [6]Brain MRI 3T Center, C. Mondino National Neurological Institute, Pavia, [7]Department of Brain and Behavioural Science, University of Pavia, Pavia, Italy, [8]National Institute for Health Research ((NIHR), University College London Hospitals, (UCLH) Biomedical Research Centre, London, United Kingdom

Background: Thalamic and cortical abnormalities are clinically relevant in multiple sclerosis (MS), which might be mediated by white matter (WM) tract pathology. It is unclear if magnetisation transfer ratio (MTR) differs within and between thalamocortical tracts and their associated thalamic nuclei (TN) and cortex.
Methods: Volumetric T1-weighted, diffusion, and high-resolution (1 mm^3) MTR images of 51 people with MS and 10 healthy controls (HC) were acquired at 3T at baseline and 24 months. Thalamic regions of interest (ROIs) were generated from Morel's atlas, and associated cortical ROIs were extracted from grey matter segmentations. In HC, average bidirectional thalamocortical WM tracts were generated using MRtrix, which connected three groups of TN with their associated cortical areas: medial group (MG) to the prefrontal cortex (PFC), lateral group (LG) to the somatosensory cortex (SMC), and the posterior group (PG) to the occipital cortex (OCC). In native space, average MTR was extracted from the normal appearing WM of these tracts, subdivided into four segments of equal length, and the corresponding TN and cortex. TN and cortical volumes were also measured. We used T-tests to compare groups and time-points.
Results: Compared to HC, the MS group had lower MTR in 23/24 WM segments (all $p< .05$, -3.67% mean difference), and 5/6 TN (all $p< .05$, -3.09%), but none of the cortical ROIs. In both groups, WM tracts had MTR gradients from the thalamus to the cortex: MG-PFC tracts showed highest MTR adjacent to the cortex, and lowest adjacent to the thalamus (difference inner and outer segment HC -4.77%, MS -2.76%), while LG-SMC and PG-OCC tracts showed the reverse (HC 4.90%, MS 4.44%, and HC 3.38%, MS 2.20%, respectively, all $p< .0001$). Patients had significantly smaller cortical (-10.93%) and thalamic (-25.84%) ROIs (all $p< .05$).
In the MS group, a significant decline of MTR over time was seen in 5/6 cortical ROIs ($p< .05$, -1.65%), in the right MG, and 5/24 WM tract segments, of which 4 were adjacent to cortex or thalamus. Cortical or thalamic volume did not change significantly.
Conclusions: MTR characteristics differ between and within thalamocortical tracts, and this should be considered when studying tract-mediated pathology in MS. MTR decline was greatest in the cortex and in WM tracts near the thalamus or cortex. Cortical MTR loss was not accompanied by volume loss, suggesting that significant microstructural damage can occur in the absence of atrophy.

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P1020

A semi-automatic method for multiple sclerosis lesion segmentation on dual-echo magnetic resonance images: application in a multicenter context

L. Storelli[1], E. Pagani[2], M.A. Rocca[2], P. Preziosa[2], A. Gallo[3], G. Tedeschi[3], M.L. Stromillo[4], N. De Stefano[4], H. Vrenken[5], D. Thomas[6], L. Mancini[6], C. Enzinger[7], F. Fazekas[8], M. Filippi[2]
[1]San Raffaele Scientific Institute, [2]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience,, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, [3]Division of Neurology, Department of Medical, Surgical, Neurologic, Metabolic and Aging Sciences, Second University of Naples, Naples, [4]Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy, [5]Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands, [6]Department of Brain Repair and Rehabilitation, Nuclear Magnetic Resonance Research Unit, UCL Institute of Neurology, London, United Kingdom, [7]Department of Neurology, Medical University of Graz, [8]Department of Neurology, Medical Universitiy of Graz, Graz, Austria

Aims: A multicenter validation of a proposed semi-automatic method for hyperintense multiple sclerosis (MS) lesion segmentation on dual-echo magnetic resonance images (MRI) is presented.
Methods: The method was validated in a cohort of 52 MS patients, with dual-echo images acquired in 6 European centers from 3 MR manufacturers (GE, Philips, Siemens). The segmentation method works on intensity standardized dual-echo images and is based on a region growing approach, initialized by a training step using manual segmentation by an expert physician. The MRI acquisitions were grouped according to scanner manufacturers. The effect of a different training to initialize the method was evaluated using a different sample size and simulated functions. From these analysis, a mathematical formulation was extracted to replace the training step of the algorithm. Statistical analysis were

performed between the segmentation errors from the different scanner manufacturers.
Results: Assessment of the segmentation errors showed no significant differences in algorithm performance between the MR scanner manufacturers ($p > 0.05$). The results were compared with manual lesion segmentation, revealing good agreement with the ground truth (Dice similarity coefficient = 0.62; Root mean square error = 19%, False positive fraction = 0.36).
Conclusions: The method proved to be robust, and no center-specific training of the algorithm was required. Adoption of the method should lead to improved reliability and lower operator time required for image analysis in research and clinical trials in MS patients.
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P1021

Significance of aquaporin-4-immunoglobulin G in longitudinally extensive transverse myelitis

D. Zelic[1], H.P.B. Skejoe[2], S.T. Lillevang[3], N. Asgari[1,4]

[1]Department of Neurology, Vejle Hospital, Vejle, [2]Department of Radiology, Aleris-Hamlet Hospital, Copenhagen, [3]Department of Clinical Immunology, Odense University Hospital, [4]Institutes of Molecular Medicine and Regional Research, University of Southern Denmark, Odense, Denmark

Background: Imaging criteria have been incorporated into the proposed diagnostic criteria for neuromyelitis optica spectrum disorder (NMOSD) and the diagnosis may be made solely based on clinical and magnetic resonance imaging (MRI)-based analysis. A common manifestation of NMOSD is the longitudinal extensive transverse myelitis (LETM). The clinical impact of aquaporin-4-immunoglobulin G (AQP4-IgG) positivity in the NMOSD patients with LETM has only been sparsely studied.
Methods: A total of 30 NMOSD patients with LETM were identified in a database originating from a population-based retrospective case series with clinical and MRI follow-up. T2W, T1W with or without gadolinium (GD) and short tau inversion recovery sequences were analyzed in spinal cord imaging by a 1.5 Tesla scanner. The neuroradiologist was blinded to the clinical and serological results. AQP4-IgG was measured with a recombinant immunofluorescence assay and evaluated by a cell-based assay.
Results: Sixteen out of thirty NMOSD patients with LETM were AQP4-IgG positive (13 females, 81.2%) and fourteen were AQP4-IgG negative (8 females, 57.1%). The AQP4-IgG positive LETM group (12/16) had a significantly higher frequency of a long length LETM ($\geqslant$5 vertebral segments involved) as compared to the AQP4-IgG negative patient group (2/14) ($p< 0.001$). Brainstem involvement and GD enhancement occurred more frequently in the AQP4-IgG positive NMOSD patients with LETM ($p < 0.02$), all females. At follow-up, six patients had recurrent LETM (all females), five of them were AQP4-IgG positive. Focal spinal cord atrophy at the site of previous LETM was only seen in AQP4-IgG negative patients. Five out of six patients with general spinal cord atrophy were AQP4-IgG positive, all females.
Conclusion: AQP4-IgG positive NMOSD patients with LETM had more frequent occurrence of long length LETM, recurrent LETM, more brainstem involvement and GD enhancement, thus suggesting that the MRI of the spinal cord may be useful in evaluation of NMOSD disease activity as well as in the diagnostic work-up.

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Clinical disability and smoking are associated with MRI disease activity in progressive multiple sclerosis

C. Ammitzbøll[1], T. Dyrby[2], M. Lyksborg[3], K. Schreiber[1], R. Ratzer[1], J. Romme Christensen[1], P. Iversen[2], M. Magyari[1], E. Garde[2], P.S. Sørensen[1], H.R. Siebner[2,4], F. Sellebjerg[1]

[1]Danish Multiple Sclerosis Center, Copenhagen University Hospital Rigshospitalet, Copenhagen, [2]Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre, Hvidovre, [3]Department of Applied Mathematics and Computer Science, Technical University of Denmark, Lyngby, [4]Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark

Background: In multiple sclerosis (MS), smoking is a possible risk factor for disease progression. In progressive MS, data on the relationship between magnetic resonance imaging (MRI) measures and clinical disability and smoking are scarce.
Objective: To investigate the relationship between clinical disability and MRI measures and the impact of smoking on MRI measures in progressive MS, using conventional and unconventional MRI techniques.
Methods: In a cross-sectional study, we studied baseline clinical and MRI data from 93 patients with progressive MS. Thirty-seven patients had primary progressive MS and 56 patients had secondary progressive MS. Patients were categorised as current smokers or non-smokers. All patients had assessment of Expanded Disability Status Scale (EDSS) scores and multiple sclerosis functional composite (MSFC) scores, including 9-hole peg test (9HPT), timed 25 foot walk (T25FW) and paced auditory serial addition test (PASAT). From 3T MRI scans, T2 lesion volume was extracted and estimated microstructural changes in lesions, normal appearing white matter (NAWM) and cortical grey matter (CGM) were assessed based on magnetisation transfer ratio (MTR) and diffusion weighted imaging (fractional anisotropy (FA) and mean diffusivity (MD)). The relationship between clinical disability scores and MRI measures was assessed by correlation analyses and corrected for multiple comparisons by calculation of false discovery rates (q-values). The effect of smoking on MRI measures was analysed by univariate analyses of covariance, adjusted for relevant covariates.
Results: Lesion volumes correlated with all clinical measures: EDSS (ρ=0.286, q=0.043), 9HPT (ρ=0.312, q=0.041), T25FW (ρ=0.313, q=0.047) and PASAT (ρ=-0.303, q=0.044). MTR in lesions correlated with EDSS (ρ=-0.278, q=0.048), and MD values in lesions correlated with T25FW (ρ=0.278, q=0.049) and PASAT scores (ρ=-0.356, q=0.025). In NAWM, FA values correlated with 9HPT (ρ=-0.359, q=0.043). Finally, in patients who were smokers, FA in NAWM was lower than in non-smokers (p=0.019).
Conclusion: In progressive MS, clinical disability is associated with increased T2 lesion volume and microstructural changes in lesions consistent with demyelination. Relationships between microstructural changes in NAWM and clinical measures are less pronounced, but smoking is associated with reduced FA values in NAWM of patients with progressive MS, suggesting that microstructural damage is accelerated by smoking.

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The influence of the cervical spinal canal size on demyelinating cord lesions in MS - an MRI study

H. Ktayen[1], C. Tench[1], R. Dineen[1], P. Morgan[2], N. Evangelou[1]
[1]University of Nottingham, [2]Nottingham university NHS trust, Nottingham, United Kingdom

Background: Within the spinal cord, demyelinating lesions are most common in the cervical region and it has been suggested that micro-trauma in this highly mobile region may play a role. Spinal trauma has been shown to disrupt the blood-brain barrier (BBB) and is more common in the context of a narrow spinal canal. Considering that BBB disruption is considered by many to be the first detectable change in Multiple Sclerosis (MS) lesion development, a narrow spinal canal may influence lesion formation.
Objective: Use magnetic resonance imaging (MRI) of the cervical spine to assess the influence of canal dimensions on the presence of demyelinating lesions in MS.
Methods: 94 randomly selected MS patients were included in the study (66 females/24 males; all major subtypes; age = 41±11 years, disease duration = 8±10 years). Routine clinical T2-weighted MR images of the cervical spine were used to measure the maximum anteroposterior (AP) diameters of the cervical spinal canal and spinal cord. The AP space available for the cord was calculated as [spinal canal diameter - spinal cord diameter].

Demyelinating spinal cord lesions were identified on the MR images and binary logistic regression was used to ascertain the effects of the size of the spinal canal on the presence of demyelinating lesions. Age, gender, disease duration, disease type and disc level were all entered as covariates. Additionally, the distance between demyelinating cord lesions and the level at which the spinal canal is smallest was also measured.

Results: A bigger AP spinal canal diameter is associated with reduced risk of a demyelinating lesion at that level (Odds ratio [OR] 0.88, 95% CI 0.77, 0.99; P=0.04), as does having more space for the cord (Odds ratio [OR] 0.86, 95% CI 0.74, 0.99; P=0.04). Additionally, lesions were more common nearer the narrowest part of the cervical canal.

Conclusion: This study has found that a narrower spinal canal is associated with a higher rate of demyelinating spinal cord lesions at that level. It is not known why spinal cord lesions preferentially develop at the cervical cord, but this study suggests that microtrauma could play a role.

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P1024

The combined use of 3D T1- and T2-weighted sequences improves cervical cord lesion detection in patients with multiple sclerosis: a multicenter study at 3T

L. Storelli[1], M. Aboul-Wafa[2], M.A. Rocca[2], P. Valsasina[2], P. Preziosa[2], M. Copetti[3], A. Rovira[4], X. Montalban[5], H. Kearney[6], O. Ciccarelli[6], L. Matthews[7], J. Palace[7], A. Gallo[8], A. Bisecco[8], C. Lukas[9], B. Bellenberg[9], G. Comi[10], M. Filippi[2]
[1]San Raffaele Scientific Institute, [2]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience,, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, [3]Biostatistics Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy, [4]Department of Radiology (IDI),, [5]Department of Neurology-Neuroimmunology and Multiple Sclerosis Centre of Catalonia (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona, Spain, [6]Department of Brain Repair and Rehabilitation, Nuclear Magnetic Resonance Research Unit, UCL Institute of Neurology, London, [7]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom, [8]I Division of Neurology, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Second University of Naples, Naples, Italy, [9]Department of Radiology, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany, [10]Department of Neurology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Background: Cervical cord lesions in multiple sclerosis (MS) are usually evaluated on T2-weighted or short-tau inversion recovery (STIR). T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE) scans might improve lesion detection at high field.

Aims: To evaluate lesion visualization on T1-MPRAGE *vs* T2/STIR by analyzing a large, multicentre dataset of MS patients acquired at 6 European sites.

Methods: Two raters blindly evaluated cord lesion number, level and transverse location from 203 MS patients. Lesions were assessed by using T2/STIR only, T1-MPRAGE only, and then T2/STIR and T1-MPRAGE together. A final consensus agreement on lesion count and location was made. Lesion counts were compared by using mixed effect models adjusted for site. Inter-observer and inter-sequence agreement on lesion number and location were assessed by using the concordance correlation coefficient (CCC) and Cohen's kappa index.

Results: Lesions detected on T2/STIR were 685 and 717 (CCC=0.88), while they were 698 and 708 (CCC=0.92) on T1-MPRAGE for rater #1 and #2, respectively. Lesion number significantly increased when using the two sequences together ($p< 0.001$; lesion number=763 and 746, respectively; CCC=0.91). Most frequent cervical lesion levels were C2 (31%), C3 (15.7%) and C4 (18.1%), with a high agreement between T2/STIR and T1-MPRAGE scans (Cohen's kappa=0.985). T1-MPRAGE scans allowed a reliable transverse lesion localization, with 59% involvement of the lateral cord columns, 31% of the posterior cord, and 10% of the anterior cord.

Conclusions: The combined use of sagittal T1-MPRAGE and T2/STIR improves MS cord lesion detection and localization. This might help diagnosis and might ameliorate correlations with disability.

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Gray matter atrophy progresses in a coherent manner between anatomically and functionally related brain areas: A 10-year source-based morphometry study in early relapsing-remitting MS patients

N. Bergsland[1,2], D. Horakova[3], M.G. Dwyer[1], T. Uher[3], M. Vaneckova[4], M. Tyblova[4], Z. Seidl[4], J. Krasensky[4], E. Havrdova[3], R. Zivadinov[1,5]
[1]Buffalo Neuroimaging Analysis Center, Department of Neurology, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, United States, [2]IRCCS "S.Maria Nascente", Don Gnocchi Foundation, Milan, Italy, [3]Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, First Faculty of Medicine and General University Hospital, [4]Department of Radiology, 1st Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic, [5]MR Imaging Clinical Translational Research Center, School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, NY, United States

Background: Although gray matter (GM) involvement is now widely recognized as a hallmark of MS, the spatial relationships of GM atrophy in disparate areas throughout the brain remain poorly understood. Multivariate, data-driven approaches offer a means to investigate atrophy patterns while combining information from multiple voxels, unlike traditional methods such as voxel-based morphometry (VBM). However, such techniques have yet to be used extensively in MS and no longitudinal studies exist.
Objectives: To investigate the spatial patterns of GM atrophy in a longitudinal setting.
Methods: 152 early RRMS patients (mean disease duration of 5 years) were scanned on the same MRI scanner with the same 3D T1 protocol at baseline and at 10 years. At 10-year follow-up, they were divided into those with confirmed disability progression (CDP) (85) or without (67) CDP, by standard treatment trial criteria. An optimized, longitudinal source-based morphometry (SBM) pipeline was implemented via a combination of VBM and independent component analysis (ICA) techniques. SBM was used to identify patterns of spatially distinct regions of GM atrophy with common covariation over 10 years in the entire cohort of patients. Next, differences in the loading factors obtained using ICA were compared between patients with CDP and without, while controlling for age and sex. Significance was set at $p < 0.05$.
Results: 20 components were estimated using ICA. The patterns are similar to those observed using resting state functional MRI, particularly as regards to the default mode and salience networks. Most relevant patterns included: 1) bilateral deep GM (including thalamus caudate, globus pallidus and putamen) and frontal cortex; 2) cerebellum; 3) bilateral thalamus, bilateral caudate and bilateral insular cortex; 4) cingulate cortex. Patients with CDP demonstrated greater atrophy in 2 of the identified patterns (Pattern 1: bilateral thalamus, bilateral precuneous and bilateral sensorimotor (p=.007); Pattern 2: bilateral hippocampi, bilateral temporal, bilateral frontal, bilateral anterior cingulate (p=.024)).
Conclusions: To the best of our knowledge, this is the first longitudinal study in MS showing that the development of GM atrophy progresses in a coherent manner between anatomically and functionally related areas. Longitudinal SBM offers a novel method to better characterize the spatial relationship of GM atrophy and disability than is possible using traditional methods.

Disclosure

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P1026

Thalamus atrophy predicting cognitive impairment in early relapsing remitting multiple sclerosis patients

J.I. Rojas, F. Sanchez, L. Patrucco, J. Miguez, G. Murphy, M.C. Fernandez, A. Golimstok, E. Cristiano
Centro de esclerosis múltiple de Buenos Aires, CEMBA, Buenos Aires, Argentina

The objective was to assess whether changes in the volume of the thalamus during the onset of multiple sclerosis (MS) may help to predict cognitive impairment after accounting for the effects of brain volume loss.
Methods: a prospective study included patients with RRMS, with less than three years of disease onset (defined as the firs demyelinating symptom), EDSS ⩽3, no history of cognitive impairment and at least two year of follow up. Patients were clinically evaluated during follow-up with annual brain MRI and neuropsychological evaluations for two years. Neuropsychological (NP) testing, acquired using standarized methods, evaluated measures of memory, information processing speed and executive function. After two years, the groups of patients with and without cognitive impairment (CI and noCI respectively) were identified. Brain dual-echo, high-resolution T1-3D weighted and DT MRI scans were acquired at baseline and every 12 months during 2 years. Between-group differences of thalamus volume, general and regional gray matter, white matter volumes and T2 lesion load were assessed using FIRST, SIENA, SIENAXr, FIRST and SepInria software (Logistic regression analysis $p < 0.05$ significant).
Results: 61 patients, mean age 38.4 years, 35 (57%) women were included. At 2 years of follow up, 17 (28%) were CI. CI patients exhibited significantly slower information processing speed and attentional deficits vs. noCI patients ($p< 0.001$ and $p= 0.02$ respectively). In the CI group a significant reduction in percentage of the thalamus volume ($p < 0.001$) was observed compared with noCI group after accounting for influence of demographics and brain volume loss.
Conclusion: We observed a significant role of thalamus atrophy in MS-related CI after controlling for the influence of general and neocortex atrophy.

Disclosure

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J. Miguez, F Sanchez declares no conflict of interest

P1027

No differences in spinal cord DTI abnormalities between neuromyelitis optica spectrum disorder and multiple sclerosis

R. Cortese[1,2], L. Magnollay[1], F. De Angelis[1], F. Prados[1,3], F. Grussu[1], C. Tur[1], M. Yiannakas[1], I.L. Simone[2], D.R. Altmann[1,4], D. Miller[1], S. Ourselin[3], C.M. Gandini Wheeler-Kingshott[1,5,6], F. Barkhof[1,3,7], O. Ciccarelli[1]
[1]Queen Square MS Centre, NMR Research Unit, UCL Institute of Neurology, London, United Kingdom, [2]Department of Basic Medical Sciences, Neurosciences, and Sense Organs, University of Bari, Bari, Italy, [3]Translational Imaging Group, Centre for Medical Image Computing (CMIC), Department of Medical Physics and Bioengineering, UCL, [4]Medical Statistics Department, London School of Hygiene and Tropical Medicine, London, United Kingdom, [5]Brain MRI 3T Research Center, C. Mondino National Neurological Institute, [6]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy, [7]Department of Radiology and Nuclear Medicine, MS Centre Amsterdam, VU Medical Centre, Amsterdam, The Netherlands

Background: It has been suggested that neuromyelitis optica spectrum disorders (NMOSD) shows more spinal cord (SC) atrophy than brain atrophy, while multiple sclerosis (MS) shows more brain atrophy. Diffusion tensor imaging (DTI) has demonstrated the pathological involvement of the white matter (WM) and grey matter (GM) of the SC in MS.
Objectives: (i) To calculate DTI measures in the GM and WM of SC, and brain and SC atrophy in patients with NMOSD; (ii) to compare them to MS; (iii) to explore their relationship with clinical disability.
Methods: 18 NMOSD (16 with LETM involving the cervical cord, 14F, mean age 52yrs[SD11]), 19 relapsing-remitting MS patients (5 with cervical cord lesions, 15F, mean age 42yrs[SD10]) and 25 HC (18F, mean age 37yrs[SD13]) were scanned at 3T. Brain parenchymal fraction (BPF), grey matter fraction (GMF), white matter fraction, cord cross-sectional area (CSA) and SC DTI metrics (fractional anisotropy, mean diffusivity, radial diffusivity, axial diffusivity) in the GM and WM columns were measured and compared among groups. Physical disability was assessed using the expanded disability status scale (EDSS), 9 hole peg test and timed 25 foot walk test (TWT). We used multiple regressions to compare imaging measures between groups and Spearman-correlation to explore the relationship between MRI parameters and clinical measures.
Results: There were no differences in SC DTI metrics in the GM and WM between NMOSD and HC, MS and HC, and patient groups. NMOSD patients showed a borderline significant smaller CSA than HC (mean[SD] 77.65 mm^2[2.40] vs 83.74 mm^2[1.98]; p:0.069); MS patients had a smaller CSA (mean 76.24 mm^2[2.16]) than HC (p:0.013), with no difference between patient groups. MS patients had lower BPF than NMOSD (mean[SD] 0.75[0.003] vs 0.76[0.003]; p:0.04) and HC (mean 0.75[0.003] vs 0.76[0.003]; p< 0.01) and lower GMF than HC (mean 0.44[0.002] vs 0.45[0.002]; p:0.03). In NMOSD, CSA correlated with EDSS [r_s:-0.46, p:0.05], and TWT [r_s:-0.5, p:0.039).
Conclusion: Pathological involvement of SC, as reflected by DTI, does not differ between NMOSD and MS, despite a different pattern and extent of SC lesions between the two diseases. However the sample size was small. Our study confirms that brain atrophy is greater in MS than NMOSD and that in NMOSD, CSA is the best correlates of clinical disability.

Disclosure

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P1028

Imaging cortical demyelination using T1/T2-weighted ratio

K. Nakamura[1], J.T. Chen[2], R.J. Fox[3], D. Ontaneda[3], B.D. Trapp[2]
[1]Biomedical Engineering, [2]Neuroscience, [3]Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland, OH, United States

Introduction: Cortical demyelination occurs in MS but cannot be detected by visual assessment of conventional MRI. It has been proposed that calculation of a ratio map of T1-weighted and T2-weighted images may improve cortical lesion detection. The validity of this image-processing method has not been tested in multiple sclerosis (MS) brains where cortical demyelination can be extensive. In this study, we used in situ MRI from 5 MS cadavers and corresponding immunostaining to determine if the ratio values differed in normally-myelinated and demyelinated cortical gray matter and compared the effect size of T1w/T2w ratio values against magnetization transfer ratio (MTR) values.
Methods: Under our rapid autopsy protocol, the cadavers were scanned in situ prior to autopsy (mean post-mortem time = 4 hours) using Siemens Trio 3T scanner. The relevant MRI for the ratio map included high-resolution 3D T2-weighted SPACE (1x1x1.2mm), T1-weighted MPRAGE (1mm isotropic). High-resolution MTR was calculated from proton-density-weighted gradient recalled echo images with and without magnetization pulse (1x1x1mm). The images were linearly co-registered and the ratio maps were calculated for each brain voxel (ratio=T1w/T2w). The cortical regions-of-interest (ROI) were previously selected uniformly in unbiased fashion from 6 cortical regions (frontal, parietal, occipital, temporal, insular, and cingulate), sectioned at 30 mm, immunostained for myelin proteolipid protein, and classified as mostly-myelinated or demyelinated cortex. For each ROI, median ratio values were calculated from MRI. We performed a linear mixed-effect model with the median T1w/T2w ratio and median MTR (dependent variables), brain (random effect), and myelin status (fixed effect). To compare the ratio maps and MTR, we calculated the effect size, defined as the difference divided by the standard error.
Results: There were 33 myelinated ROIs and 31 demyelinated ROIs from the 5 brains. The model showed statistically significant effect for the myelin status (T1/T2 ratio = 0.247 for myelinated and 0.216 for demyelinated ROIs, standard error = 0.009, $p < 0.001$). The effect size was larger for T1w/T2w ratio than MTR: 3.4 and 1.8, respectively.
Conclusion: T1w/T2w ratio maps may provide a clinically feasible marker of cortical demyelination without the need for advanced MRI sequences or sophisticated image analysis software.

Disclosure

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P1029

Quantitative analysis of normal-appearing brain tissue in MS using magnetic resonance fingerprinting

K. Nakamura[1], A. Deshmane[2], A. Shah[3,4], D.K. Guruprakash[1], Y. Jiang[2], D. Ma[3,4], E. Fisher[5], R.A. Rudick[5], J.A. Cohen[6], K. Sakaie[7], M.J. Lowe[7], V. Gulani[3,4], M.A. Griswold[3,4], D. Ontaneda[6]
[1]Biomedical Engineering, Cleveland Clinic, [2]Biomedical Engineering, [3]Radiology, Case Western Reserve University, [4]Radiology, University Hospitals, Cleveland, OH, [5]Biogen, Cambridge, MA, [6]Mellen Center for Multiple Sclerosis, [7]Diagnostic Radiology, Cleveland Clinic, Cleveland, OH, United States

Background: Magnetic Resonance Fingerprinting (MRF) is a new MRI approach that provides direct estimates of quantitative relaxation times from fast acquisition with whole-brain coverage. Quantification of abnormalities in lesional and non-lesional tissue is needed to better understand multiple sclerosis (MS) disease mechanisms and progression.
Goal: To characterize the quantitative T1 and T2 measurements from MRF in T2 lesions, normal-appearing grey matter, and normal-appearing white matter (NAWM) of MS patients and to determine the correlations between MRF and clinical measures of disability.
Methods: A cross-sectional study with 11 healthy controls (HC), 23 RRMS, and 16 SPMS undergoing a FISP-MRF protocol (1000 images, 2.3x2.3mm, 21 slices, 5mm slice thickness, 1mm gap, acquisition time = 5:15min) and conventional MRI (T1-weighted MPRAGE, FLAIR, and T2 spin-echo) was conducted. T2 lesions were segmented automatically and verified manually. Caudate and thalamus were segmented using FSL FIRST. NAWM in the frontal lobe (FNAWM) was determined by an atlas-based technique. Regions-of-interest (ROI) in splenium and genu of corpus callosum (CC) were manually segmented. Mean T1 and T2 relaxation times were measured within each ROI (FNAWM, CC, thalamus, caudate, and T2 lesions). Differences between HC and MS, RRMS and SPMS were analysed by ANCOVA with age as

covariate. Correlations were assessed between the relaxation times (T1 and T2) and clinical measures (MSFC and EDSS) using Spearman rank correlations.

Results: Significant differences between HC and MS were found in T1 values from the thalamus and CC (mean (SE): 1057 (14) and 1101 (16) ms in thalamus of HC and MS, respectively; 815 (49) vs. 966 (55) ms in CC of HC and MS; both $p < .01$). Significant differences for T1 values in FNAWM between RRMS and SPMS were found (820 (12) vs. 892 (19) ms, RRMS and SPMS, respectively) as well as for T1 and T2 values in T2 lesions (T1 = 1108 (27) vs 1277 (43) ms; T2 = 87 (4) vs. 109 (6) ms) (all p-values $\leq .001$). T1 values in FNAWM showed the highest correlation with both EDSS and MSFC (absolute $r > 0.60$). T1 and T2 values in T2 lesions also correlated with MSFC ($r = -0.68$ and -0.58 respectively, $p < .001$).

Conclusion: These results suggest that MRF may be a clinically feasible quantitative approach for characterizing tissue damage in MS. Additional studies are needed to assess sensitivity to change, predictive value, and response to treatment.

Disclosure

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P1030

A comprehensive assessment of cervical cord lesions in patients with multiple sclerosis on T1-MPRAGE at 3T: relationship with cord atrophy and disability

M.A. Rocca[1], P. Valsasina[2], P. Preziosa[2], M. Aboul-Wafa[2], M.A. Horsfield[3], G. Comi[4], A. Falini[5], M. Filippi[6]

[1]Ospedale San Raffaele - Vita-Salute San Raffaele UniversityDivision of Neuroscience, [2]Neuroimaging Research Unit, INSPE, San Raffaele Scientific Institute - Milan (Italy), Milan, Italy, [3]Xinapse Systems Ltd, Colchester, United Kingdom, [4]Dept. of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, [5]Dept. of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, [6]Neuroimaging Research Unit, INSPE, San Raffaele Scientific Institute, Milan, Italy

Aims: We characterized the spatial distribution of cervical cord T1 lesions in a large cohort of multiple sclerosis (MS) patients; assessed the influence of cord T1 lesions on atrophy quantification and analyzed their association with disability.

Methods: 3Tesla cervical cord sagittal 3D T1-weighted scans were acquired from 63 relapsing remitting (RR), 30 secondary progressive (SP), 20 primary progressive (PP), 20 benign (B) MS and 47 healthy controls. Cord T1-hypointense lesions were identified and binary lesion masks were produced. The active surface (AS) method was applied to calculate cross-sectional area (CSA). Between-group comparisons of T1 lesions and cord atrophy were performed with ANOVA models (age-adjusted).

Results: T1 hypointense lesions were detected in 114 MS patients, with a higher frequency in SPMS *vs* RRMS, and PPMS *vs* RRMS and SPMS patients. Cord atrophy was found in MS patients *vs* controls, and in RRMS and PPMS *vs* controls, RRMS *vs* BMS and SPMS *vs* RRMS patients. Whole-cord CSA was not correlated with cord T1 lesion number. The regional distribution of cord atrophy was modestly correlated with T1 lesion number. There was a strong correlation between cord atrophy and T1 lesions and disability, both at a global and regional analysis.

Conclusions: T1 hypointense cervical cord lesions were detected in a large proportion (85%) of MS patients. T1 lesions did not influence cord area estimates produced by the AS method. The association between cord T1 lesions and cord atrophy was modest. However, both cord T1 lesions and atrophy contributed, independently, to patient physical disability.

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P1031

Brain volume in early MS patients with and without IgG oligoclonal bands in CSF: a case-control study

G. Fenu[1], L. Lorefice[1], V. Sechi[2], L. Loi[2], F. Contu[2], F. Cabras[2], G. Coghe[1], J. Frau[1], C. Melis[1], L. Schirru[1], M.A. Secci[1], G. Costa[1], M.A. Barracciu[2], M.G. Marrosu[1], E. Cocco[1]

[1]Multiple Sclerosis Center, University of Cagliari, [2]Radiology Unit, Binaghi Hospital, ASL8- Cagliari, Italy, Cagliari, Italy

Background: Oligoclonal bands of IgG (O.B.) are detected in near to 90% of Multiple Sclerosis (MS) patients and are proposed as early prognostic factor of the disease (Andersson, 1994, Imrell, 2009). Growing attention is actually oriented to the brain volume evaluation as possible MRI marker of activity and severity of the disease, also to estimate the response to MS treatments (De Stefano N, CNS Drugs 2014).
Aim: to evaluate a possible relationship between IgG O.B. and cerebral volume in a cohort of early MS patients.
Methods: Consecutive MS patients were recruited at the MS Centre of University of Cagliari. Inclusion criteria were: diagnosis of Relapsing remitting MS according to 2010 revision of diagnostic criteria; CSF analysis and MRI acquired simultaneously and within 12 months from clinical onset. Acquisitions of brain MRI were obtained using a Magnetom Avanto Siemens Scanner at 1.5 T with the following sequences: 3D T1-MPRAGE: Echo time (TE): 2.37 ms, repetition time (TR): 1730 ms, inversion time (TI): 1050 ms, Field of View (FOV): 244 mm, voxel size: 1x1x1 mm. Brain parenchyma volumes were measured by SIENAX, a previously described method to obtain Normalized Brain Volume (NBV), Normalized Grey matter Volume (NGV) and Normalize White Matter Volume (NWV).
Results: In 20 patients CSF analysis did not showed IgG O.B synthesis (O.B. negative group). A control group of 25 patients with detection of IgG O.B. was also recruited (O.B. positive group). No significant difference between OB negative and OB positive group were detected in age (mean: 43.6 vs 40,4), gender (female: 10/20 vs 15/25) and EDSS (mean: 1,5 vs 2.2). Mean of NBV was 1517.10 ml (S.D. 75.14) in OB negative group and 1498.04 ml (S.D. 70.95) in OB positive group, respectively. Mean of NGV was 782.96 ml (S.D. 80.70) in OB negative and 806.25 ml (S.D.: 57.8) in OB positive group. Mean of NWV was 734.10 ml (S.D. 68.9) in OB negative and 691.68 ml (S.D. 38.02) in OB positive group. T test for independent groups showed a significant difference in NWV between OB positive and OB negative group (p value: 0.01). No difference was detected in NBV and NGV.
Conclusions: A previous study found that MS patients lacking O.B. have less global and regional brain atrophy (Ferreira D., 2014). Also our preliminary results suggested that OB positive patients show more atrophy of white matter since early phases of the disease and support the role of CSF analysis as prognostic factor at time of MS diagnosis.

Disclosure

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P1032

Longitudinal assessment of brain lesion changes in follow-up MRI scans of patients with multiple sclerosis

S. Jain[1], A. Ribbens[1], D.M. Sima[1], M. Cambron[2], J. De Keyser[2], C. Wang[3,4], M.H. Barnett[3,4], S. Van Huffel[5,6], F. Maes[6,7], A. Maertens[1], D. Smeets[1]
[1]Icometrix, Leuven, [2]UZ Brussel, Brussel, Belgium, [3]Sydney Neuroimaging Analysis Centre, The Brain and Mind Research Institute, [4]The Brain and Mind Research Institute, The University of Sydney, Sidney, NSW, Australia, [5]Department of Electrical Engineering, ESAT, STADIUS Center for Dynamical Systems, Signal Processing and Data Analytics, KU Leuven, [6]Medical IT, iMinds, [7]Department of Electrical Engineering, ESAT, PSI Medical Image Computing, KU Leuven, Leuven, Belgium

Introduction: Lesion volume measures and their changes over time are meaningful biomarkers in multiple sclerosis (MS) prognosis. Manual lesion segmentation for computing volume in a single or multiple time points is time consuming and suffers from intra and inter-observer variability. In this work, we present a fully-automatic longitudinal assessment of lesion changes from follow-up MRI scans. This has been integrated in the MSmetrix software, which is approved for clinical use in EU, Canada and Australia.
Methods: The presented approach is an iterative and unsupervised automatic method for longitudinal white matter lesion segmentation, which is based on a joint expectation-maximisation (EM) framework for two time points. 3D T1-weighted and 3D FLAIR MR images are used as input and lesions are segmented in three steps: (1) cross-sectional analysis, providing a prior on joint lesion segmentation of the two time points; (2) creation of difference image, which is used to model the lesion evolution as a Gaussian mixture model; (3) a joint EM lesion segmentation framework that takes as input the cross-sectional lesion segmentation and difference image to provide the final lesion segmentation at each time point. The accuracy and reproducibility of the software is evaluated.
Results: The accuracy of our proposed method, as evaluated by a median Dice score with a ground truth expert labeling data set, was 0.63 and the Pearson correlation coefficient was equal to 0.96. A test-retest data set was used to evaluate the reproducibility. The median absolute volume difference was 0.11 ml. Our presented method outperforms cross-sectional lesion segmentation methods and the longitudinal approach of the Lesion Segmentation Toolbox (LST).
Conclusion: Our results demonstrate that the proposed method has a high accuracy compared to expert manual labeling and a favourable reproducibility. This allows the use of lesion change measures in a clinical routine setting.

Disclosure

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P1033

Role of cognitive reserve on cognitive function and regional brain atrophy in multiple sclerosis: a two-year longitudinal study

M.A. Rocca[1], P. Del Sette[2], G. Riccitelli[2], E. Pagani[2], P. Preziosa[2], V. Martinelli[3], G. Comi[3], A. Falini[3], M. Filippi[2]
[1]Division of Neuroscience, Ospedale San Raffaele - Vita-Salute San Raffaele University, [2]Neuroimaging Research Unit, INSPE, San Raffaele Scientific Institute, [3]Dept. of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Background: The cognitive reserve (CR) hypothesis states that enriching experiences protect against dementia and cognitive decline. Its protective role against cognitive decline over time in MS is unclear.
Aims. We investigated the predictive role of CR on cognitive decline and gray matter (GM) and white matter (WM) volume changes in MS patients.
Methods: 3D T1-weighted scans and Rao's Brief Repeatable Battery were obtained from 54 MS patients and 20 healthy controls (HC) at baseline and after two years (median=2.2 years) of follow-up (FU). A reliable change index (RCI) was calculated to assess cognitive decline. A cognitive reserve index (CRI) was calculated including education, intelligence quotient and leisure activities. Regional GM atrophy was estimated using voxel-based-morphometry, whereas longitudinal GM changes were investigated using tensor-based-morphometry analysis. Between group-comparisons (SPM12) and linear regression analysis (SPSS22) were performed to evaluate the effect of CRI on cognitive performance and GM changes, controlling for demographic, clinical and structural MRI measures.
Results: At baseline, higher CRI predicted better performances at information processing speed (IPS) (β=0.30 p=0.02), verbal memory (β=0.43 p=0.001; β=0.52 p< 0.001; β=0.29 p=0.021) and fluency tests (β=0.51 p< 0.001). Compared to HC, MS patients had GM atrophy of the deep GM nuclei, fronto-temporal-parietal-occipital regions, and left (L) cerebellum. Controlling for atrophy within the previous regions, higher CRI predicted better performances at verbal memory (β=0.45 p=0.001; β=0.52 p< 0.001; β=0.29 p=0.021), attention (β=0.28 p=0.002), IPS (β=0.29 p=0.03) and verbal fluency (β=0.38 p=0.003) functions. An interaction between CRI and GM volume in the right (R) superior temporal gyrus, L lingual gyrus and L cerebellum predicted better performances respectively at IPS (β=0.30 p=0.02), verbal fluency (β=0.39 p=0.002) and attention (β=0.30 p=0.01) tests. CRI predicted GM volume in bilateral lingual gyrus (L: β=0.37 p=0.006; R: β=0.27 p=0.05). At FU, cognitive decline was predicted by GM atrophy of several fronto-temporal areas and L cerebellum, while no effect of CRI on cognitive and longitudinal structural changes was found.
Conclusions: CR in MS patients has a protective role on cognitive performance reducing the effect of GM atrophy on cognitive functions. This protective role might lose his efficacy with the progression of disease.

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P1034

Long range effects of focal lesions on normal appearing brain tissue vary depending on the disease phenotype in multiple sclerosis

A. Pitiot[1], R. Abdel-Fahim[2], O. Mougin[3], P.S. Morgan[2], P.A. Gowland[3], N. Evangelou[2]
[1]School of Psychology, [2]School of Medicine, [3]SPMIC, University of Nottingham, Nottingham, United Kingdom

Introduction: The evolution of clinical disability in Multiple Sclerosis (MS) is a complex process with significant contributions from both focal lesions and diffused abnormalities in Normal Appearing Tissues (NAT), which have been shown to be more affected in progressive MS. Yet, the role played by focal demyelination in determining NAT pathology has not been systematically explored due to the difficulties in detecting Grey Matter (GM) demyelination and very small White Matter (WM) lesions using conventional Magnetic Resonance (MR) imaging. A clearer picture of what cause diffuse damage in NAT could produce better treatment strategies.
The enhanced signal to noise ratio and sensitivity to Magnetisation Transfer (MT) respectively afforded by Phase Sensitive Inversion Recovery (PSIR) and Magnetisation Transfer Ratio (MTR) at ultra-high field make it possible to study small variations across both WM and GM.

Objective: To explore the influence of disease phenotype on the effect of focal lesions on NAT in patients with MS, using ultra-high field MR imaging.
Method: 40 MS patients (16 males/24 females; 10 participants for each major subtype; age= 46±10 years; EDSS= 3.5±2.4; disease duration= 6.3±5.7 years) were recruited from the MS outpatient clinics at Nottingham University Hospitals. Each patient was scanned at 7T to acquire high-resolution, 0.63 mm3, MTR and PSIR images. We estimated tissue maps from the PSIR images using SPM8. Finally we calculated the mean MTR ratios in NAT as a function of the topological distance to the nearest GM or WM lesion, where ratios were obtained by dividing the mean value at each distance by the overall mean across all distances.
Results: As previously reported, the NAT MTR ratios decreased with the distance to the nearest lesion with a long-range influence of WM lesions on NAWM, and a shorter-range influence of GM lesions on both NAGM and NAWM. Importantly, the decrease was modulated by the disease subtype and was twice as strong in primary and secondary progressive MS patients than in relapsing remitting and clinically isolated syndrome patients.
Discussion: Our findings suggests that MS lesions continue to have a destructive effect on NAT over many years and are possibly associated with continuing inflammation at the borders of the lesions. Prevention of lesion development and better control of residual inflammation are possible strategies to reduce long lasting progressive NAT damage.

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P1035

Pronounced brain connectivity disruption in adult patients with pediatric-onset MS

A. Giorgio[1], J. Zhang[1], M.L. Stromillo[1], F. Rossi[1], M. Mortilla[2], E. Portaccio[3], B. Hakiki[3], M.P. Amato[3], N. De Stefano[1]
[1]University of Siena, Siena, [2]Ospedale Pediatrico Meyer Firenze, [3]University of Florence, Florence, Italy

Background: Natural history studies have shown that pediatric-onset MS (POMS) reaches irreversible disability, despite slower progression, at a much younger age than adult-onset MS (AOMS). It is unclear whether young adult POMS shows more pronounced brain tissue damage and/or disrupted connectivity with respect to AOMS of similar age and disability
Goals: To assess brain tissue integrity and connectivity in young adult POMS patients with mild disability in comparison with age- and disability-matched AOMS patients
Methods: Multimodal brain MRI was acquired on a 3T MR scanner in POMS (n=15, age=24.8±7 years, duration=9.8±6.2 years) and age-matched AOMS (n=14, age=27.8±3 years, duration=5.2±2.2 years) and NC (n=20, age=27.1±4 years). The two MS groups had similar disability (median EDSS: 1 in both). Anatomical connectivity (AC) along white matter (WM) tracts was assessed with TBSS while intra- and inter-networks functional connectivity (FC) was evaluated with ICA-AROMA/MELODIC/dual regression and with FSLNets. FSLVBM was used to assess local grey matter (GM) volumes. Voxelwise analysis of variance was performed with nonparametric permutation testing ($p< 0.01$, corrected).
Results: POMS had slightly higher T2-lesion volume (LV) than AOMS (10.7±12 cm^3 vs 6.6±4.5 cm^3, p=0.8). The two patient groups were similar in global and regional brain volumes. POMS showed altered AC (lower fractional anisotropy and/or higher diffusivities) in comparison to NC (thalamic radiations, inferior fronto-occipital fascicle, inferior longitudinal fascicle, posterior corona radiata [PCR], corpus callosum, fornix) and AOMS (PCR). No between-group differences in intra-network FC were found. However, inter-network FC measures between default mode network (DMN) and secondary visual network were lower in POMS than in both NC (full correlation: -4.06 vs -2.6) and AOMS (partial correlation: -0.82 vs -0.22) whereas no differences were found between AOMS and NC.
Conclusion: POMS show macroscopic tissue damage (i.e., brain lesions and atrophy) comparable with that of AOMS patients of similar age and mild disability, despite longer disease duration. However, POMS show reduced AC along the corticospinal tract, a clinically eloquent tract for physical disability, and reduced long-range FC involving a relevant hub for cognition such as DMN. This connectivity disruption of POMS patients might explain, at a relatively early disease stage, their unfavourable clinical outcome in the long term.

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P1036

Toward a standardized quantitative imaging protocol for multiple sclerosis: a NAIMS multisite study of magnetization transfer and quantitative T_1 imaging techniques

I. Tagge[1], D. Schwartz[1], K. Powers[1], R. Bakshi[2], P. Calabresi[3], T. Constable[4], J. Grinstead[1,5], R. Henry[6], G. Nair[7], J. Oh[3,8], N. Papinutto[6], D. Pelletier[9], D.S. Reich[7], N. Sicotte[9], J. Simon[1], W. Stern[6], W. Rooney[1]
[1]Oregon Health & Science University, Portland, OR, [2]Brigham and Women's Hospital,Harvard Medical School, Brookline, MA, [3]Johns Hopkins, Baltimore, MD, [4]Yale, New Haven, CT, [5]Siemens Medical Solutions, USA, Portland, OR, [6]University of California San Francisco, San Francisco, CA, [7]National Institute

of Neurological Disease and Stroke, National Institute of Health, Bethesda, MD, United States, [8]University of Toronto, Toronto, ON, Canada, [9]University of Southern California, Keck School of Medicine, Los Angeles, CA, United States

Introduction: The North American Imaging in Multiple Sclerosis (NAIMS) Cooperative was formed with the goal of developing sensitive, reliable imaging-based surrogates for disease progression in MS. The current lack of standardization in MRI protocols leads to increased variability, particularly in semi-quantitative techniques such as MTR, and makes comparisons between studies almost impossible. These efforts will accelerate MS research by creating standardized quantitative imaging protocols, a centralized database, multiple analytic tools, and data sharing across NAIMS sites.
Methods: A single subject with clinically stable RRMS travelled to seven North American sites and underwent two distinct 3T MRI sessions following a standardized protocol at each site. Informed consent was obtained at each imaging center. The variable flip angle (FA) method (FA 3°, 6°, 10°, 20°) was employed to create whole-brain quantitative T_1 (qT_1) maps. Magnetization transfer images were acquired with two saturation pulse offset frequencies (4kHz, 100kHz) at 8 mT amplitude, sufficient for magnetization transfer ratio (MTR) calculation.
Results: Imaging sessions were successfully completed at all sites between October 2015 and February 2016. MTR maps were of similar quality (characterized by signal-to-noise ratio, homogeneity) across all sites. Mean (±standard deviation) white matter, cortical grey matter, and lesion MTR values for all imaging sessions were: 0.27 (0.005), 0.20 (0.009), and 0.21 (0.006), respectively. Mean intra-session MTR variance was 0.0001 across all sites. Despite applying corrections, B_1 inhomogeneity contributed to substantial inconsistencies in qT_1 maps, particularly in the most superior and inferior regions of the brain where radio frequency coil performance is variable and sensitive to subject placement within the instrument.
Discussion: Both MTR and qT_1 mapping have been shown to have potential in elucidating tissue characteristics and underlying pathology. MTR is effectively a self-bias-correcting technique and demonstrated greater reproducibility across sites than did qT_1 mapping. This work demonstrated that use of carefully standardized protocols produces consistent quantitative and semi-quantitative measurements across sites in MS brain tissue in-vivo. Future work will combine the qT_1 and MTR maps for quantitative calculations of macromolecular fraction.

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P1037

Signal mass as a more comprehensive measure of tissue loss in MS

R.A. Brown, S. Narayanan, D.L. Arnold
McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, QC, Canada

Background: Brain volume loss (BVL) on MRI is among the best imaging correlates of MS disease progression. However, measures of BVL can require hundreds of participants and long follow-up to see changes due to treatment. Some tissue pathology, e.g. demyelination and axonal loss, with a resulting increase in extracellular space, represent tissue loss that is not fully captured by BVL measurements, but, rather, decrease the density (and alter signal intensity) of remaining brain tissue. Other factors, e.g. edema and hydration, can spuriously affect BVL. We propose a method to combine measurements of tissue density and volume into "signal mass," (SM) a more comprehensive measure of tissue loss and atrophy in MS.
Objectives: Compare SM and Jacobian Integration (JI) for detecting overall tissue loss (atrophy) in MS versus healthy controls.
Methods: 9 MS and 9 healthy controls had T1-weighted (T1w) and magnetization transfer ratio (MTR) MRI at baseline and two years, at 1.5 and 3T. MTR was used for SM because it is sensitive to changes in tissue integrity and is consistent over time on the same scanner. T1w images were co-registered using a rigid skull-constrained transform to a half-way space, followed by nonlinear registration. MTR images were registered to the T1w images, then transformed using the T1w transforms. Parenchyma masks were made using tissue maps from SIENAX. Jacobian determinant maps (J) were computed from the nonlinear transforms. The percent brain volume change (PBVC) was the voxel-wise average of

J within the parenchyma mask. MTR SM at baseline was $S_1 = I_1 \prime vol$ where I_1 is the baseline MTR image and *vol* is the voxel volume. At followup this was $S_2 = I_2 \prime vol \prime J$. Percent SM change (PSMC) was the percent difference between S_1 and S_2. JI and SM were both annualized. Required N for one-tailed *t*-tests comparing healthy control to MS were computed for each measurement using $a = 0.05$ and $b = 0.9$, at each field strength.

Results: At 1.5 T PBVC loss was 0.13 %/year greater in patients than controls, $s = 0.34$; PSMC loss was 0.33 %/year greater, $s = 0.56$. The required N per arm to detect these differences are 108 for JI and 45 for SM. A trial expecting a 50% treatment effect would require N of 430 for JI and 181 for SM. These results were confirmed in the 3 T data.

Conclusions: Signal mass demonstrated a better than 2x improvement in N over JI for detecting a difference from normal, and may be a more comprehensive measurement of tissue loss in MS.

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P1038

Concomitant use of quantitative magnetization transfer and susceptibility mapping in longitudinal study of early multiple sclerosis patients

O. Mougin[1], A. Samaraweera[2], N. Geades[1], M. Cronin[3], P. Gowland[1], N. Evangelou[2]

[1]SPMIC, School of Physics and Astronomy, University of Nottingham, [2]Department of Clinical Neurology, Division of Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom, [3]Brain Imaging and Analysis Centre, Duke University, Durham, NC, United States

Purpose: Myelin evolution of Multiple Sclerosis (MS) lesion can be monitored via MRI by using the traditional Magnetization Transfer Ration (MTR). However, inflammation, oedema and axonal loss together with myelination influence the MTR. Quantitative Magnetization Transfer (qMT) measure macromolecules content independently from T1 change due to oedema or inflammation. It can be measured via Chemical Exchange Saturation Transfer (CEST), and can be used to monitor accurately myelination changes inside and at the rim of the lesion taking into account the water content of the tissue. Recently susceptibility of the tissue, quantified by Quantitative Susceptibility Mapping (QSM) and indicating iron concentration, also showed evolution at the edge as well as inside the lesion during its formation. Here we present a longitudinal MS study aimed at tracking and quantifying lesion evolution with qMT together with QSM data.

Methods: With ethics approval, 4 patients with early Multiple Sclerosis were scanned 6 times with 6 weeks between scans (30 weeks total) using a 7T MRI. Imaging protocol includes Quantitative MT derived from CEST data as well as QSM derived from multi-echo T2star, standard FLAIR and PSIR images. FLAIR images were used to track MS lesions and create masks for ROI processing. Mean percentage MT pool sizes and susceptibility in an ROI drawn where white matter (WM) lesions appeared during the 30 weeks, were compared to regions of normal appearing WM close to the lesion site.

Results: We detected demyelination and remyelination as seen by changes of qMT in acute lesions as reported before. In addition we found a correlation of qMT with QSM inside the lesions both in crossectional analysis (r=-0.31, p=1e-9). The correlation in lesions was stronger than in the normal appearing tissue (r=-0.14, p=1e-9). However when the rim of acute lesions were studied we detected loss of qMT with initially associated loss of QSM. QSM increased signal appeared within 6 weeks. The differential appearance of QSM and qMT rings in acute lesions suggests degradation of myelin first and local accumulation of iron as a secondary effect.

Conclusion: Concomitant use of QSM and qMT concentration measurements appear to provide additional information about pathological changes in white matter lesions in MS and show promise for the study of early evolution of MS lesions.

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P1039

An automated and robust method for dentate nucleus T1 signal hyperintensity quantification in MS patients receiving gadolinium-based contrast agents

C. Chien

NeuroCure Clinical Research Center, Charité - University Medicine Berlin, Berlin, Germany

Background: Gadolinium-based contrast agents (GBCAs) are widely used during magnetic resonance imaging (MRI) in MS patients. It has been of recent concern that gadolinium from GBCAs are accumulating in the brain, mainly in the dentate nucleus (DN). Past studies investigated this issue with manual region-of-interest analysis. This approach is compromised by subjectivity and labour intensive analysis. So far, there is no automated, objective and robust method for hyperintensity quantification within the dentate nucleus. We propose such a method and evaluate optimal parameters.

Methods: T1-weighted images from 35 MS patients receiving 2 doses of 6ml/60kg Gadopentetate in a longitudinal study were analysed.

Cerebellum and brainstem Images were isolated and registered with the MATLAB SUIT toolbox.

Dentate nucleus masks at varying threshold values (0 to 1) from a probabilistic cerebellar nuclei atlas were created with an additional pons mask. Dentate-to-Pons Signal Intensity Ratio (DPSIR) were calculated. Baseline DPSIR and DPSIR after 2 Gadopentetate doses were compared using a paired student's t-test.

Results: A clear increase of DPSIR was observed over time. Significant differences (mean difference range = 0.004 - 0.009) were observed with a dentate nucleus mask threshold ranging from 0.25 to 0.85. The most significant difference was observed at 0.7 threshold (mean ± SD = 0.0085 ± 0.02, p = 0.0136). The variability remained comparatively stable over all thresholds (SD range = 0.017 - 0.027).
Conclusions: An automated and objective method for dentate nucleus T1 hyperintensity quantification is introduced, that allows for comparable and reproducible results. This method would be useful for quantification of dentate nucleus T1 signal hyperintensity to better characterise and investigate gadolinium deposition in MS patients.

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P1040

3T-PET/MRI analysis of cortical metabolism in MS patients discloses various patterns of association with white and grey matter pathology

D. Poggiali[1], D. Cecchin[2], A. Favaretto[1], A. Lazzarotto[1], A. Riccardi[1], S. Pravato[1], M. Margoni[1], F. Bui[2], P. Gallo[1]
[1]The Multiple Sclerosis Centre - Veneto Region (CeSMuV), Department of Neurosciences, [2]Unit of Nuclear Medicine, Department of Medicine - DIMED, University of Padova, Padova, Italy

Background: Cortical damage (lesions and atrophy) can be demonstrated in MS patients at clinical onset and its progression partly explains the accumulation of physical and cognitive disability. Likely, cortical pathology associates with metabolic changes. However, to what extent cortical metabolic dysfunction may precede or follow structural damage has not been investigated yet.
Objectives**:** We studied cortical metabolic changes and their association with MRI parameters of white matter (WM) and grey matter (GM) damage in MS patients by means of a fully integrated 3T-Positron Emission Tomography/Magnetic Resonance Imaging (PET/MRI) system that allows the measurement of the absolute glucose metabolic rate (aMRglu) in Desikan Killiany cortical areas.
Methods: 31 patients were enrolled in the study: 14 were clinically isolated syndromes or very early relapsing remitting MS (CIS/eRRMS) with no sing of cognitive impairment, 17 were RRMS with a long disease duration and clinical evidence of cognitive dysfunction. Physical and mental examinations were done by means of EDSS and Rao´s BRB. 3T ^{18}F-FDG-PET/MRI (Siemens Biograph mMR PET System) images were analysed with Patlak plot method to obtain aMRglu. Regional cortical thickness (CTh) was obtained from an anatomical 3D-T1 by Freesurfer suite.
Results: CTh of left frontal (p=0.016), parietal (p=0.03) and occipital (p=0.02) lobes and in right frontal (p=0.019) and parietal (p=0.01) lobes was significantly lower in CIS/eRRMS compared to RRMS. These groups did not differ in aMRglu. Surprisingly, no correlation between CTh and cortical aMRglu was observed in both CIS/eRRMS and RRMS. When all the patients were analysed as a single group a correlation was found between aMRglu and WM (p=0.02) and GM (p=0.04) focal lesions. No correlation between aMRglu and either CTh or lesion volume could be demonstrated after patient stratification on the basis of WM and GM lesion number. Interestingly, when CIS/eRRMS with lower lesion number were analysed, higher values of aMRglu were observed compared to RRMS with high lesion load.
Discussion: Various patterns of association between aMRglu and WM and GM pathology were observed in CIS/eRRMS and RRMS. These findings indicate that cortical metabolism is a dynamic parameter especially in the early disease phases, probably linked to variable state of activation of both neurons and glial cells.

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P1041

Clinical correlations of brain lesion location in multiple sclerosis: voxel-based analysis of a large clinical trial dataset

A. Altermatt[1,2], L. Gaetano[1,2], S. Magon[1,2], D. Tomic[3], D. Häring[3], E.-W. Radue[2], J. Wuerfel[2], L. Kappos[1], T. Sprenger[1,2,4]
[1]Universitätsspital Basel, [2]Medical Image Analysis Center (MIAC AG), [3]Novartis Pharma AG, Basel, Switzerland, [4]DKD Helios Klinik, Wiesbaden, Germany

Aim: We aimed at studying the relationship between lesion distribution and physical disability using a cross-sectional voxel-based lesion mapping approach in a very large dataset of MS patients.

Methods: Baseline data of relapsing-remitting MS patients participating in the FREEDOMS (n=1270) and FREEDOMS II (n=1078) phase 3 clinical trials were analyzed. T2-weighted lesion masks were normalized to standard stereotaxic space by non-linear registration. Relations between WM lesion location and disability measures were assessed using a non-parametric ANCOVA (for Expanded Disability Status Scale, EDSS; Multiple Sclerosis Functional Composite, MSFC, and subscores; Modified Fatigue Impact Scale, MFIS) or multinomial ordinal logistic regression (in case of EDSS functional subscores). Age, gender and disease duration were added as covariates. All statistical tests were adjusted for multiplicity; across scales a Bonferroni correction (i.e. α=0.05/13 disability measures) and within scale a Benjamini & Hochberg procedure were applied.
Results: The stereotaxic registration procedure was successful in 81% of the patients and these data were included in the analysis (female: 1362; age: 38.5±8.8; disease duration: 9.1±7.3 years). In general, lesion mapping showed similar areas of correlation among different disability scales: periventricular regions in temporal, frontal, and the limbic lobes were most affected, interrupting mostly WM tracts reflecting the posterior thalamic radiation, and the posterior and superior parts of the corona radiata. However, the extent of involvement of those areas depended on the score considered: EDSS, MSFC and its subscores showed a higher number of voxels with significant correlations than EDSS subscores and MFIS.
Conclusion: Overall, these results indicate significant associations between lesion location and disability scores in MS. Most impairments were best explained by lesions in periventricular regions. This first large scale study of the relationship between lesion location and a wide range of clinical disability measures has important implications for our understanding of MS related disability.

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P1042

White matter correlates of complex processing speed performance in relapsing-remitting multiple sclerosis

R. Manca[1], M. Mitolo[2], B. Sharrack[1], A. Venneri[1,2]
[1]University of Sheffield, Sheffield, United Kingdom, [2]IRCCS Fondazione Ospedale San Camillo, Venice, Italy, Venice, Italy

Background: Slowed processing speed (PS) is the cognitive deficit most commonly reported in people with multiple sclerosis (MS). PS is influenced by demyelination processes that characterise MS pathology and cause breakdown in neural transmission. The association between PS performance and degeneration of specific white matter (WM) tracts in MS patients has not been clarified yet. The current literature, mainly comprising exploratory studies, has highlighted variable and inconsistent results.
Objectives: This study investigated the differential relationships between WM microstructural integrity and complex PS performance on common tests, and the influence of PS on higher order cognition and WM integrity in relapsing-remitting MS (RRMS).
Methods: Twenty-nine RRMS patients (Expanded Disability Status Scale $\leqslant$ 6, age = 44.1 ± 9.2, disease duration = 8.9 ± 6.2) were recruited. The whole sample underwent neuropsychological and magnetic resonance (MR) diffusion tensor imaging (DTI) assessments. Tract-based spatial statistics (TBSS) was used to correlate DTI indices with cognitive performance on: different versions of the Paced Auditory Serial Addition Test (PASAT), the Digit Symbol Coding (DSC) test, and both PS-dependent and PS-independent neuropsychological tests. A new PS difference score (PASAT 3s - PASAT 1.5s) was additionally investigated.
Results: Correlations with DTI indices were detected for the DSC and the PS difference score while neither the PASAT versions nor the higher order tests were associated with WM integrity. The anterior corpus callosum and bilateral fronto-parietal associative tracts were the main structures involved in PS performance.
Conclusions: Associative and callosal WM fibres, mainly connecting frontal areas, seem to be the neural correlate of abnormal PS performance in this form of MS. These findings highlight for the first time clearly that this association is crucial for timed tasks depending on the visual modality, challenging for MS patients, or when more elaborate indices, i.e. PS difference score, are used.

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P1043

The virchow robin spaces in multiple sclerosis brain: a phase sensitive inversion recovery study

A. Favaretto[1], S. Pravato[1], A. Lazzarotto[1], A. Riccardi[1], M. Margoni[1], D. Poggiali[1], M. Anglani[2], D. Seppi[1], P. Gallo[1]
[1]The Multiple Sclerosis Centre - Veneto Region (CeSMuV), Department of Neurosciences, [2]Neuroradiology Unit, University Hospital of Padova, Italy., University of Padova, Padova, Italy

Background: Virchow Robin spaces (VRS) are small, interstitial fluid-filled ducts that host small vessels in the subarachnoid space. Their involvement in inflammatory brain disorders and the significance of their implication in multiple sclerosis (MS) are still controversial. Indeed, enlarged VRS are found in MS, but only few and conflicting data are available on their association with physical and cognitive impairment in this disease. Moreover, methodological constraints currently limit the identification and characterization of VRS.
Aim: We applied Phase Sensitive Inversion Recovery (PSIR) to study VRS in MS patients and in normal controls (NC) with the aim of finding possible correlations between VRS number and volume and 1) clinical and cognitive disability and 2) brain atrophy.
Methods: Forty-three MS patients [21 clinically isolated syndrome (CIS)/early relapsing-remitting (eRRMS, < 3 years of disease duration), 15 RRMS, 7 secondary progressive (SPMS)], having a wide range of disability (EDSS) and disease duration, and 9 NC were studied. 3DT1, 3DFLAIR and 2DPSIR images were obtained with a 3T MRI (Philips) and analysed in parallel. VRS number and volume were calculated by manual segmentation (ITKSNAP). Brain parenchymal fraction (BPF) was assesed by means of Freesurfer. All patients underwent clinical (EDSS) and cognitive (Rao's BRB, DKEFS) evaluation.
Results: Significantly higher number and volume of VRS were obtained with PSIR compared to both T1 and FLAIR ($p < 0.001$ for all comparisons). VRS number and volume were significantly increased in CIS/eRRMS compared to NC ($p < 0.05$), in PMS and RRMS compared to CIS/eRRMS ($p < 0.05$) and in male versus female patients ($p < 0.05$). VRS total volume increased significantly with disease duration ($r=0.56$) but did not correlate with the EDSS score. Mild inverse correlations were found between VRS number and SPART D and DKEFS FS ($r=-0.47$ and $r=-0.46$, respectively). Finally, no correlation was found between VRS number and volume and the BPF ($r=0.2$).
Discussion: PSIR proved to be superior to both T1 and FLAIR in calculating both the number and the volume of VRS. Although no association was found with physical disability and BPF, the correlation observed with some cognitive tests seems to suggest that the diffuse loss of tissue associated with the enlargement of VRS may contribute to determine the cognitive decline observed in MS.

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P1044

Low corpus callosum and thalamus volume at baseline are associated with higher future whole brain volume loss

A. Raji[1], R. Opfer[2], L. Spies[2], G. Winkler[1]
[1]Center of Neurology, [2]jung diagnostics GmbH, Hamburg, Germany

Background: Brain volume loss is an important biomarker of neurodegeneration in multiple sclerosis (MS). Thalamic and corpus callosum atrophy are conjectured to precede global brain atrophy.
Objectives: To investigate whether low corpus callosum (CC) or thalamus (TH) volume at baseline is associated with a higher degree of future whole brain volume loss (BVL) in a clinical cohort of Multiple Sclerosis (MS) patients.
Methods: 64 patients, 48 relapsing-remitting MS and 16 secondary-progressive MS, from an outpatient facility specialized to MS (Neurozentrum Hamburg) were included who received at least 2 MRI examinations between 2014 and 2016. MRI acquisition was performed on a single 3 Tesla GE scanner using the same 3D MPRAGE protocol. Mean (± std) age was 45.3 ± 12.4 years and mean disease duration (DD) was 9.3 ± 8.2 years. Expanded Disability Status Scale (EDSS) was assessed by an experienced neurologist (EDSS = 2.7 ± 1.9). Mean time interval between baseline and the latest MRI scan was 2.1 ± 0.88 years. Global brain parenchyma (BP), CC and TH volumes were calculated deploying a previously described atlas based volumetry approach implemented in SPM12. Volumes were adjusted for intracranial volume and age. BVL between baseline and the latest MRI scan was computed using FSL/SIENA. Pearson correlation coefficients (r) between the annualized BVL (aBVL) and age, EDSS, DD, and adjusted BP, adjusted CC and adjusted TH volumes were computed.
Results: Mean aBVL of all 64 patients was 0.44 ± 0.51 %. No correlations were found between aBVL and age ($r=0.03$, $p=0.8$), aBVL and DD ($r=0.12$, $p=0.37$)) and between aBVL and adjusted BP volume ($r=-0.16$, $p=0.21$). Significant correlations were found between aBVL and EDSS ($r=0.37$, $p=0.003$), aBVL and CC volume ($r=-0.35$, $p=0.005$) and between aBVL and TH volume ($r=-0.28$, $p=0.027$).
Conclusions: In the investigated patient cohort low CC or TH volume at baseline was associated with a higher degree of aBVL. This finding needs to be confirmed in a bigger and independent patient cohort. If confirmed this finding might be useful to stratify patients with a single baseline MRI scan into groups of patients with high and low risk of future brain atrophy.

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P1045

The effect of dimethyl fumarate on cerebral gray matter atrophy in multiple sclerosis

S. Dupuy, S. Tauhid, S. Hurwitz, R. Chu, F. Yousuf, R. Bakshi
Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Objective: To compare the amount of cerebral gray matter (GM) atrophy over one year in patients starting dimethyl fumarate (DMF) for multiple sclerosis (MS) to patients on no disease modifying treatment (noDMT).
Background: DMF is an established therapy for relapsing-remitting (RR) MS. Although the clinical and conventional MRI treatment effects of DMF are known, the effect on GM damage has not been studied.
Design / Methods: We retrospectively analyzed 20 RRMS patients who had recently started DMF [age (mean±SD) 46.1±10.2 years, Expanded Disability Status Scale (EDSS) score 1.1±1.2, timed 25-foot walk (T25FW) 4.6±0.8 seconds, disease duration (DD) 12.4±8.0 years] and 8 patients on noDMT [age 42.5±6.6 years, EDSS score 1.7±1.1, T25FW 4.4±0.6 seconds, DD 6.7±6.8 years]. Baseline and one year high-resolution 3D T1-weighted sequences from 3T MRI were applied to automated pipelines to assess percent whole brain volume change (PBVC, SIENA), and deep gray matter (DGM) atrophy (FSL-FIRST). MRI differences were assessed by analysis of covariance with time between scans as a covariate.
Results: During the one year observation period, the DMF group showed a lower mean PBVC than the noDMT group (-0.37±0.49% vs. -1.04±0.67%, $p< 0.05$). In addition, the DMF group had smaller putamen volume changes (-0.06±0.22 ml vs. -0.32±0.28 ml, $p< 0.05$). There were no differences between groups in caudate, globus pallidus, thalamus, total DGM volume, EDSS, or T25FW on-study change (all $p>0.05$).
Conclusions: These results suggest that a treatment effect of DMF on GM atrophy can be detected as early as one year after starting therapy. However, due to the non-randomized comparison, retrospective study design, and small sample size, these results require confirmation in future studies.

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P1046

Utility of the central vein sign to diagnose multiple sclerosis; A comparison of 3T T2* and FLAIR-SWI

M. Clarke[1,2], A.P.R. Samaraweera[3], O. Mougin[4], M. South[5], R.A. Dineen[6], P.S. Morgan[7], N. Evangelou[3]
[1]Clinical Neurology, Nottingham University Hospitals NHS Trust, [2]School of Psychology, [3]Division of Clinical Neuroscience, School of Medicine, [4]Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, [5]School of Medicine, [6]Radiological Sciences, [7]Medical Physics, Nottingham University Hospitals NHS Trust, University of Nottingham, Nottingham, United Kingdom

Background: White matter lesion (WML) central veins seen on MRI may be a useful imaging biomarker for the diagnosis of multiple sclerosis (MS). Various T2*-weighted sequences, including susceptibility weighted imaging (SWI) have been proposed to best delineate WMLs and central veins, but quantitative comparisons are lacking. Identifying a subset of WMLs with central veins will also ease clinical translation.
Objectives: We assessed the accuracy of diagnosis of MS and ischaemic small vessel disease (SVD) when using T2* and a fusion of fluid attenuated inversion recovery (FLAIR) and SWI (FLAIR-SWI) at 3T.
Method: 23 patients with RRMS and 16 with SVD were scanned on a 3T Philips Achieva MR scanner. T2*-weighted imaging with a high EPI factor and FLAIR imaging were acquired for each patient. SWI was produced by combination of the phase mask and magnitude images. FLAIR-SWI was produced by a fusion of FLAIR and SWI. Two blinded raters made a diagnosis of MS or SVD based only on counting a subset of WMLs with central veins using T2* and then FLAIR-SWI. Each rater repeated the process 1 week later. Only the presence of WML central veins was used in the radiological diagnosis of MS. Cohen´s kappa (κ) was used to determine a level of agreement of the radiological diagnosis based on the central vein sign and the actual clinical diagnosis. Sensitivities and specificities were calculated.
Results: Both raters, without any access to clinical details had good agreements with the clinical diagnosis irrespective of the vein imaging sequence. Rater 1 at two separate time points; (T2* κ=0.79 and 0.84) and (FLAIR-SWI κ=0.79 and 0.73), sensitivity = 91.3% and specificity ranging from 87.5-93.8% with T2* and 81.3 - 87.5% with FLAIR-SWI. Rater 2 at two separate time points; (T2* κ=0.65 and 0.73) and (FLAIR-SWI κ=0.61 and 0.84), sensitivity = up to 91.3% and specificity ranging from 81.3-100% with T2* and 93.8-100% with FLAIR-SWI.
Conclusions: T2* is just as effective as FLAIR-SWI when making a diagnosis of MS using the central vein sign. Good-very good agreements with the actual diagnosis were achieved with both sequences. This may aid translation of the central vein sign, especially for smaller hospitals that may not have the expertise to produce FLAIR-SWI.

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P1047

Longitudinal changes in structural cortical networks in early PPMS

C. Tur[1], A. Eshaghi[1,2], Z. Khaleeli[1], D.R. Altmann[1,3], F. Prados[1,4], T. Charalambous[1], J.D. Clayden[5], S. Ourselin[4], C.A.M. Gandini Wheeler-Kingshott[1,6,7], D.H. Miller[1], A.J. Thompson[1], A.T. Toosy[1], O. Ciccarelli[1]

[1]Queen Square MS Centre, University College of London, UCL Institute of Neurology, [2]Centre for Medical Image Computing (CMIC), Department of Computer Science, UCL, [3]Medical Statistics Department, London School of Hygiene and Tropical Medicine, University of London, [4]Translational Imaging Group, CMIC, UCL, [5]Institute of Child Health, University of London, London, United Kingdom, [6]Brain MRI 3T Research Center, C. Mondino National Neurological Institute, [7]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

Introduction: Structural cortical networks (SCN) are defined by the co-variance between cortical thicknesses (CT) of different brain areas: a strong statistical correlation between CT of 2 areas may indicate an underlying functional/structural connection between them. Abnormal patterns of SCN may relate to irreversible accrual of disability in MS. Their role in early progressive MS is unknown.
Aims: 1) To estimate SCN metrics and evaluate their changes over time in early primary progressive MS (PPMS)
2) To assess SCN metrics in PPMS with fast clinical progression
Methods: PPMS patients within 5 years of symptom onset and a group of healthy controls (HC) underwent regular clinical and brain MRI assessments for 5 years (1.5T, axial proton-density and 3DT1-weighted). An EDSS increase > 0.2/year (i.e. median in the whole group) was considered as fast progression.

At each time point (TP) we obtained brain CT values (100 areas) using GIF segmentation. These were transformed into a) centred; b) centred and lesion load-adjusted CT values. Both types of CT values were used (separately) to obtain pairwise correlation matrices at each TP. Matrices were binarised (0=no connection/1=connection) according to different thresholds, and from these we obtained SCN metrics: a) connectivity: number of connections/total number of possible connections; b) mean nodal degree: network average of number of connections of that each brain area has. Logistic/linear regression models (using nonparametric bootstrap) assessed changes in SCN metrics over time.
Results: We included 31 PPMS patients and 15 HC. At baseline, HC and PPMS showed similar SCN metrics. Over time, PPMS patients showed a subtle but consistent increase in SCN connectivity as well as an increase in nodal degree ($p < 0.05$ for some thresholds; $p < 0.1$ for others), whereas HC did not change. A greater increase in connectivity and mean nodal degree ($p < 0.05$ for both) was also observed in PPMS patients with faster clinical progression than in those with slow progression, especially after adjusting for lesion load.
Conclusions: Patients with PPMS, especially those with faster progression, show an abnormal increase in structural cortical connectivity over time independent of visible inflammation, suggesting an increasing similarity across brain cortical thicknesses over time. This could be explained by a faster thinning of cortical regions with a thicker cortex, possibly with deleterious clinical consequences.

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P1048

Treatment with interferon reduces the appearance of lesions in clinically relevant white matter tracts in patients with clinically isolated syndrome

M. Battaglini[1], H. Vrenken[2], R. Tappa Brocci[1], G. Gentile[1], L. Luchetti[1], A. Versteeg[2], M.S. Freedman[3], B. Uitdehaag[4], L. Kappos[5], G. Comi[6], F. Barkhof[2], N. De Stefano[1]
[1]Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy, [2]Department of Radiology, VU University Medical Center, Amsterdam, The Netherlands, [3]University of Ottawa, Ottawa, ON, Canada, [4]VU University Medical Center, Amsterdam, The Netherlands, [5]Department of Neurology and Biomedicine, Univerisity Hospital Basel, Basel, Switzerland, [6]Department of Neurology, Scientific Institute H. San Raffaele, University Vita-Salute, Milano, Italy

Background: Studies have shown that lesion location in clinically relevant brain regions is of paramount importance for the prognosis of patients with clinically isolated syndrome (CIS) and for their conversion to multiple sclerosis (MS).
Objective: To assess whether treatment with subcutaneous (sc) interferon (IFN) β-1a can reduce lesion appearance in specific clinically relevant brain regions.
Methods: MRI data of REFLEX, a study comparing two dosing frequencies of sc IFN β-1a and placebo in CIS patients, were used in a exploratory analysis. We created lesion probability maps (LPMs) of the baseline scan and of the of new/enlarging lesions present at the 2-year follow-up scan in CIS patients i) who were

treated either with placebo (n=134) or sc IFN β-1a (n=273) ii) who converted (n=305) and did not convert to MS (n=102) during the study. The LPMs of the different patient groups were compared for lesion location and frequency of lesion occurrence. Voxelwise analyses were performed with a nonparametric permutation-based approach ($p < 0.05$, cluster-corrected).

Results: At baseline LPM, the overall distribution of lesions across the white matter (WM) was similar between placebo and treated patients (ratio: 0.99) and the two groups did not show significant differences in lesion frequency. Over the follow-up, the LPM showed an overall distribution of new/enlarging lesions across the WM similar between the placebo and treated patients (ratio: 0.95). However, the treated patient group showed lower new/enlarging lesion frequency ($p< 0.05$) than the placebo group in the anterior thalamic radiation (ATR), superior longitudinal fasciculus (SLF), cortical spinal tract (CST) and inferior longitudinal fasciculus. In contrast, LPMs did no show significant differences between placebo and treated groups in new/enlarging lesion frequency in usually involved WM tracts such as forceps major and minor. When the LPMs of the patients converting and non-converting to MS were considered, the proportion of WM occupied by new/enlarging lesions was more than tenfold (14.6) higher in converting than in non-converting LPM. Significant clusters of new/enlarging lesion frequency were found in the converting group, when compared to the non-converting group, in ATR and CST.

Conclusions: Treatment with sc IFN β-1a significantly reduces lesion appearance in specific, clinically relevant brain locations. These regions seem to be involved in the conversion from CIS to MS.

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P1049

Inter-scanner MRI variability of multiple sclerosis lesion and tissue volumes in the NAIMS cooperative

R.(. Shinohara[1], P.A. Calabresi[2], C. Davatzikos[3], J. Doshi[3], R.G. Henry[4], G. Kim[5], K.A. Linn[3], G. Nair[6], J. Oh[7], N. Papinutto[4], D.L. Pham[6], D.S. Reich[6], W. Rooney[8], S. Roy[6], N.L. Sicotte[9], W. Stern[4], S. Tummala[5], F. Yousuf[5], A. Zhu[4], R. Bakshi[5], NAIMS Cooperative

[1]Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, [2]Johns Hopkins University, Baltimore, MD, [3]University of Pennsylvania, Philadelphia, PA, [4]UCSF, San Francisco, CA, [5]Brigham and Women's Hospital, Boston, MA, [6]NIH, Washington, DC, United States, [7]University of Toronto, Toronto, ON, Canada, [8]Oregon Health & Science University, Portland, OR, [9]Cedars-Sinai Medical Center, Los Angeles, CA, United States

Background: MRI is an established tool to measure cerebral lesion and tissue compartment volumes in multiple sclerosis (MS) multicenter studies. Unfortunately, differences in acquisition methods have the potential to bias MRI metrics. The North American Imaging in Multiple Sclerosis (NAIMS) cooperative was established to accelerate the pace of imaging research, in part by creating harmonized MRI protocols across sites.

Objectives: This pilot study tested the feasibility of multi-site standardization of MRI acquisition for the quantification of lesion and tissue volumes. We compared intra- and inter-site scan-rescan variability.

Methods: We implemented a standardized high-resolution 3T MRI scan protocol of the brain, and performed scan-rescan pairs on a single subject with relapsing-remitting MS, at seven NAIMS sites using Siemens 3T MRI instruments. Scans included 3D FLAIR, MPRAGE, and T2 sequences. MRI processing included native space manual quantification of T1 hypointense and FLAIR hyperintense lesion volumes (LV), and the application of a variety of automated pipelines, which yielded total LV and measures of global and regional brain atrophy. Statistical analyses assessed accuracy and variability of output MRI metrics across sites, as well as systematic site biases in the manual and automated volumetric measurements that remained.

Results: Average manually delineated LV were 18.0mL (sd 1.3mL) on FLAIR and 14.6mL (1.0mL) on T1. Systematic biases due to site differences in lesion measurements were statistically significant ($p< 0.01$ for both FLAIR and T1 LV), with site explaining more than 90% of the variation in manually measured LV. Site also explained more than 80% of the variation in most automated volumetric measurements of the caudate (mean=5.1mL ± sd= 0.1mL), putamen (8.8mL ± 0.3mL), thalamus (13.3mL ± 0.7mL),

normal-appearing white matter (380mL ± 7.3mL), and total gray matter (768mL ± 15mL). Automated pipelines provided differing coefficients of variation for the volumes, with multi-atlas label fusion techniques generally exhibiting the least noise.
Conclusions: Even after careful protocol harmonization with a single MRI manufacturer, in this multi-center study, we observed systematic differences that resulted in major biases in volumetric analyses. New statistical methods for correcting these systematic biases are necessary, especially for studies in which patient populations may differ across sites.
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P1050

Analysis of atrophy, focal lesions and Virchow Robin spaces of the basal ganglia by phase sensitive inversion recovery discloses associations with physical and cognitive disability in multiple sclerosis

A. Favaretto[1], S. Pravato[1], A. Riccardi[1], A. Lazzarotto[1], M. Margoni[1], D. Poggiali[1], M. Anglani[2], D. Seppi[1], P. Gallo[1]
[1]The Multiple Sclerosis Centre - Veneto Region (CeSMuV), Department of Neurosciences, [2]Neuroradiology Unit, University Hospital of Padova, Italy., University of Padova, Padova, Italy

Background: Basal ganglia (BG) atrophy was suggested to play a role in determining cognitive impairment and fatigue in multiple sclerosis (MS). Nevertheless, no data are available in literature about the impact of focal lesions (FL) and Virchow Robin Spaces (VRS) in determining BG atrophy and their role in clinical and cognitive decline. Phase Sensitive Inversion Recovery (PSIR), a MRI sequence with a high signal-to-noise ratio, may help to inspect FL and VRS in the BG of MS patients.
Aim of the study: We compared T1, FLAIR and PSIR for the detection of VRS and FL in the BG of MS patients, in order to analyse possible correlations between BG volume, FL/VRS in this site and clinical, cognitive and fatigue parameters.
Methods: 43 MS patients [21 clinically isolated syndrome (CIS)/early relapsing-remitting (eRRMS), 15 RRMS, 7 progressive (PMS)], and 9 normal controls (NC) were studied. 3DT1, 3DFLAIR and 2DPSIR images were obtained with a 3T MRI and analysed in parallel. BG volume was calculated by means of Freesurfer, while VRS and lesion number/volume/site with manual segmentation (ITKSNAP). All patients underwent clinical (EDSS), cognitive (Rao's BRB, DKEFS) and fatigue (FSS) assessment.
Results: BG volume, estimated on T1 images, did not differ prior to and after the subtraction of FL and VRS volume. Significantly higher VRS number and volume in the BG of all patient groups were demonstrated by PSIR compared to both T1 and FLAIR ($p< 0.001$). VRS number and volume were lower in NC ($p< 0.05$) and significantly increased in MS with disease duration (PMS>RRMS>CIS/eRRMS)($p< 0.05$). BG FL volume calculated on PSIR images was higher compared to that obtained on T1 and FLAIR ($p< 0.05$). PMS showed a higher number of BG FL compared to both CIS/eRRMS and RRMS ($p< 0.05$) while the number of BG FL was significantly higher in males than in females ($p< 0.05$). Moreover the number and volume of BG FL correlated with the pyramidal EDSS score ($r=0.58$). Interestingly, a negative correlation was observed between FL number and volume in thalamus ($r=-0.56$) and SDMT score, while the number and volume of FL in the BG correlated with DKEFS-SRz test ($r=0.6$). Finally, the volume of thalamus inversely correlated with FSS scores ($r=-0.57$).
Discussion: PSIR proved to be superior to both T1 and FLAIR in evaluating FL and VRS number and/or volume in BG. The analysis of BG pathology, by means of three MRI sequences, showed correlations with both physical and cognitive disability in MS.

Disclosure

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P1051

The relationship of grey and white matter abnormalities with distance from the surface of the brain in multiple sclerosis

M. Pardini[1,2], C.H. Sudre[3,4], F. Prados[2,4], Ö. Yaldizli[2,5], V. Sethi[2], N. Muhlert[6], R.S. Samson[2], S.H.P. van de Pavert[2], M.J. Cardoso[3,4], S. Ourselin[3,4], C.A. Gandini Wheeler-Kingshott[2,7,8], D.H. Miller[2,9], D.T. Chard[2,9]
[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy, [2]Queen Square MS Centre, University College of

London, UCL Institute of Neurology, [3]Translational Imaging Group, Centre for Medical Image Computing (CMIC), Department of Medical Physics and Bioengineering, University College London, [4]Dementia Research Centre, UCL Institute of Neurology, London, United Kingdom, [5]Department of Neurology, University Hospital Basel, Basel, Switzerland, [6]School of Psychology and Cardiff University Brain Research Imaging Centre, Cardiff University, Cardiff, United Kingdom, [7]Brain MRI 3T Center, C. Mondino National Neurological Institute, [8]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy, [9]National Institute for Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre, London, United Kingdom

Background: Multiple sclerosis (MS) can affect any part of the brain, but it does not do so uniformly. Histopathological and imaging studies have shown that demyelinating lesions in white matter (WM) and grey matter (GM) tend to occur close to the inner (periventricular) and outer (subpial) surfaces of the brain, and in GM neuronal loss is also greater towards the outside of the brain. Using high-resolution magnetisation transfer ratio (MTR) imaging, consistent with this we found a gradient in cortical GM abnormality, and more recently a similar gradient normal-appearing (NA) WM abnormality around the lateral ventricles.
Objective: To determine whether or not the association between proximity to the inner (ventricular and aqueductal) and outer (pial) surfaces of the brain and the distribution of WM and GM MTR abnormalities, and white matter (WM) lesions, is similar throughout the brain.
Methods: Sixty-seven people with relapse-onset MS and 30 healthy controls were included in the study. Volumetric T1-weighted images and high-resolution (1 mm^3) MTR images were acquired. These images were co-registered, and the T1-weighted images segmented into 12 bands between the inner and outer surfaces of the brain. The first and last bands were discarded to limit partial volume effects with cerebrospinal fluid. Mean MTR values were computed for each bands in supra-tentorial and cerebellar NAWM, brainstem NA tissue, and cortical and deep GM. Proportion of each band occupied by WM lesions was also measured.
Results: In supra-tentorial and cerebellar NAWM, brainstem NA and in deep and cortical GM, proximity to the ventricular and pial surfaces was associated with progressively lower MTR values in the MS group compared with controls. The density of WM lesions was associated with proximity to the ventricles only in the supratentorial compartment, and no link was found with distance from the pial surfaces.
Conclusions: In MS, MTR abnormalities in WM and GM are consistently related to distance from the inner and outer surfaces of the brain, and this suggests that there is a common factor underlying their spatial distribution. A similar pattern was not found for WM lesions, raising the possibility that different factors promote their formation.

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P1052

Measurement of volume of subcortical structures in multiple sclerosis: agreement between 2D and 3D T1-weighted images

À. Vidal-Jordana[1], D. Pareto[2], J. Sastre-Garriga[1], C. Auger[2], E. Ciampi[1], X. Montalban[1], Á. Rovira[2]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, [2]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, Bar elona, Spain

Background: Grey matter (GM) pathology is known to occur in multiple sclerosis (MS) and it is related to disease outcomes. FIRST, a model-based segmentation tool, has been developed for measuring subcortical GM in 3-dimensional (3D) gradient-echo (GE) T1w images. Unfortunately, most historical MS cohorts with long-term follow-up do not have 3D-GE but 2-dimensional (2D) spin-echo (SE) T1w images.
Objective: We aimed to evaluate if volume of subcortical structures measured with FIRST could be reliably measured in 2D-SE images as compared to the same measures obtained with 3D-GE images, and to investigate the strength and direction of clinical-radiological correlations.
Methods: Thirty-eight patients with MS and 2D-SE and 3D-GE T1w images obtained at the same time were included in the analysis. FIRST was used to obtain volumes of subcortical structures in all 2D and 3D images. To assess reliability, the intraclass correlation coefficient (ICC) between these two measures was calculated. ICC measures were classified as: slight (0.01 to 0.20), fair (0.21 to 0.40), moderate (0.41 to 0.60), substantial (0.61 to 0.80), and almost perfect agreement (0.81 to 1.0). Total intracranial volume (TIV) was calculated by obtaining the matrix determinant of each scan (using the *avscale* utility of FSL) and applying the following formula: (FIRST template volume / matrix determinant) x 1000. Normalized subcortical volume was then calculated to study clinical-radiological associations with Pearson correlation coefficient.
Results: Measurement of subcortical volumes showed good agreement between 2D-SE and 3D-GE images, with 68.8% of the

structures having either a substantial or an almost perfect agreement. The highest ICCs values included relevant structures for MS patients such as thalamus, caudate, and brainstem. Disease duration and EDSS showed a significant moderate correlation with most of the normalized subcortical structures measured with 3D-GE images, but almost all correlations were non-significant if measures from 2D-SE images were used; probably due to the poor agreement of TIV between both images (ICC 0.175)

Conclusion: Measuring volume of subcortical structures with FIRST in 2D-SE images seems to produce reliable results that could be used in longitudinal studies; however, if normalized subcortical volumes measures are to be used in transversal correlations with clinical data, use of 2D-SE images should not be recommended, probably due to the TIV estimation procedure

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P1053

Toward a standardized advanced imaging protocol for multiple sclerosis: inter- and intra-site variability in multiband diffusion measurements acquired by NAIMS

D.L. Schwartz[1], I. Tagge[1], R. Bakshi[2], G. Nair[3], P. Calabresi[4], T. Constable[5], J. Grinstead[6], R. Henry[7], J. Oh[8], N. Papinutto[7], D. Pelletier[9], D.S. Reich[3], N. Sicotte[9], W. Stern[7], J. Simon[1], W. Rooney[1]

[1]OHSU, Portland, OR, [2]Harvard Medical School, Boston, MA, [3]National Institute of Neurological Disease and Stroke, National Institute of Health, Bethesda, [4]Johns Hopkins University, Baltimore, MD, [5]Yale, New Haven, CT, [6]Siemens Medical Solutions, USA, Portland, OR, [7]UCSF, San Francisco, CA, United States, [8]University of Toronto, Toronto, ON, Canada, [9]University of Southern California, Keck School of Medicine, Los Angeles, CA, United States

Introduction: The North American Imaging in Multiple Sclerosis (NAIMS) Cooperative was formed with the goal of developing sensitive and reliable imaging surrogates for disease progression in MS to accelerate research and treatment trials. A standardized quantitative protocol which is sensitive and tailored for MS pathology will expedite data collection across multiple sites.

Methods: A single subject with clinically stable relapsing-remitting MS travelled to 7 North American sites and underwent two identical 3 Tesla MRI sessions at each site. Informed consent was obtained at each site. Multiband (MB=2) 65 direction 2.2mm isotropic whole brain diffusion-weighted imaging (DWI, [b=0,1000,2000 s/mm^2]) data were acquired in 5.6 min. Lesion and contralateral normal appearing white matter (NAWM)-seeded tractography and juxtacortical tensor measurements were taken for each site and session and compared to one another (Student's t). Intrasite (Pearson's r), and intersite (intraclass correlation coefficient [ICC]) agreement was also calculated. Signal-to-noise ratios (SNR) were computed on a single region in b=0 volumes.

Results: Imaging sessions were completed at all sites between Oct. 2015 and Feb. 2016. SNR varied 22.5% across all sites and sessions. Variations in slice orientation, resolution, b-values, and gradient directions were observed. Measurements in NAWM were in intrasite (fractional anisotropy [FA] /λ_{II}/mean diffusivity [MD] $r_{(33)}$=0.94/0.97/0.96) and intersite agreement (ICC =0.904). Measurements in the largest lesion (2385 mL) and in a symmetric NAWM region were different (FA/λ_{II}/MD $t_{(13)}$=-35.2/23.1/23.5), and were in intrasite (FA/λ_{II}/MD $r_{(12)}$=0.96/0.99/0.99) and intersite agreement (ICC=0.914). Seeded tractography exhibited NAWM>lesion differences in crosscallosal, longitudinal fasciculus, and superior dorsal cortical fiber bundles in all sessions and at all sites.

Discussion: Multiband DWI yielded sensitive and reliable measures in NAWM and an MS lesion across all sessions and sites. Tensor measurements were in agreement across session and sites, though differences in acquisition technique remain. Tractography was readily performed and seeded bundles from a lesion and mirrored NAWM exhibit qualitative differences in projections outside the region, suggesting that the sequence is sensitive to perilesional diffusion effects. The sequence is powered, sensitive, and reliable for the study of MS pathology across multiple sites.

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P1054

Grey matter and Corpus Callosum atrophy is associated with disability increase in natalizumab treated patients: a longitudinal three-year study using FreeSurfer

E. Ciampi[1,2], D. Pareto[3], J. Sastre-Garriga[1], À. Vidal-Jordana[1], C. Tur[1,4], J. Río[1], M. Tintoré[1], C. Auger[3], Á. Rovira[3], X. Montalban[1]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, Spain, [2]Neurology Department, Hospital Clínico Universidad Católica de Chile, Santiago de Chile, Chile, [3]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, Barcelona, Spain, [4]MS Queen Square Centre, National Hospital for Neurology and Neurosurgery, London, United Kingdom

Background: Brain volume loss (BVL) is a key outcome in MS trials. Natalizumab is highly effective on inflammation with moderate impact on atrophy. FreeSurfer is a set of automated tools for reconstruction of the brain´s cortical surface from structural MRI data and for the study of cortical and subcortical anatomy.
Objective: To explore longitudinal BVL using FreeSurfer in patients receiving natalizumab for at least 3 years.
Methods: We performed longitudinal FreeSurfer analysis in a consecutive cohort of patients receiving natalizumab 300 mg IV every 4 weeks uninterruptedly for 3 years, with three-monthly EDSS and yearly MRI using 3D-T1 weighted images. Cortical and Subcortical Grey Matter (GM) volumes, Corpus Callosum (CC) volume and Cortical Thickness (CTh) were assessed. Clinical and radiological correlations of interest were evaluated, with an emphasis on disability accrual.
Results: Thirty-eight (38) patients were included, 23 women, mean age 36.8 years, mean disease duration 10.3 years, median EDSS 4.0 and 47% had gadolinium enhancement at baseline. First year analysis showed significant volume loss in CC (p=0.002), total GM (p=0.02), subcortical GM (p< 0.001), thalamus (p=0.04), brainstem (p< 0.001), and cerebellum (p< 0.001), and cortical thinning in the left insula (p=0.02). In the second year, significant volume loss occurs in CC (p=0.03), thalamus (p=0.003), hippocampus (p=0.03) and cerebellum (p=0.04). During the third year, only a significant decrease within the cerebellar cortical volume was found (p=0.02). Six patients (15.8%) experienced confirmed EDSS worsening sustained up until the 36 month follow-up time-point, and these patients had smaller baseline left thalamus (0.395 vs 0.443, p=0.037) and corpus callosum volume (0.023 vs 0.038, p=0.014), and evolved with larger volume loss during the first year in left pallidum (-12.5% vs -4.4%, p=0.055), bilateral cortical (-3.18% vs -0.19%, p=0.014), and total GM volume (-3.0% vs -0.51%, p=0.019), and larger bilateral mean CTh decrease during the first year (-2.18% vs 0.01%, p=0.049). No influence of gadolinium enhancing lesions at baseline was observed in any of the FreeSurfer derived parameters at any time-point.
Conclusion: BVL develops mainly during the first year of natalizumab therapy. GM and CC changes are independent of baseline inflammation and correlate with disability

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MT has received compensation for consulting services and speaking honoraria from Bayer-Schering, Merck-Serono, Biogen-Idec, Teva, Sanofi-Aventis, Roche and Novartis
CA has nothing to disclose around the present work
AR serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, and on the editorial board of the American Journal of Neuroradiology and Neuroradiology, has received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, Stendhal, Novartis and Biogen Idec, and has research agreements with Siemens AG
XM has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi-Genzyme and Teva Pharmaceutical

P1055

MSmetrix validation of normative brain volume population graphs to serve as a reference in the clinical follow up of MS patients

D.M. Sima, S. Jain, A. Maertens, E. Van Vlierberghe, W. Van Hecke, D. Smeets
Icometrix, Leuven, Belgium

Introduction: Whole brain (WB) and grey matter (GM) volume decrease faster in MS patients compared to a healthy population. In order to provide a reference for a patient's brain volume at a certain time, the brain volume can be compared against volumes of a healthy population. MSmetrix is an MRI-based brain segmentation tool that provides WB and GM volumes, including a comparison against an age and sex matched population. After normalization for head size, the result is a normative percentile. In this work, the stability and thus the usability in clinical practice of the healthy population graphs used in MSmetrix are validated.
Materials and methods: Data included in the population graphs consists of 1281 healthy subjects (761 females, 520 males; ages 18-96) retrieved from publicly available MRI collections. A leave-one-out approach is used, where each subject is consecutively removed from the population and placed onto an independently computed population graph, obtained from the remaining subjects. Normalized WB and GM volumes computed by MSmetrix are used for constructing three different population graphs, based on the female, male and all datasets, respectively. Validation experiments are designed to test the stability of the population graph for each

possible combination: WB or GM for female, male, or all datasets. For each of the combinations, the separated subjects' brain volume is compared to the remaining population to construct a sample of percentiles. A Kolmogorov-Smirnov test was performed to evaluate whether the sample of percentiles computed through this leave-one-out process spans the interval (0, 100) uniformly.

Results: For all population graphs (WB or GM; female, male, or all), the cumulative distribution of the percentiles and true uniform distribution are very close, with a maximum distance below 0.03, and all p-values for the Kolmogorov-Smirnov goodness-of-fit test in the range 0.82 - 0.99. Therefore there is no evidence, at 0.1 significance level (p-value < 0.1), to reject the hypothesis that the percentiles of the leave-one-out subjects would not be uniformly distributed.

Conclusion: The validation experiments indicate that the computation of the population graph is stable, for both normalized WB and normalized GM, as well as for the three types of population graphs (female, male, all). This means the population graphs are a reliable reference for brain volume measurements, which is useful in the clinical follow up of MS patients.

Disclosure

Diana M. Sima: employee of icometrix
Saurabh Jain: employee of icometrix
Anke Maertens: employee of icometrix
Eline Van Vlierberghe: employee of icometrix
Wim Van Hecke: shareholder of icometrix
Dirk Smeets: employee of icometrix

P1056

Structural cortical networks in optic neuritis (early CIS)

C. Tur[1], A. Eshaghi[1,2], T.M. Jenkins[1], D.R. Altmann[1,3], F. Prados[1,4], T. Charalambous[1], J.D. Clayden[5], S. Ourselin[4], C.A.M. Gandini Wheeler-Kingshott[1,6,7], D.H. Miller[1], A.J. Thompson[1], O. Ciccarelli[1], A.T. Toosy[1]

[1]Queen Square MS Centre, University College of London, UCL Institute of Neurology, [2]Centre for Medical Image Computing (CMIC), Department of Computer Science, UCL, [3]Medical Statistics Department, London School of Hygiene and Tropical Medicine, University of London, [4]Translational Imaging Group, CMIC, UCL, [5]Institute of Child Health, University of London, London, United Kingdom, [6]Brain MRI 3T Research Center, C. Mondino National Neurological Institute, [7]Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy

Introduction: Structural cortical networks (SCN) are defined by the co-variance between cortical thicknesses (CT) of different brain areas: a strong statistical correlation between CT of 2 areas may indicate an underlying functional/structural connection between them. SCN may provide complementary information to other connectivity techniques, which often require MRI sequences not readily available in clinical practice. So far in early relapse-onset MS, the role of SCN has not been investigated.

Aim: To estimate SCN parameters after a first episode of optic neuritis (ON)

Methods: Patients within four weeks of acute ON and age-matched healthy controls (HC) underwent clinical and brain MRI assessments (1.5T, axial proton-density [PD, 0.9x0.9x5mm^3] and 3DT1-weighted [1.2x1.2x1.2mm^3]).

We obtained brain cortical thickness (CT) values (100 areas) using GIF segmentation for all subjects. All CT values were transformed into a) centred; b) lesion load-adjusted CT values. Both types of CT values were used (separately) to obtain between-area correlation matrices, which were then binarised according to different thresholds (0.3-0.9). Binary matrices were considered as numerical representations of networks: nodes represented brain areas; edges indicated presence of connection between 2 areas. For each network we obtained: i) connectivity: number of edges/total number of possible edges; ii) mean nodal degree: network average of number of edges emerging from each node. Logistic or linear regression models assessed differences in SCN parameters between groups (cross-sectional analysis). We used bias-corrected nonparametric bootstrap (BS) (1,000 replicates) to obtain p-values.

Results: Eighteen patients and 8 HC were included. At the time of ON, patients showed lower connectivity than HC (e.g. threshold 0.3: 0.415 [BS 95% Confidence Interval: 0.41-0.42] vs. 0.55 [BS 95%CI 0.54-0.56]), and lower mean network degree (42.05 [BS 95%CI 41.90-42.96] vs. 54.9 [BS 95%CI 54.1-56.5]). These differences were maintained after adjusting for lesion load.

Conclusions: In very early clinically isolated syndrome, as we see in this early demyelinating cohort, overall structural cortical connectivity seems to be reduced compared with healthy controls, suggesting loss of structural integrity. The mechanism for these differences is independent of the effects of white matter lesions, pointing towards a primary neurodegenerative process to be investigated with further studies.

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P1057

Cross-sectional and longitudinal myelin water fraction differences in the brainstems of MS and NMOSD cohorts compared to healthy control subjects

L.E. Lee[1], A. Combes[1,2], K. McMullen[1], R. Carruthers[1], D.K.B. Li[3], J. Palace[4], L. Matthews[4], A.L. Traboulsee[1], S.H. Kolind[1,3]
[1]Department of Medicine, University of British Columbia, Vancouver, BC, Canada, [2]Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom, [3]Department of Radiology, University of British Columbia, Vancouver, BC, Canada, [4]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

Background: Myelin water fraction (MWF) can be used as an in-vivo marker of myelin in demyelinating diseases such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). A recent study showed that MWF measurements in normal appearing cervical cord tissue were lower in relapsing-remitting MS (RRMS) and NMOSD cohorts compared to healthy controls. Furthermore, MWF decreased over one year in RRMS but not in NMOSD or controls. We investigated the MWF reduction patterns in the normal appearing brainstem tissue of the same populations.
Objective: To determine if the patterns of MWF differences observed in normal appearing cervical cord tissue are also demonstrated in non-lesional brainstem regions of the same RRMS and NMOSD cohorts at baseline and over one year.
Methods: Multi-component driven equilibrium single pulse observation of T1/T2 (mcDESPOT) data were acquired in 11 RRMS patients (mean age: 42 (range: 28-62)), 7 anti-aquaporin-4 seropositive NMOSD patients (48 (27-76)), and 13 age-matched healthy controls (49 (26-76)), using a 3T scanner with 1.7x1.7x1.7 mm voxels at baseline and at 12 months. Images were registered using FSL-FLIRT. The brainstem regions of interest (ROIs) including medulla, midbrain and pons were manually drawn on three slices per scan, excluding any lesions. Mean MWF was calculated within each ROI. Parametric statistics were used to compare cohorts at baseline and over one year.
Results: CROSS-SECTIONAL: There was no significant difference in normal appearing brainstem MWF between controls (medulla MWF at baseline = 0.17 ± 0.02), RRMS (0.16 ± 0.02) and NMOSD (0.17 ± 0.01). Similar results were seen for midbrain and pons. LONGITUDINAL: There was no significant difference in normal appearing brainstem MWF changes over one year between controls (medulla one-year percentage change in MWF = 2.83% ± 8.30%), RRMS (-1.59% ± 7.78%) and NMOSD (-0.74% ± 7.09%).
Conclusion: In contrast to myelin differences seen in the normal appearing cervical spinal cords in the same cohorts, similar differences were not detectable in the brainstem. This suggests that pathological changes occurring in the spinal cord are at least partially independent of brain and brainstem changes.

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Investigation of microscopic tissue changes in multiple sclerosis: a sodium (^{23}Na) MRI study

P. Eisele[1], S. Konstandin[2,3], M. Griebe[1], K. Szabo[1], M.E. Wolf[1], A. Alonso[1], C.J. Schwarzbach[1], A. Ebert[1], C. Roßmanith[1], C. Weiß[4], M. Ong[5], S.O. Schoenberg[5], L.R. Schad[3], A. Gass[1]
[1]Department of Neurology, Universitätsmedizin Mannheim, University of Heidelberg, Mannheim, [2]MR-Imaging and Spectroscopy, Faculty 01 (Physics/Electrical Engineering), University of Bremen, Bremen, [3]Computer Assisted Clinical Medicine, Universitätsmedizin Mannheim, University of Heidelberg, [4]Department for Statistical Analysis, [5]Institute of Clinical Radiology and Nuclear Medicine, Universitätsmedizin Mannheim, University of Heidelberg, Mannheim, Germany

Background: Conventional magnetic resonance imaging (MRI) is currently the most applied biomarker in multiple sclerosis (MS),

but not all MRI parameters correlate with clinical impairment. Microscopic tissue damage causing diffuse axonal damage seems to play a major pathogenetic role in MS. Recent studies using sodium (^{23}Na) imaging suggested that increased total sodium concentrations (TSC) are likely to reflect neuroaxonal damage leading to disease progression and disability.

Objective: To detect and quantify different degrees of disease-related tissue changes in the microstructure outside macroscopically visible lesions using a multiparametric MRI protocol.

Methods: We performed ^{23}Na, ^{1}H and diffusion MRI in 14 healthy controls (HC), 18 patients with a clinically isolated syndrome (CIS), 47 patients with early relapsing-remitting multiple sclerosis (RRMS, < 5 years disease duration), 20 patients with advanced RRMS and 10 patients with secondary progressive multiple sclerosis (SPMS).

Results: Normal appearing grey and white matter (GM, WM) TSC were significantly higher in advanced RRMS (GM: 46.7 ± 3.1 mM, WM: 40.5 ± 2.7 mM) and SPMS (GM: 52.5 ± 5.4, WM: 46.2 ± 5.0) vs. HC (GM: 40.1 ± 3.3, WM: 34.9 ± 2.4), CIS (GM: 41.5 ± 2.7, WM: 35.6 ± 2.2) and early RRMS (GM: 43.8 ± 2.5, WM: 38.1 ± 2.6). Total brain volume (TBV) and grey matter volume (GMV) and white matter (WMV) was significantly lower in advanced RRMS (TBV: 1396 ± 68 ml; GMV: 706 ± 44 ml; WMV: 690 ± 34 ml) and SPMS (TBV: 1352 ± 69; GMV: 684 ± 38; WMV: 668 ± 37) vs. HC (TBV: 1477 ± 52; GMV: 744 ± 28; WMV: 732 ± 37), CIS (TBV: 1472 ± 67, GMV: 748 ± 41; WMV: 724 ± 34) and early RRMS (TBV: 1454 ± 56; GMV: 748 ± 35; WMV: 706 ± 33). Apparent diffusion coefficients of the NAWM were significantly higher in SPMS (0.79 ± 0.07 x 10^{-3} mm/s^2) vs. HC (0.66 ± 0.04), CIS (0.71 ± 0.04) and early RRMS (0.72 ± 0.06, $p < 0.05$). Strong correlations between MRI parameters and EDSS were observed for TBV and TSC of the NAGM and NAWM.

Conclusion: TSC increase, loss of TBV, GMV, WMV and increased diffusion were already present in patients with CIS and progress in later stages of MS and SPMS. The loss of TBV, GMV, WMV and increase of TSC in NAGM and NAWM showed strong correlation with EDSS suggesting that these parameters are highly sensitive to irreversible tissue damage. Our findings indicate that increased sodium tissue concentrations are closely reflecting tissue damage in MS.

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P1059

Individual mapping of neuronal damage in early relapsing-remitting MS using [^{11}C]Flumazenil PET

E. Poirion[1,2], B. Bodini[1], M. Battaglini[3], T. Soulier[1], L. Freeman[4], D. Lorenzo-Garcia[1], G. Bera[5], A. Vignaud[2], M. Bottlaender[6], B. Stankoff[1,5]

[1]Institut du cerveau et de la moelle epiniere (ICM), Sorbonne Universités, UPMC Univ Paris 06, UMR S 1127/CNRS UMR 7225, Paris, [2]CEA/DRF/I2BM/Neurospin/UNIRS, Gif-sur-Yvettes, France, [3]Department of Neurological and Behavioural Sciances, Siena, Italy, [4]Department of Neurology, University of Texas Health Science Center, Houston, TX, United States, [5]AP-HP, Hopital Saint-Antoine and Hopital Pitié-Salpêtrière, Paris, [6]CEA/DRF/I2BM/Neurospin/UNIACT, Gif-sur-Yvettes, France

Introduction: Grey matter damage has been identified as the major pathological mechanisms responsible disability progression in MS. The underlying substrate of grey matter (GM) damage is complex, and includes cortical demyelination, inflammation, synapse and dendrite loss, and neuronal cell death. The neuronal component of GM damage has not yet been selectively assessed at the earliest stage of disease. Positron emission tomography (PET) with [^{11}C]Flumazenil (FMZ) has been proposed as a promising biomarker for measuring the neuronal component of GM pathology in-vivo. The aim of this study is to assess neuronal damage using [^{11}C]FMZ PET at the earliest phase of relapsing-remitting MS, and to extract individual cortical maps of neuronal pathology.

Methods: Nine patients with early relapsing-remitting MS underwent a full neurological evaluation and, along with five age- and gender-matched healthy controls, a [^{11}C]FMZ PET and conventional MRI. [^{11}C]FMZ binding was estimated using the partial saturation protocol providing voxel-wise absolute quantification of Bmax, reflecting $GABA_A$ receptor concentration. Cortical voxels with a significant neuronal damage were identified based on voxel-based analysis of Bmax between patients and controls. Individual maps of pathological voxels were extracted for each patient and the percentage of abnormal voxels over the whole cortical volume was calculated. The Spearman´s rank coefficient was used to investigate the correlation between the extent of neuronal damage and T2-w lesion load.

Results: In the MS group, mean disease duration was 1.3 years (± 1.2) and mean EDSS was 0.56 (± 0.9). A global cortical analysis showed a non-significant decrease in mean cortical Bmax in patients (105±7 pmol/ml) compared to controls (112±10 pmol/ml). Overall 13% ± 4% of cortical voxels were identified as pathological in patients, with large individual variations (5-20%) and variable cortical localizations. A significant correlation was found between the extent of neurodegeneration and T2 lesion load ($p=0.02$, rho=0.6).

Conclusions: [^{11}C]FMZ PEt allows to generate individual maps of neuronal damage in early relapsing-remitting MS. The longitudinal follow-up will establish whether these maps of early neuronal damage have the potential to provide prognostic indices and predict further patterns of cortical atrophy.

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P1060

Individual remyelination profiles in cortical grey matter and in white matter lesions: a combined PET and MTR study

B. Bodini[1,2], E. Poirion[1], M. Battaglini[3], M. Veronese[4], C. Lubetzki[1,2], M. Bottlaender[5], N. De Stefano[3], F. Turkheimer[4], B. Stankoff[1,6]
[1]Institut du cerveau et de la moelle epiniere (ICM), Sorbonne Universités, UPMC Univ Paris 06, UMR S 1127/CNRS UMR 7225, [2]APHP - Pitié-Salpêtrière Hospital, Paris, France, [3]Department of Neurological and Behavioural Sciences, University of Siena, Siena, Italy, [4]Department of Neuroimaging, Institute of Psychiatry, King's College London, London, United Kingdom, [5]CEA/DRF/I2BM/Neurospin/UNIACT, Gif-sur-Yvettes, [6]APHP - St. Antoine Hospital, Paris, France

Introduction: We have shown that [11C]PIB positron emission tomography (PET) allowed the quantification of myelin dynamics in lesional white matter (WM) in patients with MS. Reduced magnetization transfer ratio (MTR) has been associated with decreased myelin content in cortical grey matter (GM). The aim of this study is to explore for the first time *in-vivo* cortical remyelination using MTR, investigating its relationship with WM myelin repair, measured with PET, and its clinical relevance.
Methods: Patients with relapsing-remitting MS (n=16) were clinically assessed, and along with healthy controls (HC,n=8), underwent a longitudinal protocol which included [11C]PIB PET and MT imaging. Voxel-wise maps of [11C]PIB binding, reflecting myelin content, were generated, and an index of WM remyelination was derived for each patient. Voxel-wise cortical maps of significantly decreased MTR in patients compared with HC were employed to identify cortical demyelinated areas in each patient at baseline. The percent volume of cortical demyelinated regions recovering normal MTR values at the second time-point was defined for each patient as the index of cortical remyelination, which reflected the individual potential of cortical myelin repair. The Spearman´s rank coefficient was used to investigate the correlation between the index of remyelination in the cortex and in the WM, and between the index of cortical remyelination and clinical scores.
Results: At baseline, the volume of demyelinated cortical regions ranged between 15% and 27% of total cortical volume. During follow-up, a high between-patient variability was found for the index of cortical remyelination, which ranged from 12% to 28% of the baseline demyelinated cortical volume across the cohort. The index of cortical remyelination significantly correlated with the index of WM remyelination (p=0.01,rho=0.61). There was a strong, inverse correlation between the index of cortical remyelination and both the Expanded Disability Status Scale (p=0.001,rho=-0.74) and the MS Severity Scale (p=0.001,rho=-0.73).
Conclusions: Longitudinal GM MTR may allow to measure individual profiles of cortical remyelination, which significantly correlates with the WM remyelination index measured with [11C]PIB PET, and with clinical scores. A combined approach of WM PET and GM MTR should be considered to stratify patients according to their global remyelination potential and to measure the effects of novel promyelinating drugs.

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P1061

Toward a standardized quantitative imaging protocol for multiple sclerosis: inter- and intra-site variability in multiband rsfMRI measurements acquired by NAIMS

D.L. Schwartz[1], I. Tagge[1], R. Bakshi[2], G. Nair[3], P. Calabresi[4], J. Grinstead[5], R. Henry[6], J. Oh[7], N. Papinutto[6], T. Constable[8], W. Stern[6], J. Simon[1], D. Pelletier[9], D.S. Reich[3], N. Sicotte[9], W. Rooney[1]
[1]OHSU, Portland, OR, [2]Harvard Medical School, Boston, MA, [3]National Institute of Neurological Disease and Stroke, National Institute of Health, Bethesda, [4]Johns Hopkins University, Baltimore, MD, [5]Siemens Medical Solutions, USA, Portland, OR, [6]UCSF, San Francisco, CA, United States, [7]University of Toronto, Toronto, ON, Canada, [8]Yale, New Haven, CT, [9]University of Southern California, Keck School of Medicine, Los Angeles, CA, United States

Introduction: The North American Imaging in Multiple Sclerosis (NAIMS) Cooperative was formed with the goal of developing sensitive and reliable imaging-based surrogates for disease progression in MS. A standardized quantitative imaging protocol which is sensitive and tailored to MS pathology will facilitate more rapid data collection across multiple sites.

Methods: A subject with clinically stable relapsing-remitting MS travelled to seven North American sites and underwent two distinct 3 Tesla MRI sessions at each site. Informed consent was obtained at each site. Whole brain resting state fMRI (rsFMRI) was acquired in 4:28 min (repetition time=1s, 256 volumes, multiband=4, 2.0mm isotropic). A network of five automated regions of interest were placed in left/right inferior parietal lobule (L/RIPL), left/right middle frontal gyrus (L/RMFG), and bilateral posterior cingulate gyrus (BiPCC), and preprocessed time courses were transformed to correlation matrices and converted to Fisher's z. Intrasite (Pearson's r) and intersite (intraclass correlation coefficient [ICC]) measures of agreement were calculated over region-to-region correlation scores.
Results: Imaging sessions were completed between October 2015 and February 2016. Spatial signal-to-noise ratios (SNR) across six sites (one site was an outlier) and sessions varied 24%. Temporal SNR varied 412% over seven sites. Slice orientation was the most notable acquisition difference between sites. Motion decreased between the first and second sessions at six out of seven sites. Intrasite correlation measurements across the network were in agreement at each site ($r_{(8)}$=0.65-0.98, median Fisher's z=1.472); however, intersite agreement was poor to moderate (ICC =0.402).
Discussion: The multiband rsFMRI protocol yielded high inter-regional correlations within each session, and high reproducibility within each site. However, intersite agreement was very poor and site-specific measures inversely correlated with temporal and spatial SNR, suggesting a role for noise in between-site variance. The degree of motion correction was variable between sites and motion may be the cause of temporal noise. Despite intersite variance, measurements taken with this sequence yielded consistent pairwise correlations relative to one another in the network. Relative or mean-centered correlation measures within a network and within scan may be more reliable than absolute measures of network correlation when using multisite data.

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P1062

Grey matter atrophy in the fronto-striato-thalamo-cortical circuit and in the insula play a role in the pathophysiology of fatigue in multiple sclerosis

M. Palotai[1], A. Nazeri[1,2], M. Cavallari[1], B.C. Healy[3,4], B. Glanz[3], T. Chitnis[3], C.R.G. Guttmann[1]
[1]Center for Neurological Imaging, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, [2]Division of Graduate Medical Sciences, Boston University, [3]Partners Multiple Sclerosis Center, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, [4]Biostatistics Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

Background: Fatigue is a highly prevalent, debilitating symptom in multiple sclerosis (MS), yet its multifactorial pathogenesis is not well understood. Several studies point to the involvement of the frontal cortex-striatum-thalamus (FCST) pathway, but, these findings were not consistently reproducible by other groups.
Objectives: To assess if FCST and other grey matter (GM) structures are associated with longitudinal patterns of fatigue, namely reversible (RF) versus sustained fatigue (SF).
Methods: MS patients enrolled in our CLIMB prospective cohort were grouped based on their longitudinal Modified Fatigue Impact Scale (MFIS) scores: 1. SF: MFIS⩾38 at the two most recent yearly assessments; 2. RF: MFIS< 38 at last assessment, but presence of at least one previous MFIS⩾38; 3. Never Fatigued (NF): at least five MFIS< 38. Accordingly, we selected 98 patients (30 SF, 31 RF, 37 NF; age-range:29-66, female/male:76/22, Extended Disability Status Scale (EDSS)⩽6; 13 patients with secondary progressive MS and 85 with relapsing remitting in remission). Disability and depression were assessed using the EDSS and the Center for Epidemiologic Studies Depression Scale (CES-D), respectively. 3 Tesla T1-weighted MRI were used for voxel based morphometry (VBM) on the pooled 98 patients to survey for GM atrophy associated with fatigue, controlling for age, sex and EDSS (family-wise error (FWE) corrected p-value< 0.05). Group-wise volumetric comparison was performed on deep GM structures identified by VBM after automated segmentation, controlling for age, sex, EDSS and CES-D score (Bonferroni-corrected p-value< 0.0055).
Results: *VBM showed significant inverse relation between the MFIS cognitive subscale and the volume of the bilateral fronto-medial (FMC) and fronto-orbital cortices, anterior striata, thalami, temporal poles, insulae and left lateral occipital cortex*

(peak FWE-p value of 0.021); and between the total MFIS and its physical subscale with the volume of the bilateral frontal poles, and FMC (peak FWE-p value of 0.033 and 0.043 respectively). Volumetric analysis showed significant atrophy in the putamen (RF < NF p< 0.0004; SF< NF p< 0.0009) and thalamus (RF< NF p< 0.0005), but not in the caudate.

Conclusions: Beyond the role of FSCT, the insula may also be involved in the pathogenesis of fatigue. Cognitive and physical MFIS were associated with different GM atrophy patterns. Moreover, GM atrophy is associated with fatigue irrespective of its temporal course.

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P1063

Central vein sign in Susac´s Syndrome and Multiple Sclerosis at 7T

D. Ontaneda, S.-H. Oh, R. Rennebohm, M. Lowe, D. Conway
Cleveland Clinic, Cleveland, OH, United States

Introduction: Susac's syndrome (SS) is an autoimmune, microendotheliopathy affecting the retina, cochlea, and cerebrum. It is characterized clinically by branch retinal artery occlusion, encephalopathy, and hearing loss. Brain MRI shows characteristic white matter lesions with predilection for the central corpus callosum. Multiple sclerosis is a chronic demyelinating disease for which SS is a common differential diagnosis. Biomarkers to differentiate these two conditions are needed, and central vein sign identification has been proposed as a potentially useful non-invasive method for discrimination.

Methods: After IRB approval, 3 patients with relapsing remitting multiple sclerosis and 3 patients with SS were enrolled into a cross-sectional imaging study. Ultra high field MRI at 7T was acquired for all patients. 7T MRI sequences included 3D MP2RAGE (0.75 mm3 isotropic voxel, flip angle = 4° and 5°, TI1/TI2 = 700/2600 ms), 3D FLAIR (1mm3 isotropic voxel), 2D GRE T2* (0.38 x 0.39 x 1.5 mm3, flip angle = 20°), 3D SWI (0.49 x 0.49 x 0.8 mm3, flip angle = 20°). White matter lesions where identified on T2 FLAIR images measuring greater than 3 mm and then examined on GRE and SWI sequences for identification of a central vein. A determination of central vein presence was made when a central area of GRE/SWI hypo-intensity, as a thin line (when imaged across the long axis) or dot (when imaged across the short axis) were seen. Proportions were derived for presence/absence of a central vein in each group. Fisher's exact test was used to compare the proportion of central veins in the multiple sclerosis and SS groups.

Results: A total of 105 lesions were identified in MS subjects. Central veins were identified in 85 (81%) of MS lesions. No central vein was identified in 18 lesions (17.1%), and 2 lesions (1.9%) were excluded due to uncertainty regarding central vein presence. A total of 22 lesions were detected in the SS patients, with only 1 lesion showing a central vein (4.5%). The proportion of central vein lesions was statistically higher in multiple sclerosis as compared to SS (Fisher's exact test $p < 0.0001$). One SS lesion demonstrated a peri-lesional rim of GRE hypo-intensity.

Conclusion: The central vein sign at 7T is a viable measure to differentiate MS and SS. As described in prior studies, the majority of MS lesions demonstrate a central vein. The presence of a rim of GRE/SWI hypo-intensity should be explored further as a diagnostic marker of SS.

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P1064

Asymptomatic spinal cord lesions do not predict long term disability in patients with CIS or early MS

I. Dekker[1,2], M.H. Sombekke[1], B.I. Witte[3], J.J.G. Geurts[4], F. Barkhof[2], B.M.J. Uitdehaag[1], J. Killestein[1], M.P. Wattjes[2]
[1]Neurology, Neuroscience Amsterdam, VUmc MS Center Amsterdam, [2]Radiology & Nuclear medicine, Neuroscience Amsterdam, VUmc MS Center Amsterdam, [3]Epidemiology and Biostatistics, [4]Anatomy & Neuroscience, Neuroscience Amsterdam, VUmc MS Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

Background: Asymptomatic spinal cord (SC) lesions are frequently present in patients with a clinically isolated syndrome (CIS) or relapsing remitting multiple sclerosis (RRMS). The presence of asymptomatic spinal cord lesions predicts conversion to clinically definite multiple sclerosis (CDMS). Whether spinal cord abnormalities also predict future disability is less well established.

Objective: To determine the prognostic value of asymptomatic SC lesions in CIS and early relapsing remitting MS with respect to the development of long term disability.

Methods: Shortly after diagnosis of CIS or RRMS, clinical and imaging data (brain and spinal cord MRI) were collected in a well-documented prospective patient cohort. Patients were clinically and radiologically followed-up for 27 to 175 months (median 71 months). Expanded Disability Status Scale (EDSS) scores were measured by certified raters. Based on the presence of SC

symptoms and SC lesions on the baseline MRI, patients were grouped into four groups: 1. Asymptomatic SC lesions, 2. Symptomatic SC lesions, 3. No SC lesions but SC symptoms, 4. No SC lesions nor SC symptoms. Kaplan-Meier curves with log-rank tests were used to analyze time to reach EDSS of 3 or 6.
Results: 204 patients from the Amsterdam Multiple Sclerosis Cohort were included (46 patients with asymptomatic SC lesions, 97 patients with symptomatic SC lesions, 24 patients without SC lesions, but reporting SC symptoms, 37 patients without SC symptoms or lesions). EDSS of 3 was reached by 81 patients (39.7%) after a median of 25 months (IQR 9 - 47). Only 11 patients (5.4%) reached an EDSS of 6.
Conclusion: Asymptomatic SC lesions did not predict disability progression in patients recently diagnosed with CIS or early RRMS.

Disclosure

MHS BIW JJGG do not report any competing interests.
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BMJU has received consultancy fees from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche and Teva.
FB serves as a consultant for Bayer-Schering Pharma, Sanofi-Aventis, Biogen, Teva, Novartis, Roche, Synthon BV, Genzyme and Jansen Research.
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The effect of fingolimod on cerebral gray matter atrophy in multiple sclerosis

F. Yousuf, S. Dupuy, S. Tauhid, R. Chu, G. Kim, S. Tummala, T. Chitnis, B.C. Healy, R. Bakshi
Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Background: Cerebral gray matter (GM) atrophy occurs early in the disease process and has shown high clinical relevance in patients with multiple sclerosis (MS). Fingolimod is an established disease modifying therapy for MS with known effects on limiting clinical and conventional MRI worsening. However, the effect of fingolimod on GM involvement has not been determined.
Objective: To retrospectively compare the rate of GM atrophy over two years in relapsing forms of MS in patients starting fingolimod therapy vs. those untreated.
Methods: In the group starting fingolimod (n=24), patients had a baseline age (mean±SD) 41.2±11.6 years, disease duration (DD) 13.6±7.2 years, and Expanded Disability Status Scale (EDSS) score 1.1±1.4; 58% women. Untreated patients (n=29) had an age 45.7±8.4 years, DD 12.6±9.6 years and EDSS score of 1.0±1.2; 93% women. Baseline, year 1 and year 2 brain MRI was applied to an SPM12 pipeline to assess brain parenchymal fraction (BPF) and cortical gray matter fraction (cGMF). The change over time in subjects was modeled using a mixed effects linear regression model with a random slope and fixed effects for time, group and the time by group interaction. The difference in the slope between the groups was assessed using the interaction term.
Results: Regarding within group changes over two years, cGMF remained stable in the fingolimod group ($p>0.05$) and decreased in the untreated group ($p< 0.001$). The difference change between groups over two years was highly significant ($p< 0.001$), and was dominated by differences in the second year of observation. BPF did not show any differences between groups for any of the comparisons (all $p>0.05$).
Conclusion: These results suggest that a treatment effect of fingolimod on GM atrophy can be detected two years after starting therapy. GM atrophy is more sensitive to treatment effects than whole brain atrophy. However, due to the non-randomized comparison, retrospective study design, and small sample size, these results require confirmation in future studies.

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P1066

Cortical lesions dynamics in multiple sclerosis at 7T MRI: A longitudinal study

C.A. Treaba[1,2], T. Granberg[1,2,3], E. Herranz[1,2], R. Ouellette[1,2], C. Louapre[1,2], R.P. Kinkel[4], J.A. Sloane[5], C. Mainero[1,2]
[1]Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, [2]Harvard Medical School, Cambridge, MA, United States, [3]Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden, [4]Department of Neurosciences, University of California, San Diego, CA, [5]Department of Neurology, Beth Israel Deaconess Medical Center, Boston, MA, United States

Background: Cortical lesions (CL) are a main determinant of disease progression in multiple sclerosis (MS). Seven Tesla (7T) T2* gradient-echo imaging has shown increased *in vivo* visualization of focal CL in MS, confirmed pathologically to correspond to cortical areas with the greatest degree of demyelination.
Objective: To assess, using ultra-high field MRI, the dynamic of CL appearance and evolution in a heterogenous MS cohort.
Methods: This prospective study used 7T T2* two-dimensional gradient echo images (0.33x0.33x1.00 mm^3 resolution) in 27 consecutive MS cases, 19 with relapsing remitting MS (RRMS, disease duration: 6.2±6.4 years, median EDSS 2, range 1-2.5) and 8 with secondary progressive MS (SPMS, disease duration: 20.6±10.1 years, median EDSS 5, range 3-6), to characterize *in vivo* the appearance and evolution of MS lesions on two occasions at least 1 year apart. The presence of CL was noted by consensus of two observers, lesions were classified as intra-cortical (ICL) and leuko-cortical (LCL, extending across cortex and white matter,

WM) and their annual percent volume change was calculated. Changes in WM lesions volume were also assessed. Any change in lesion classification at follow-up was taken into account.
Results: The rate of accumulation of new ICL over a mean of 1.6 (range 1-5.5) years was higher in SPMS (mean 4.6, range 1-16) than in RRMS (mean 1.1, range 1-3) patients (Mann-Whitney p=0.005) and was accompanied by the highest annual percent volume change (SPMS: 38.3%±68.9 RRMS: 14.3%±18.8). LCL accumulation rate was also higher in SPMS (mean 3.2, range 0-16) than in RRMS (mean 0.3, range 0-5). Among new LCL, 82% occurred *de novo*, while the rest seemed to evolve from previous either IC or WM lesions. Nevertheless, overall, LCL showed only a slight annual percent volume change (all MS: 8.4%±45.8). All CL seen at baseline remained visible at follow-up. Changes in CL counts or volume did not correlate with the changes in WM lesion volume (WM gross annual percent volume change reached 9.3%±22.0), and were generally greater than WM lesions changes.
Conclusions: Cortical lesion pathology seems to be different both in terms of new lesions formation and volume change and favors the intra- over the leuko-cortical location. CL formation was more common in SPMS than in RRMS patients. The rate of CL accumulation at ultra-high field MRI, relative to previous studies, increases by 2.8 (compared to 3T) and 5 (compared to 1.5T).

Disclosure

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P1067

The impact of brain atrophy on cognitive deficit in multiple sclerosis

E. Tóth[1], P. Faragó[1], A. Király[1], D. Sandi[1], K. Bencsik[1], Z.T. Kincses[1], L. Vécsei[1,2]
[1]Department of Neurology, Albert Szent-Györgyi Clinical Center, University of Szeged, [2]Neuroscience Research Group, Hungarian Academy of Sciences and University of Szeged, Szeged, Hungary

Introduction: Atrophy of the cortical and subcortical gray matter is known to be an important biomarker of multiple sclerosis. However the contribution of the atrophy to various cognitive functions is not completely understood yet. In our investigation we aimed to identify the brain structural correlations of cognitive functions as measured by Brief International Cognitive Assessment for MS (BICAMS).
Method: Fifthy-three MS patients were scanned on a 1.5 T GE scanner. High resolution T1 weighted and FLAIR images were acquired. Lesions were segmented manually on the FLAIR image. Gross gray, white matter and brain parenchymal fractions were estimated by SIENAX. Subcortical segmentation and volumetry were carried out by FIRST. The contribution of these MRI structural parameters (volume of the subcortical structures and total brain, gray matter and white matter volume) to cognitive dysfunction in the various tests was evaluated by stepwise regression analysis. The contribution of localized gray matter atrophy to cognitive dysfunction was evaluated with voxel-based morphometry (VBM).
Results: The lesion load did not correlate with the performance on any of the three tests. The VBM analysis indicated that performance on the brief visuospatial memory test (BVMT) and symbol digit modality test (SDMT) correlated with the gray matter density of the bilateral thalami, caudate nuclei, hippocampus, amygdalae, insulae, intraparietal sulcus and posterior cingulate. In case of the California verbal learning test (CVLT) test performance correlated with the gray matter density in the bilateral thalamus, caudate nucleus, hippocampus, calcarine sulcus. The regression analysis showed that the SDMT was most defined by the volume of the left caudate nucleus ($R=0.32$; $p< 0.019$). The volume of the right hippocampus influenced most the performance on the BVMT ($R=0.335$; $p< 0.014$). In case of the CVLT the volume of the right hippocampus was the most significant determinant ($R=0.403$; $p< 0.003$).
Conclusion: Our results indicate that the cognitive performance on various cognitive domains is defined by a common pattern of the subcortical gray matter atrophy. These structural MRI parameters are more significantly related to cognitive functions than the frequently measured brain parenchymal fractions or lesion load.

Disclosure

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The authors declare that they have no conflict of interest.

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Longitudinal quantitative T2* imaging at 7T reveals progression of microstructural damage in cortical lesions

R. Ouellette[1,2], T. Granberg[1,2,3], E. Herranz[1,2], C.A. Treaba[1,2], S.T. Govindarajan[1,2], C. Giannì[1,2], C. Louapre[1,2], R.P. Kinkel[4], C. Mainero[1,2]
[1]Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, [2]Harvard Medical School, Cambridge, MA, United States, [3]Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, Sweden, [4]Department of Neurosciences, University of California, San Diego, San Diego, CA, United States

Background: Quantitative T2* (q-T2*) imaging using ultra-high field MRI is sensitive to microstructural MS pathology, reflecting demyelination and iron loss. The longitudinal dynamics of these changes and their clinical relevance have yet to be studied.
Objective: To longitudinally study, in a heterogeneous MS cohort, 7T q-T2* changes in different types of cortical lesions and in normal appearing cortical grey matter (NACGM)
Methods: Eleven MS patients (1 CIS, 7 RRMS, 3 SPMS; age 42±11 years; disease duration 13±8 years; median EDSS 2.5, range 1-4.5) and 7 age-matched healthy participants (38±8 years) underwent longitudinal (mean follow-up time 1.5±0.1 years) 7T multi-echo T2* imaging (12 echoes, 0.33x0.33x1.0 mm^3) for

manual segmentation of intracortical lesions (ICL) and leukocortical lesions (LCL) and for obtaining cortical q-T2* maps. 3T MEMPR scans (0.9 mm isotropic) were used for cortical surface reconstruction using FreeSurfer. Longitudinal q-T2* changes in cortical lesions and NACGM were assessed using paired t-test.

Results: Cortical lesions were found at baseline in all patients, (ICL in 10 and LCL in 7). The mean global cortical lesion volume at baseline was 1944±2995 mm^3, range 93-9894 mm^3, where the mean ICL lesion volume was 699±821, range 0-2737, mm^3 and mean LCL lesion volume 1245±2254, 0-7157 mm^3. The annual lesion accumulation rate was 10.5±15% for ICL and 0.78±14.2% for LCL. q-T2* increased in cortical lesions at follow up (39.0±6.9 vs. 40.8±5.7 ms, p=0.04), attributed to the increases in both LCL q-T2* (44.2±8.2 vs. 48.1±7.4 ms, p=0.02), and ICL (40.8±5.7 vs. 44.1±5.4 ms, p=0.04). There was a slight but not significant q-T2* increase in the NACGM (33.9±1.8 vs. 36.3±5.3 ms, p=0.09).

Conclusions: Cortical lesions, including both ICL and LCL, are characterized by progressive increases in q-T2* suggesting that destructive pathology (myelin and iron loss) might prevail over remyelination processes. These findings suggest that q-T2* is a sensitive method to quantify the underlying microstructural pathology in MS.

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P1069

Neuroinflammation and cortical demyelination in multiple sclerosis and their contribution to cognition: a ^{11}C-PBR28 MR-PET and quantitative 7T imaging study

E. Herranz[1], C. Louapre[1], S. Govindarajan[2], C.A. Treaba[1], C. Gianni[1], R. Ouellette[2], T. Granberg[1,3], G. Mangeat[2,4], J. Sloane[5], E.C. Klawiter[1], R.P. Kinkel[6], C. Mainero[1]

[1]Massachusetts General Hospital, Harvard Medical School, [2]Massachusetts General Hospital, Boston, MA, United States, [3]Intervention and Technology, Karolinska Institute, Stockholm, Sweden, [4]Institute of Biomedical Engineering, Polytechnique Montreal, Montreal, QC, Canada, [5]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, [6]University of California San Diego, San Diego, CA, United States

Background: Cortical demyelination contributes to cognitive decline in multiple sclerosis (MS), but the underlying pathophysiological mechanisms are still unknown. Histopathological examinations suggested that cortical demyelination in MS might develop following meningeal inflammation accompanied by cortical microglia activation.

Aim: To assess, using quantitative T2* (q-T2*) at 7T and ^{11}C-PBR28 MR-PET: 1) whether MS cortical demyelination is characterized by the presence of microglial pathology 2) the relative contribution of cortical demyelination and cortical microglia activation to decreased information processing speed.

Methods: Sixteen MS patients (mean age: 50 ± 10 years) and 12 age- and translocator protein affinity binding matched healthy controls (HC) underwent ^{11}C-PBR28 MR-PET. Anatomical MR scans were acquired for FreeSurfer cortical surface reconstruction. Normalized 60-90 minute standardized uptake value (SUVR) maps (1.25 mm isotropic voxels) were registered to cortical surfaces and sampled at 50% depth from the pial surface. Subjects also underwent multi-echo T2* imaging at 7T (0.33x0.33x1 mm^3) for intracortical laminar assessment of q-T2* at 25%, 50% and 75% depth from the pial surface. A general linear model was used to assess vertex-wise in the cortex i) differences between MS and HC in q-T2* at each cortical depth ii) the relationship, in MS, between Symbol Digit Modalities Test (SDMT) and cortical q-T2* at all 3 depths and ^{11}C-PBR28 at 50% depth. Finally, in clusters showing significant q-T2* differences in MS vs HC, the corresponding ^{11}C-PBR28 SUVR were extracted and compared between the groups using multi-linear regression. Age and PBR affinity were included as nuisance regressors ($p< 0.05$ corrected for multiple comparison).

Results: MS patients showed relative to HC several cortical clusters of increased q-T2* (indicative of myelin and iron loss) in juxtameningeal cortical layers (25% depth) and deeper cortical laminae (50%, 75% depth). Clusters with increased q-T2* in patients also had significantly higher ^{11}C-PBR28 SUVR relative to HC ($p< 0.05$). In patients, increase in cortical q-T2* at 25%, 50% and 75% depth and in cortical ^{11}C-PBR28 SUVR at 50% depth negatively correlated with SDMT scores in widespread frontal, parietal, temporal and occipital regions.

Conclusions: MS cortical demyelination is accompanied by increased microglia activation. Both pathological processes contribute to decreased information processing speed.

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P1070

Heterogeneity in individual patterns of microglial activation in MS measured non-invasively with ^{18}F-DPA-714 PET

B. Bodini[1,2], E. Poirion[1], D. García-Lorenzo[1], M. Battaglini[3], C. Louapre[1,2], G. Bera[1], E. Maillart[2], S. Marquez[1], N. De Stefano[4], M. Bottlaender[5], B. Stankoff[1,6]

[1]Institut du cerveau et de la moelle epiniere (ICM), Sorbonne Universités, UPMC Univ Paris 06, UMR S 1127/CNRS UMR 7225, [2]APHP - Pitié-Salpêtrière Hospital, Paris, [3]Department of Neurological and Behavioural Sciences, University of Siena, Siena, [4]Department of Neurological and Behavioural Sciances, Paris, [5]CEA/DRF/I2BM/Neurospin/UNIACT, Gif-sur-Yvettes, [6]APHP - St. Antoine Hospital, Paris, France

Introduction: Evidence from neuropathological studies suggests that activated microglia, the resident brain innate immune response system, plays a key role in the pathogenesis of MS, particularly in its progressive form. Microglial activation can be measured in-vivo using a second generation positron emission tomography (PET) radiotracer binding to the 18-kDa translocator protein (TSPO), the ^{18}F-DPA-714. The objective of this study is to investigate individual profiles of microglial activation using ^{18}F-DPA-714 PET in different forms of MS.
Methods: Patients with relapsing-remitting (n=7) and progressive MS (n=22), and 17 healthy controls (HC), stratified according to the rs6971 TSPO gene polymorphism, underwent a ^{18}F-DPA-714 PET and conventional MRI. In all subjects, voxel-wise maps of ^{18}F-DPA-714 binding were generated non-invasively, using a supervised procedure for the automatic extraction of a reference region and the application of the Logan graphical method. Voxel-wise maps of differences in tracer binding between TSPO gene polymorphism-matched patients and HC, were employed to identify voxels of increased binding in each subject, reflecting the presence of activated microglia. In each patient, the percent volume of activated microglia (PVAM) over total T2-w lesional, perilesional, normal-appearing white matter (NAWM) and cortical volume, was calculated. In HC, the PVAM was calculated over WM and GM volume. Multiple linear regressions adjusted for age and gender were used to compare the PVAM in the different regions between patients and HC.
Results: In patients, a high heterogeneity was found in the PVAM in T2-w lesions (range=4%-54%), perilesional WM (range=7%-45%), NAWM (range=4%-34%) and in the cortex (range=6%-31%). In patients compared to HC's WM, the PVAM was significantly higher in T2-w lesions (p=0.0001), perilesional WM (p=0.0001), and NAWM (p=0.0001). The PVAM calculated in the cortex was significantly higher in patients than in HC (p=0.001).
Conclusions: ^{18}F-DPA-714 PEt allows a non-invasive measure of individual profiles of activated microglia in MS. Microglial activation was heterogeneous across patients in the different areas of the brain, but was consistently greater in patients compared with HC. This technique will enable a large-scale *in-vivo* exploration of the pathogenic role of microglia in MS, and will allow to clarify whether each disease form could be associated with specific microglial signatures.

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P1071

Restriction Spectrum Imaging and neurological disability in multiple sclerosis

P. Sowa[1,2], H.F. Harbo[2,3], N.S. White[4], E.G. Celius[3,5], H. Bartsch[4], P. Berg-Hansen[2,3], S.M. Moen[3], L.T. Westlye[6,7], O.A. Andreassen[7], A.S. Dale[4,8], M.K. Beyer[1,9]
[1]Dep. of Radiology and Nuclear Medicine, Oslo University Hospital, [2]Institute of Clinical Medicine, University of Oslo, [3]Dep. of Neurology, Oslo University Hospital, Oslo, Norway, [4]Dep. of Radiology, UCSD, San Diego, CA, United States, [5]Institute of Health and Society, [6]Dep. of Psychology, University of Oslo, [7]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway, [8]Dep. of Neuroscience, UCSD, San Diego, CA, United States, [9]Dep. of Life Sciences and Health, Oslo and Akershus University College of Applied Sciences, Oslo, Norway

Background and purpose: Restriction Spectrum Imaging (RSI) is a newly validated magnetic resonance imaging (MRI) technique that enables quantitative estimates of tissue microstructure based on the size and orientation of the diffusion-hindered and restricted water compartments. The technique may enable a detailed characterization of brain tissue but its clinical utility in multiple sclerosis (MS) has not been investigated. The purpose of this study was to determine the relation between diffusion parameters calculated from RSI and neurological disability in patients with MS.
Methods: MRI including the RSI sequence was performed on a 3 Tesla scanner in 82 MS patients (65 females and 17 males, mean age 40.1 ± 10.4 years) at different stages of the disease. Parameter maps representing tubularity index (TI), fractional anisotropy (FA), fast (f-ADC) and slow apparent diffusion coefficient (s-ADC) were calculated from the RSI sequence. Masks of white matter and of white matter lesions (WML) in each patient were created. The parameters were derived from the whole volume of WML and from normal appearing white matter (NAWM). Patients were divided into three subgroups according to their levels of neurological disability as measured by expanded disability status scale (EDSS) score: group 1: no or minimal disability with EDSS< 2.5; group 2: low disability with EDSS of 2.5-3; group 3: substantial disability with EDSS>3.
Results: Compared to MS patients with no or minimal disability, patients with substantial disability had lower FA (p=0.026), higher f-ADC (p=0.004) and higher s-ADC (p< 0.001) in WML. No group differences were found for TI in WML (p=0.576). In NAWM all four tested parameters differed significantly between the EDSS subgroups: patients with substantial disability had lower TI (p=0.018) and FA (p=0.009) and higher f-ADC (p=0.008) and s-ADC (p=0.018) than those with no or minimal disability. There was a significant correlation between TI in NAWM and EDSS (r=-0.4, p< 0.001).
Conclusions: TI differed between the EDSS subgroups and correlated with EDSS only when obtained in NAWM. TI obtained in NAWM varies with disability in a similar way as FA and may be useful for disease monitoring.
Abbreviations
ADC=apparent diffusion coefficient (f-ADC=fast ADC; s-ADC=slow ADC), EDSS=expanded disability status scale, FA=fractional anisotropy, NAWM=normal appearing white matter, RSI=restriction spectrum imaging, TI=tubularity index, WML=white matter lesion

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Cortical surface magnetization transfer ratio decreases in multiple sclerosis are age and region dependent

D.A. Rudko, J. Maranzano, D.L. Arnold, S. Narayanan
McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, QC, Canada

Background: Cortical pathology may be a substrate of worsening clinical symptoms in MS patients. However, the rate at which cortical pathology develops and the brain locations affected are not well known. The goal of this study was to evaluate longitudinal, age-related reductions in cortical surface magnetization transfer ratio (csMTR) of MS patients. Such reductions may be sensitive to sub-pial demyelination occurring over time.
Methods: 25 MS patients and 12 controls, recruited from the MS Clinic of the Montreal Neurological Institute, were imaged using anatomical and magnetization transfer imaging with 3 T MRI. To evaluate longitudinal changes in csMTR, 18 patients and 10 controls were imaged at baseline and at a two-year time point. Cortical surface meshes were generated on the inner, middle and outer cortex. csMTR values were smoothed onto these surfaces. ROIs defined by the Desikan-Killiany cortical atlas were projected onto the three cortical surfaces. Using these ROIs, longitudinal, mixed model analysis was conducted to examine: (i) group-level, age-related decline in csMTR of MS patients relative to controls (ii) age-adjusted group mean differences in csMTR between MS patients and controls.
Results: Reductions in csMTR in MS patients relative to controls were significantly related to age, and were more prevalent in ROIs confined to the outer and mid cortices. Specifically, in ROIs defining the rostral anterior cingulate, paracentral, posterior cingulate and supramarginal gyri and the precuneus, age-related csMTR decreases were found only along the outer/mid cortices. These regions are involved in executive function and processing speed through thalamo-cortical circuits. In affected outer cortical ROIs, there was an average 0.092% MTR units/yr decrease with age. By contrast, along the mid and inner cortices, the corresponding csMTR decreases were 0.039% MTR units/yr and 0.046% MTR units/yr respectively. In the outer caudal anterior cingulate, precentral and postcentral cortices, group mean csMTR differed between MS patients and controls.
Conclusion: Reductions of csMTR in MS patients increase with age, but appear to hit a plateau in regions such as the outer caudal anterior cingulate, precentral and postcentral cortex, known to have high myelin content. We hypothesize that, for these regions, initial demyelination may be more severe, or may have occurred earlier in the disease course, resulting in csMTR values reaching minimum values earlier.

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P1073

Functional brain network organisation is related to cognition and fatigue in MS

T. Welton[1], C.S. Constantinescu[2], D.P. Auer[1], R.A. Dineen[1]
[1]Radiological Sciences, [2]Clinical Neurology, University of Nottingham, Nottingham, United Kingdom

Background: Cognitive impairment and fatigue are some of the most common and impactful symptoms of MS. Graph analysis of brain networks based on magnetic resonance imaging (MRI) data has the potential to provide useful markers of cognitive impairment and fatigue by modelling disruption to brain networks. These markers may be useful in trials to identify effective treatments for those symptoms.
Hypotheses: (1) There will be differences between people with and without MS in summary graph metrics derived from functional MRI (fMRI) data. (2) Cognitive impairment, as measured by the Paced Auditory Serial Addition Task (PASAT), and fatigue, as measured by the Modified Fatigue Impact Scale (MFIS), will be related to summary graph metrics in people with MS.
Methods: 21 people with MS (aged 45±12 years, 81% females) and 10 age- and gender-matched controls (aged 41±13 years, 80% females) underwent cognitive testing and 3-Tesla MRI, including resting-state fMRI which measures blood oxygenation, an indicator of brain activity. Functional connectivity (correlation between fMRI timeseries) was calculated between every pair of the 62 regions in the Harvard-Oxford structural brain atlas. From these data, graphs were constructed and three summary graph metrics (characteristic path length, mean clustering coefficient and small-worldness) were calculated for each subject. Mann-Whitney U-tests were used to compare group means and correlations with cognition and fatigue scores were tested using a Pearson correlation coefficient. A false discovery rate-corrected alpha of .016 was used to control for multiple comparisons.

Results: None of the assessed graph metrics based on fMRI connectivity were significantly different between groups (t=.353, p=727; t=.111, p=.912; t=224, p=824). Amongst the MS patients, cognitive performance positively correlated with small-worldness (r=.502, p=.016) whereas fatigue scores positively correlated with the characteristic path length metric (r=.529, p=.012).
Conclusions: Graph-theoretic brain network metrics may be useful as objective and quantitative markers of cognitive impairment and fatigue in MS. Our findings mirror those from similar studies in other diseases [1]. Future work should test the reliability and responsiveness of these measures, as well as developing a theory for their correct neurobiological interpretation.

References

[1] Stam CJ, 2014. *Nat Rev Neurosci* 15:683-695.

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P1074

Regional brain volume differences in patients with CIS. A voxel- based morphometry study

R. Alyafeai[1], D. Pareto[2], J. Sastre-Garriga[1], À. Vidal-Jordana[1], M. Alberich[2], C. Auger[2], M. Tintoré[1], Á. Rovira[2], X. Montalban[1]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Dept & Epidemiology Dept, [2]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, Barcelona, Spain

Background & aim: Relevant brain atrophy is present in patients with clinically isolated syndromes (CIS), particularly in the thalami and other deep grey matter structures. In this study we aim to further characterize the clinical correlates of regional grey matter damage at CIS presentation and its short-term evolution using voxel-based morphometry (VBM).
Materials and methods: From a longitudinal on-going CIS inception cohort 133 consecutive patients were included. A Brain 3T-MRI at baseline (3 mo.) and follow-up (12 mo.) was acquired. Patients with CIS were classified according to: 1) the number of Barkhof criteria fulfilled at baseline MRI: 0-1-2 Barkhof Low (BL, n=80) or 3-4 Barkhof High (BH, n=34); 2) the presence of oligoclonal bands: OCB+ (n=53) or OCB- (n=47); 3) the initial clinical presentation: Optic Neuritis (ON, n=51) or other CIS topography (OTHER, n=63). Images were segmented and normalized following the established VBM pipelines in SPM8. Transversal and longitudinal comparisons were performed. Changes were considered significant at $p< 0.05$ FWE-corrected level, and an extended threshold of 30 voxels.
Results: 114 patients (66 females) were analyzed (19 patients were excluded mostly due to incomplete or non-standardized MRI protocol, or segmentation errors). Baseline mean age was 33.4 years (SD 7.9) and median EDSS 1.5 (range 0 - 4). The transverse group comparisons showed significant grey matter (GM) atrophy in BH versus BL patients mainly affecting the thalami, while no changes were observed for the other transversal comparisons at baseline. In the longitudinal analysis of the whole cohort (n=114), significant GM losses in the postcentral, cingulate and paracentral giri were observed. The longitudinal analysis in the different subgroups showed significant GM losses in: the cingulate of the BH group; the cingulate, postcentral and supplementary motor area of OCB+ patients, and the lingual occipital area in patients presenting with ON. Longitudinal GM losses were not significant for patients neither in the BL group, OCB- patients nor in patients presenting with OTHER. No areas of increased GM over time were observed for any group.
Conclusion: Patients with multiple sclerosis show significant grey matter losses in specific brain regions already from the CIS stage. Grey matter damage is more significant in patients with other signs of severity (presence of OCB or fulfillment of Barkhof criteria) and is associated with clinical presentation.

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P1075

Dynamic functional connectivity analysis in Multiple Sclerosis

H.H. Kitzler[1], H. Wahl[1], J.C. Eisele[2], T. Ziemssen[2], B. Morton[3], J. Linn[1]
[1]Neuroradiology, [2]Neurology, Technische Universität Dresden, Dresden, Germany, [3]Psychology, University of Western Ontario, London, ON, Canada

Introduction: Multifocal neuroinflammatory and neurodegenerative processes in Multiple Sclerosis (MS) may lead to a functional multiple disconnection syndrome. However, the impact of structural tissue changes on the extent of neurocognitive deficiency is obscured by functional compensation in performance on demand like in test batteries. Task-free functional magnetic resonance imaging (f-MRI) data obtained from the brain at rest may provide an objective quantification of functional restriction. Although easily and quickly to be acquired, resting state f-MRI analysis is still subject to research. We applied a dynamic functional connectivity exploration based on independent component analyses (ICA) on a cohort of clinically definite MS patients.
Methods: Relapsing-remitting MS patients (n = 33; mean age 37.6±11.6; F/M 20/13) were compared with an age and sex matched healthy control group. Imaging data was acquired on a

SIEMENS Verio 3T scanner using EPI-BOLD sequences: TR 2580 ms, TE 30 ms, 180 measurement volumes, 3.5 mm^3 resolution. Functional connectivity (FC) was extracted via ICA within *a priori* known visual (VIS), somatomotor (SM), auditory (AUD), ventral attentional (VA), cognitive control (CC), cerebellar (CB), subcortical (SC), and default mode (DMN) networks. Applying k-means clustering to all FC windows generated dynamic connectivity states.

Results: Different dynamic connectivity states (7) were observed. The frequency, i.e., the proportion of each subject's states and average number of successive time frames residing in a particular state, defined as mean dwell time were registered. This allowed the determination of the *inter transition interval* (ITI), the average length of time residing in any state before transitioning to another and the *number of transitions* (NT), the total number of state transitions that occurred over the whole acquisition. In comparison to healthy controls we found an increased ITI (8.75±2.40, vs. 9.58±2.16; mean±STD) and inversely reduced NT (16.56±4.69, vs. 14.53±4.13) in the MS patients.

Conclusion: This study demonstrates quantifiable brain functional restrictions in MS. This approach provides the potential to serve as a robust quantification and surrogate of neurocognitive deficiency. It is now important to correlate mensurable changes in brain function with the underlying lesion burden of disease or even specific quantitative MRI techniques like myelin imaging.

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All authors: nothing to disclose.

P1076

Cerebellar lesion mapping reveals divergent profiles of white matter involvement between cognitively impairment and cognitively preservation in relapsing remitting multiple sclerosis

S.M. Tobyne[1], W.B. Ochoa[1,2], J.D. Bireley[1], V. Smith[1], J.D. Schmahmann[1], E.C. Klawiter[1]

[1]Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [2]VU University Medical Center, Amsterdam, Department of Anatomy and Neurosciences, Amsterdam, The Netherlands

Objective: To map the probability of cerebellar white matter lesions in relapsing remitting multiple sclerosis (RRMS) and explore the relationship of cerebellar lesion location and volume with cognitive impairment.

Introduction: Motor control, cognitive processing and emotion modulation are topographically organized in the human cerebellum. Cerebellar involvement is common in MS and cerebellar atrophy and lesion volume are associated with cognitive dysfunction, an important cause of disability in MS.

Methods: High-resolution anatomical T1, T2 and FLAIR data were acquired in 36 RRMS subjects (mean age: 41.61 ± 10.52, 27 females; mean disease duration: 8.4±6.47; median EDSS: 2 (1-6.5)) at 3T. Cognitive testing was used to dichotomize subjects into cognitively impaired (CI; N=19) and cognitively preserved (CP; N=17) groups. Hyperintense cerebellar WM lesions were identified on T2 images and resulting lesion maps were normalized to a high-resolution atlas of the cerebellum. A lesion probability map was calculated separately for CI and CP by computing the probability of a lesion occurring within any cerebellar voxel.

Results: CP MS subjects demonstrated a lower lesion load and a more restricted pattern of WM tissue involvement, compared with CI MS subjects. Lesions in the CP group were restricted to the inferior cerebellar peduncle (ICP) while lesions in the CI group exhibited a predilection for the middle cerebellar peduncle (MCP) ($z=2.78$, $p< 0.05$). Working memory performance on the WAIS-IV Digit Span was significantly impaired in patients with lesions of the right middle and superior cerebellar peduncles ($z=3.07$, $p< 0.05$). Impaired performance on the Boston Naming Test, a semantic language task, was related to lesions proximal to left Crus II and lobule VIIb ($z=4.45$, $p< 0.05$) and bilateral ICP ($z=3.36$, $p< 0.05$). Impaired abstract reasoning on the DKEFS was associated with lesions proximal to lobule IV ($z=3.89$), right Crus I ($z=2.38$) and ICP ($z=248.75$).

Conclusion: CI was associated with a distinct pattern of cerebellar lesions that extended into the MCP, compared to CP subjects in whom lesions were primarily restricted to the ICP. Cognitive impairments in CI subjects were in the domains of working memory, semantic processing and abstract reasoning tests, which are known to be involved in the cerebellar cognitive affective syndrome. Cerebellar involvement may significantly contribute to cognitive dysfunction in RRMS.

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P1077

Local subcortical grey matter volume changes and hippocampal white matter atrophy are associated with memory impairment in patients with Multiple Sclerosis

S.D. Broicher[1], O. Geisseler[1], J. German[2], T. Pflugshaupt[3], R.S.C. Amaral[2], M. Linnebank[4], P. Brugger[1], B. Schuknecht[5], S.E. Leh[6]

[1]Neurology, University Hospital Zürich, Zurich, Switzerland, [2]Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada, [3]Centre of Neurology and Neurorehabilitation, State Hospital Lucerne, Lucerne, Switzerland, [4]Department of Neurology, Helios-Klinik Hagen-Ambrock, Hagen, Germany, [5]Medical Radiological Institute, [6]Division of Psychiatry Research and Psychogeriatric Medicine, University of Zurich, Zurich, Switzerland

Background: Cortical grey matter (GM) involvement of the Multiple Sclerosis pathology is now well established. Here we investigated differences between patients with relapsing remitting multiple sclerosis (RRMS) and healthy subjects (HC) in local subcortical GM volume, hippocampal subfields and extra-hippocampal white matter. The relation between structural changes and cognitive functioning was also analysed.

Methods: Recently developed analyses techniques (MAGeT Brain, Chakravarty et al., 2013) were applied to investigate subcortical volumes of the thalamus, basal ganglia and amygdala, and their relation to cognitive functions in forty-eight patients RRMS

and in 48 gender- and education-matched HC. In addition, automated hippocampus segmentation was performed in the same group by using a novel in-vivo atlas of human hippocampal subfields (Pipitone et al., 2014; Winterburn et al., 2013), including the cornu ammonis (CA) areas, the dentate gyrus, strata radiatum/lacunosum/moleculare, subiculum and associated white matter, the alveus, fimbria and fornix (Amaral et al. submitted).

Results: Compared to controls, patients with RRMS showed volume reduction in bilateral thalamus (right t=-6.88, q< .01; left t=-6.60, q< .01), globus pallidus (GP) (right t=-2.68, q< .05; left t=-2.58, q< .05), striatum (right t=-3.70, q< .01; left t=-3.86, q< .01) and right amygdala (t=-3.03, q< .05; all FDR corrected for multiple comparisons). With respect to the hippocampus, bilateral hippocampal white matter as opposed to GM volumes, were smaller in RRMS compared to HC (left fimbria t=-3.49, q< .01; right fimbria t=-4.02, q< .01; right fornix t=-2.92, q< .05). Bilateral atrophy of the fimbria and the CA2/CA3 hippocampal subfield was significantly correlated with verbal and non-verbal memory deficits.

Conclusion: Our results reveal significant volume reductions in several subcortical grey matter areas such as the thalamus, GP, striatum and right amygdala in RRMS compared to HC. We also found region-specific vulnerability of hippocampal white matter to RRMS pathology and identify distinct hippocampal subfield atrophy patterns related to memory impairment. Identifying MR imaging markers of subcortical GM damage may help develop specific neuroprotective treatment strategies. Automated techniques that allow investigation of large data sets can reliably and efficiently help in monitoring and possibly predicting disease progression.

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P1078

Lateral Ventricle Volume change is associated with neurological and cognitive disability in multiple sclerosis: a 5-years follow-up study using an automated lateral ventricle segmentation algorithm

E. Ruberte[1], M. Amann[1,2], Y. Naegelin[2], I.K. Penner[3], M. Pardini[4], J. Kuhle[2], T. Derfuss[2], C. Stippich[2], L. Kappos[2], J. Wuerfel[1], Ö. Yaldizli[2]
[1]Medical Image Analysis Center (MIAC AG), [2]University Hospital Basel, Basel, Switzerland, [3]Universitätsklinikum Düsseldorf, Düsseldorf, Germany, [4]Universita di Genova, Genova, Italy

Background: As pars pro toto, the lateral ventricle volume (LVV) might give an indirect estimate of brain volume (BV). ALVIN (automatic lateral ventricle delineation) is an algorithm that has been primarily validated in Alzheimer's disease and segments the LV from structural MRI.

Objectives: To investigate the association between LVV and disability in multiple sclerosis (MS) longitudinally.

Methods: High-resolution 3D T1 MPRAGE MRI data with 3 and 5 years follow-up were derived from a longitudinal MS cohort. T1 hypointense lesions were marked using Amira (Mercury Computer Systems Inc.) and filled using FMRIB Software Library. ALVIN applies a binary mask to spatially normalized CSF segmented images using the unified segmentation option in SPM8 and calculates the normalized LVV. Neurological and cognitive disability was assessed using the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) and Symbol Digit Modalities Test (SDMT). Associations between LVV and clinical outcomes were investigated using Spearman correlation. Sample size calculation was based on two group t-test for differences between independent means. For comparison, normalized (N)BV was calculated using SienaX.

Results: In total, 132 patients were included: 76% relapsing-remitting (RR)MS, 66% female, mean age 44.4±10.6 and disease duration 13.1±9.1 years, median EDSS 3.0 (range 0-6.5). At baseline, mean LVV was 29.8±14.3 ml and correlated with age (rho=0.24; p=0.006), disease duration (rho=0.38; p< 0.001), T1 lesion volume (rho=0.56, p< 0.001), T2 lesion volume (rho=0.56, p< 0.001) and NBV (rho=-0.57; p< 0.001). Mean LVV was higher in progressive MS than clinically isolated syndrome or RRMS (p< 0.001). However, this difference did not remain significant when adjusted for age and gender (p=0.07). The mean LVV increased by 3.6±4.6 ml over 5 years corresponding to a mean annual LVV change of 0.7 ml (2.3%). Mean LVV change was marginally higher in men than women (p=0.06). LVV correlated with EDSS, MSFC and SDMT at all time-points (rho=0.34-0.47; all p< 0.001). Based on LVV changes observed, in future trials, sample size calculation estimates 126 patients in each treatment arm required to detect a 50% difference in LVV change over 3 years (80% power, alpha=0.05).

Conclusions: The LVV measured using ALVIN correlated with NBV assessed using SIENAX and with neurological and cognitive disability in MS.

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J Kuhle´s institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: consulting fees from Novartis, Protagen AG; speaker fees from the Swiss MS Society, Biogen, Novartis, Roche, Genzyme; travel expenses from Merck Serono, Novartis, Roche; grants from ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation, Bayer (Schweiz) AG, Genzyme, Novartis, Roche.
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L Kappos´ Institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: steering committee, advisory board and consultancy fees from Actelion, Alkermes, Almirall, Bayer, Biogen, Excemed, GeNeuro SA, Genzyme, Merck, Mitsubishi Pharma, Novartis, Receptos, Roche, sanofi-aventis, Santhera, Teva, Vianex and royalties from Neurostatus Systems AG. For educational activities the institution received honoraria from Allergan, Almirall, Bayer, Biogen, Excemed, Genzyme, Merck, Novartis, Pfizer, Sanofi-Aventis, Teva and UCB.
Wuerfel J is CEO of MIAC AG, Basel, Switzerland. In the past he served for advisory boards of Biogen, Genzyme, Novartis and received speaker´s honoraria/travel support from Bayer, Biogen, Novartis and Teva. He has received support from the German Ministery of Science (BMBF), the German Ministery of Economy (BMWi) and the European Union (Horizon2020).
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P1079

Validation of an automated lateral ventricle delineation algorithm (ALVIN) in multiple sclerosis

E. Ruberte[1], M. Amann[1,2], Y. Naegelin[2], I.K. Penner[3], M. Pardini[4], J. Kuhle[2], T. Derfuss[2], C. Stippich[2], L. Kappos[2], J. Wuerfel[1], Ö. Yaldizli[2]
[1]Medical Image Analysis Center (MIAC AG), [2]University Hospital Basel, Basel, Switzerland, [3]Universitätsklinikum Düsseldorf, Düsseldorf, Germany, [4]Universita di Genova, Genova, Italy

Background: ALVIN is an algorithm for the automated lateral ventricle segmentation in SPM8 that ha been primarily validated in Alzheimer's disease.
Objective: To assess scan re-scan reliability, the correlation between ALVIN and manual segmentation and the effect of lesion-filling on the association between lateral ventricle volume(LVV) and disability in multiple sclerosis(MS).
Methods: High resolution 3D T1 MPRAGE images were acquired on a 1.5T MRI system from 132 MS patients (75% relapsing-remitting MS; 66% female, mean age 44.4±10.6 and disease duration 13.1±9.1 years) with follow-ups at 3 and 5 years. T1 hypointense lesions were filled using FSL. ALVIN applies a binary mask to spatially normalized CSF segmented images using the unified segmentation option in SPM8 and calculates the normalized LVV. Scan re-scan reliability was assessed in 17 healthy controls(HCs) re-scanned immediately after the first scan in the same scanner. Manual segmentation of the LV was performed in 45/132 patients. The association between ALVIN and manual segmentation was assessed using the intraclass correlation coefficients(ICC) and Bland Altman limits of agreements. To assess disability we used the EDSS, MSFC and SDMT. Associations between LVV and clinical outcomes were investigated using Spearman correlations and further explored using linear regression models. Akaike information criterion was used to compare the goodness-of-fit between linear regression models.
Results: Scan re-scan reliability was high(ICC=0.99) with a mean LVV difference between the two scans of 0.007±0.273 ml(95% CI: -0.542 ml; 0.528 ml). In patients, the mean LVV at baseline using ALVIN was 29.8±14.3 ml. The agreement between ALVIN and manual segmentation was high(ICC=0.986). ALVIN tended to overestimate the LVV with a mean difference of 0.91±1.55 ml compared to the manual segmentation. At baseline, the volume of hypointense MS lesions on T1-weighted images was 2.4±3.6 ml and had influence on the ALVIN. LVV was lower when ALVIN used lesion-filled compared to non-lesion filled images with a mean difference of 0.41±0.68, 0.30±0.61 and 0.41±0.62 ml at baseline, 3 and 5 years, respectively(all $p < 0.001$). When using lesion-filled images, the associations between LVV and clinical outcomes were closer compared to lesion-unfilled images.
Conclusion: Scan re-scan reliability of ALVIN in HCs is high. ALVIN correlates with manual segmentation in MS. ALVIN overestimates the LVV when lesion-unfilled images are used.

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J Kuhle's institution (University Hospital Basel) received in the last 3 years and used exclusively for research support: consulting fees from Novartis, Protagen AG; speaker fees from the Swiss MS Society, Biogen, Novartis, Roche, Genzyme; travel expenses from Merck Serono, Novartis, Roche; grants from ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation, Bayer (Schweiz) AG, Genzyme, Novartis, Roche.
T Derfuss serves on scientific advisory boards for Novartis Pharmaceuticals, Merck Serono, Biogen Idec, Genzyme, GeNeuro, Mitsubishi Pharma, Teva Pharmaceuticals and Bayer Schering Pharma; has received funding for travel and/or speaker honoraria from Biogen Idec, Genzyme, Novartis, Merck Serono and Bayer Schering Pharma; and receives research support from Biogen Idec, Novartis Pharma, the European Union, the Swiss National Foundation and the Swiss MS Society.
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Wuerfel J is CEO of MIAC AG, Basel, Switzerland. In the past he served for advisory boards of Biogen, Genzyme, Novartis and received speaker´s honoraria/travel support from Bayer, Biogen, Novartis and Teva. He has received support from the German Ministery of Science (BMBF), the German Ministery of Economy (BMWi) and the European Union (Horizon2020).

P1080

Exploring the volumetry of subcortical structures as a potential surrogate of brain volumes in multiple sclerosis

M.E. Zandoná, G.R. dos Passos, L.I. Gonçalves, J.L.P. Burger, A.R. Franco, G.H. Tomasi, D.K. Sato, I. Gomes, J. Becker
Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil

Introduction: Estimation of brain volumes, either as a whole (WB) or segmented by white (WM) and gray (GM) matter, seems to be useful in the monitoring of multiple sclerosis (MS), but is often time-consuming. Recently, simple measurements of the corpus callosum were proposed as possible surrogates of brain volume, especially that of the WM. We aimed to investigate which, if any, of six subcortical structures would also correlate with brain volumes.
Methods: Patients with relapsing-remitting MS underwent 3.0 T brain magnetic resonance imaging (MRI). The Icometrix© software was used to estimate the WB, WM and GM volumes. The FreeSurfer© software allowed for the estimation of the volumes of six subcortical structures: thalamus, caudate nucleus, putamen, pallidum, hippocampus, and amygdala. The volume of each structure was considered to be the arithmetical mean between right and left sides. Pearson's correlation coefficient was calculated with the SPSS© software.
Results: Twenty-one patients with relapsing-remitting MS were included. All structures presented correlation with the WB volume, especially the thalamus (very strong, $r=0.804$, $p < 0.001$), the caudate nucleus (strong, $r=0.728$, $p < 0.001$), and the putamen (strong, $r=0.708$, $p < 0.001$). Those correlations were mainly at the expense of the WM volume for some structures, namely the thalamus ($r=0.804$, $p < 0.001$) and the hippocampus ($r=0.466$, $p=0.033$), and mainly at the expense of the GM volume for other structures, as the caudate nucleus ($r=0.607$, $p=0.004$), the putamen ($r=0.699$, $p < 0.001$), and the pallidum ($r=0.522$, $p=0.015$). The amygdala did not correlate with any brain volume.
Conclusion: Some subcortical structures, especially the thalamus, may be potential targets for the development of simple measurement techniques that could act as surrogates of brain volumes, maybe creating easier-to-implement alternatives to the time-consuming techniques of brain volumetric analysis used nowadays.

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P1081

The influence of reconstruction slice thickness on the accuracy of T2 sagittal sequence in the Magnetic Resonance Imaging diagnosis of optic neuropathy, in patients with multiple sclerosis

G.M. Healy[1], H. Fleming[1], C.E. Redmond[1], A.G. Carroll[1], C. McGuigan[2], R.P. Killeen[1,3]
[1]Department of Radiology, [2]Department of Neurology, St Vincent's University Hospital, [3]Department of Radiology, Royal Victoria Eye and Ear Hospital, Dublin, Ireland

Background: Sagittal T2-weighted Magnetic Resonance Imaging (MRI) is an integral component of the routine radiological assessment of patients with multiple sclerosis. The reconstruction slice thickness for this T2 sagittal sequence in our institution has recently been reduced from 4mm to 3mm. For patients suspected to have optic neuropathy (ON), MRI orbits with coronal Short Tau Inversion recovery (STIR) is used and this sequence is considered the gold standard. This study compared the influence of slice thickness on the accuracy of the T2 sagittal sequence of the brain for identification of ON.
Materials and methods: Forty-one consecutive patients who underwent MRI brain and orbits, incorporating both T2 sagittal (with 4mm reconstruction) brain and coronal STIR orbit sequences, have been included. Each STIR sequence was reviewed by a neuroradiologist and radiology resident, in consensus, in a blinded fashion and assigned as positive or negative for optic neuropathy based on the presence of increased T2 signal within a segment of optic nerve. On a separate occasion, the sagittal T2 sequences of the brain were reviewed in a similar blinded fashion. The location of abnormality was noted (intraorbital, intracanalicular or intracranial). Since the reduction in T2 sagittal slice thickness at our institution, consecutive patients undergoing both sequences have been recorded and recruitment is ongoing, aiming to included another forty-one cases.
Results: The forty-one consecutive cases with 4mm T2 sagittal reconstruction have been analysed. Twelve patients had ON evident on STIR imaging, eight intraorbital and four intracanalicular. The T2 sagittal sequence achieved a sensitivity of 42% (95% CI 13.9-70.1) and specificity of 86% (95%CI 73.4-98.6) for ON with positive and negative predictive values of 0.56 and 0.78 respectively. Six out of the seven cases of ON missed by sagittal T2 sequence were intra orbital. Analysis of the patients with 3mm T2 sagittal reconstruction will be performed once all patients have been recruited.

Conclusion: Routine T2 sagittal brain imaging with 4mm slice thickness has poor sensitivity but high specificity for optic neuropathy. The T2 sagittal slice thinkness has now been reduced and recruitment of patients is ongoing.

Disclosure

No disclosures

P1082

Uptake of [C11]PK11195 in the thalamus of Multiple Sclerosis (MS) patients versus Healthy Controls (HC)

U. Kaunzner, Y. Kang, E. Morris, N. Nealon, J. Perumal, T. Vartanian, S. Gauthier
Weill Cornell Medical College, New York, NY, United States

Background: Thalamic volume is known to decrease in MS patients over time, and has been attributed to increased fatigue and decreased cognitive function. PK11195-PET is used to detect microglia/macrophage (MG/MΦ) activation by binding translocator protein (TSPO), a protein found on the outer mitochondrial membrane of MG/MΦ. PK uptake is known to be high within the thalamus of healthy controls (HC), and has also been described for the thalamus in MS patients. A comparison of PK uptake between HC and MS patients has yet to be obtained.
Objective: To determine thalamic [11C[PK11195 uptake in MS patients versus HC subjects.
Methods: Pharmacokinetic quantification was done using a segmented MRI, obtaining the thalamic volume for both hemispheres. PK11195-PET imaging was acquired cross-sectionally for 23 MS patients and 9 HC. PK uptake within the thalamus was quantified by volume of distribution (VT) calculation using image-derived input function. Thalamic VT was calculated in reference to each patient's white matter, to consider physiologic variability, and Vt ratio (VTr) was obtained. VTr was analyzed based on age, gender, EDSS for MS pt, and analyzed for age for HC.
Results: The MS cohort consisted of 4 secondary progressive and 19 relapsing remitting patients. Mean age was 37.9 for MS patients, while mean age for HC was 49.5 years. VTr is higher in MS patients (mean VTr=1.28) compared to HC (mean VTr=1.23, p=0.01, paired T -test). Thalamic VTr was not associated with patients age, gender, disease duration or EDSS.
Conclusion: Our results show that VTr is increased in MS patients in comparison to HC. This finding is unrelated to disease characteristics and the reason remains speculative, since only small to medium amounts of MG/MΦ have been described in deep gray matter. However, given the known thalamic atrophy in MS, increased thalamic MG/MΦ activation might contribute to this observation.

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OCT

P1083

Retinal fibre layer thickness is associated with clinical, MRI and neurophysiological measures of nervous damage but not with markers of disease activity in early relapsing MS

M. Pisa[1], T. Croese[1], S. Guerrieri[1], G. Di Maggio[1], S. Medaglini[2], L. Moiola[2], U. Del Carro[2], V. Martinelli[2], G. Comi[2], R. Furlan[1], L. Leocani[1]
[1]Institute of Experimental Neurology - San Raffaele Hospital - Milan, Milano, [2]San Raffaele Hospital, milan, Italy

Background: Previous studies demonstrated that brain MRI lesion load and evoked potential (EPs) abnormalities correlate with disability. Optical coherence tomography (OCT), with measurement of nervous layers, revealed useful in assessing axonal optic nerve damage and controversial studies suggest a correlation with disability. The present study aims at investigating, in early relapsing MS, correlation between RNFL and clinical and instrumental markers of nervous damage.
Methods: 110 patients (pts) affected by multiple sclerosis (MS) or clinical isolated syndromes suggestive of MS (CIS) were hospitalized at San Raffaele Hospital between June 2013 and March 2016 for neurological assessment and underwent contrast-enhanced MRI, multimodal EPs, OCT and cerebrospinal fluid examination with micovesicles count (MVs). RNFL was calculated as mean binocular value; only contralateral RNFL thickness was considered in pts with recent acute optic neuritis (< 6 months).
Results: Of 110 pts 71 were relapsing remitting MS, 39 were CIS. Mean age: 34 ± 12 yrs; mean disease duration: 1.8 ± 3.3; mean EDSS 1.45 ±0.97 yrs; 60 patients had a relapse within 3 months. RNFL was significantly associated with EDSS and disease duration (R -0,213 p=0,025 and R -0,244 p=0,01 respectively). It was also associated with the number of T2 white matter lesions (WML) evaluated into 3 classes: 0-2 lesions, 3-8 lesions and more than 8 lesions (ANOVA: F=11.3; p< 0,001), being lower in both moderate/high vs low lesion load group (post-hoc Ttest p< 0,001). RNFL was also associated with multimodal EPs, also considering only MEPs and SEPs. EPs were associated with EDSS. RNFL was not associated with concurrent disease activity, either as from brain gadolinium enhancing lesions and from microvesicles count in the cerebrospinal fluid, which are both considered as markers of inflammatory activity. On the other hand, microvesicles counts was significantly higher in the presence of gadolinium enhancing lesions (Mann-Whitney; p< 0,001) but not associated with WML.
Conclusions: The present study demonstrates that, even in early MS, RNFL is associated with the accumulation of nervous damage revealed by clinical, neurophysiological and neuroimaging measures, by reflecting parallel processes occurring in the optic pathways or transynaptic neuroaxonal loss. On the other hand, RNFL is not related to concurrent disease activity.

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P1084

Optical coherence tomography measures correlate with brain volume and disability in relapsing multiple sclerosis patients

À. Vidal-Jordana[1], J. Sastre-Garriga[1], D. Pareto[2], J. Río[1], R. Horno[1], M. Tintoré[1], C. Auger[1], Á. Rovira[2], X. Montalban[1]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, [2]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, Bar elona, Spain

Background: Optical coherence tomography (OCT) has demonstrated retinal nerve fibre layer (RNFL) and macular volume (MV) thinning in multiple sclerosis (MS), ant it has been related to brain volume (BV) measures.
Objective: To investigate the association between OCT and BV measures in relapsing MS patients starting disease modifying drugs (DMD), and to assess if OCT and BV measures are associated with disability.
Methods: Cross-sectional analysis of a longitudinal, on-going cohort of patients starting DMD in our centre. Clinico-radiological data, including previous history of optic neuritis (ON), was collected. Baseline brain MRI and spectral-domain OCT scans were performed before DMD onset. Mean values of RNFL and MV of both eyes were calculated. Voxel Based Morphometry (VBM) analysis was performed with Statistical Parametric Mapping 8, and RNFL and MV associations with grey matter (GM) pathology were assessed. Global and regional BV measures [Brain parenchymal fraction (BPF), grey and white matter fraction (GMF and WMF)] were also obtained. Bivariate association analyses between BV, RNFL, MV and clinico-radiological data were conducted. Uni and backward multivariate logistic regression analyses, including in the model both OCT and BV measures, to predict an EDSS of 3.0 were performed.
Results: 48 patients were included, mean age was 37.4 (SD 11.3), mean disease duration was 8.6 years (SD 10.2), annualized relapse rate was 1.8 (SD 1.1), median EDSS was 2.0 (range 0-6.5), and 17 (31.5%) patients had an EDSS of 3.0 or more. Mean RNFL and MV were 89.7 um and 8.4 mm3; mean BPF, GMF and WMF were 0.82, 0.46 and 0.37, respectively. Lower values of RNFL were associated with longer disease duration ($p< 0.001$), higher EDSS ($p< 0.001$), and lower GMF and BPF values ($p=0.039$ and $p=0.001$). Lower values of GMF and BPF were both significantly associated with older age, longer disease duration, and higher EDSS. In the backward multivariate logistic regression analysis to predict an EDSS of 3.0, and correcting for disease duration and ON, only RNFL and disease duration were retained (OR 0.92, 95%CI 0.86-0.99, $p=0.035$; and OR 1.09, 95%CI 0.98-1.21, $p=0.083$, respectively). In VBM analyses, RNFL thickness significantly correlated with cortical and subcortical clusters of GM loss.
Conclusion: Patients with higher disability and longer disease duration presented lower RNFL and BV estimates. In this cohort, RNFL seems to outperform BV measures to predict disability.

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RH has nothing to disclose around the present work
MT has nothing to disclose around the present work
CA has nothing to disclose around the present work
AR serves on scientific advisory boards for Biogen Idec, Novartis, Genzyme, and OLEA Medical, and on the editorial board of the American Journal of Neuroradiology and Neuroradiology, has received speaker honoraria from Bayer, Genzyme, Sanofi-Aventis, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, Stendhal, Novartis and Biogen Idec, and has research agreements with Siemens AG.

P1085

Optical coherence tomography for the analysis of FTY720-mediated protection from retinal degeneration in mouse models of optic neuritis and traumatic nerve injury

M. Dietrich[1], N. Helling[2], A. Issberner[2], A. Hilla[2], A. Heskamp[2], C. Berndt[2], O. Aktas[2], D. Fischer[2], H.-P. Hartung[2], P. Albrecht[1]
[1]Neurology, [2]Heinrich Heine University, Medical Faculty, Düsseldorf, Germany

Background: Neurodegeneration is a major cuase of disability in Multiple Sclerosis (MS). This degeneration is not accessible to conventional immunosuppressant and most immunomodulatory therapy. Fingolimod (FTY720) is used as immunomodulatory treatment of MS. It has been reported to reduce cerebral volume loss in MS patients, to diminish the size of infarctions in animal models of ischemic stroke and to protect from light induced retinal degeneration in rats suggesting possible neuroprotective effects.
Objective: We aimed to analyze the protective capacities of FTY720 on retinal degeneration in myelin oligodendrocyte glycoprotein induced experimental autoimmune encephalomyelitis (EAE) in C57BL/6 mice, as animal model of MS and optic neuritis and after optic nerve crush (also C57BL/6) as a model for non-inflammatory axonal injury.
Design/Methods: To assess retinal neurodegeneration we used latest generation spectral domain optical coherence tomography (OCT), histological staining of retinal ganglion cells in retinal wholemounts as well as histological evaluation of microglial activation, lymphocytic infiltration and demyelination in optic nerves.
Results: A prophylactic FTY720 treatment improved the clinical EAE score and prevented from the degeneration of the inner retinal layers, consisting of the retinal nerve fiber layer, ganglion cell layer and inner plexiform layer. Staining of the ganglion cells in retinal wholemounts and histology of the optic nerves in EAE

revealed similar protective effects of FTY720 on ganglion cells and less lymphocytic infiltrates, less microglial activation and less demyelination in optic nerves, respectively.
In the optic nerve crush model, the beneficial effects could not be confirmed by OCT or histology.
Conclusion: This research is of high relevance as it evaluates the effects of FTY720 on neurodegeneration *in vivo* under well controlled experimental conditions using state of the art optical coherence tomography (OCT) technology. Our data provide further evidence that FTY720 treatment can prevent neuro-axonal loss in the context of autoimmune diseases of the central nervous system. At the same time, our results suggest that FTY720 may not be the ideal substance to prevent non-inflammatory neuroaxonal degeneration.

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P1086

Relationship between gray matter, retinal nerve fiber layer thickness and cognitive performances in multiple sclerosis: a cross sectional study

G. Coghe[1], G. Fenu[1], J. Frau[1], L. Lorefice[2], F. Cabras[3], L. Loi[3], M.A. Barracciu[3], E. Cocco[1], M.G. Marrosu[4]
[1]Department of public health, clinical and molecular medicine, University of Cagliari, [2]Department of public health, clinical and molecular medicine, University of cagliari, [3]ASL 8 Cagliari, [4]Department of medical sciences, University of Cagliari, Cagliari, Italy

Background: Retinal nerve fiber layer (RNFL), as measured by ocular coherence tomography (OCT), may have a relationship between cognitive performances and brain structural changes in MS. The published data suggest correlations between RNFL thickness and measures of brain atrophy on MRI with grey matter (GM) atrophy remaining a hot topic.
Aims: The purpose of this study was to assess in a cross sectional design the relationship between RNFL, cognitive performances and MRI findings.
Materials and methods: Patients were enrolled at MS Center of Cagliari. An MS expert neurologist performed the EDSS, the BICAMS assessment and the OCT. Eyes with previous optic neuritis (either clinical or subclinical) were excluded. All subject underwent brain MRI with a 1.5 Tesla Siemens scanner. Normalized Brain Volume (BV), Normalized Grey matter Volume (GM) and Normalized White Matter Volume (WM) were estimated with SIENAX. Relationship between peripapillary RNFL (pRNFL), symbol digit modality test, California verbal learning test II and brief visual memory test (corrected for age and education) and MRI data were assessed by means of the Spearman product moment correlation analysis also after correcting for age and disease duration.
Results: Out of 43 patients (16 male, 27 female) 84 eyes met the inclusion criteria. The study population characteristics were: mean EDSS 2.27 (SD ± 1.57), age 43.98 (SD ± 10.85), disease duration 11.63 (SD ± 8.07). 16 patients (32 eyes) showed cognitive impairment (CI) while 27 patient (52 eyes) were not impaired. pRNFL showed a significant but mild relationship with disease duration (r=-0.26 p=0.01), WB (r=0.27 p=0.01) and GM(r=0.27 p=0.01). After correcting for age and disease duration GM and pRNFL remained significantly associated (r=0.26 p=0.02). When considering separated groups, the relationship between GM and pRNFL became 40% (r=0.40 p=0.02) in cognitive impaired patients and not significant in not impaired patients (r=0.18 p=0.15). None of the cognitive tests showed significant relationship in the whole population and in the sub-groups.
Conclusions: Our data confirm the strong relationship between pRNFL and GM impairment while white matter appear completely disjointed. We didn't confirm the relationship between pRNFL and cognitive performances found by other groups. Indeed it is relevant that the more is the cognitive impairment, the strongest is the correlation between pRNFL and GM.

Disclosure

The authors report no financial or other conflict of interest relevant to the subject of this article.

P1087

No evidence of trans-synaptic degeneration in the visual pathway of MS at clinical onset

L. Federle[1], M. Puthenparampil[1], D. Poggiali[1], S. Pravato[1], A. Signori[2], S. Miante[1], F. Rinaldi[1], M.P. Sormani[2], P. Gallo[1]
[1]Mulitple Sclerosis Centre, Department of Neuroscience, University of Padua, Padua, [2]Department of Health Sciences, Section of Biostatistics - University of Genova, Genova, Italy

Background. Analysis of the optic pathway may help to clarify the mechanisms involved in grey matter damage in MS. We investigated the relationship between white matter inflammation and neurodegeneration to achieve evidence of trans-synaptic degeneration in the optic pathway in MS at clinical onset. To overcome the effect induced by optic neuritis (ON) in the optic pathway, by disease duration and by concomitant medications, we focused on patients with no history of ON.
Methods. 56 clinically isolated syndromes/early relapse-onset MS with a mean disease duration of 4.0±3.5 months were enrolled in the studied. 3T MRI scans consisted in the following sequences: 3D-T1, 3D- Fluid Attenuated Inversion Recovery (3D-FLAIR), 3D-Double Inversion recovery (3D-DIR). Visual (V1, V2, V3, V4

and V5) cortical thickness (TH) and volume were analyzed on T1-3D sequences by means of ANTs; furthermore, lateral geniculate body (LGB) volume was calculated. 3D-DIR sequences allowed the measurement of cortical lesions volume (i.e. Grey Matter Lesion Volume, GMLV) and percentage (GMLV in a specific visual area/ grey matte volume of the specific visual area) in each visual cortical area. The Optic radiation white matter lesion volume (WMLV), also expressed by percentage (optic radiation WLMV/optic radiation volume), was evaluated on 3D-FLAIR sequences. Global peripapillary retinal nerve fiber layer (g-RNFL) TH, the 6 RNFL-sectors (TI, T, TS, NS, N and NI) THs, the Macular (foveal, inner ring, outer ring) Volumes and THs were analyzed by optic coherence tomography (OCT).
Results. No correlation between visual cortical areas (V1, V2, V3, V4 and V5) thickness or volume and white (optic radiation WMLV and WMLV%) and grey matter (GMLV in V1, V2, V3, V4 and V5, expressed also as percentage) focal inflammation was observed. LGB volume did not correlate with any white matter or grey matter inflammatory parameters. Only a mild correlation between LGB and ipsilateral T-RNFL was found (r:0.3, $p< 0.001$). No correlation between retinal and white or grey matter parameters were detected. Multivariate analysis failed to explain any RNFL or Macular thickness values based on MRI parameters; moreover, Visual Cortex Thickness was not explained by any MRI or OCT parameters.
Conclusions. No evidence of trans-synaptic degeneration was found at clinical onset in the optic pathway of MS patients having no history of ON. In these patients trans-synaptic degeneration may occur in later disease phases.

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P1088

Primary retinal pathology in neuromyelitis optica detected by optical coherence tomography

N.-H. Kim[1], I.H. Jeong[2], H.J. Kim[2], J.Y. Cho[3], C.-Y. Park[4]
[1]Neurology, Dongguk University Ilsan Hospital, [2]Research Institute and Hospital of National Cancer Center, [3]Neurology, Inje Unversity Ilsan Paik Hospital, [4]Ophthalmology, Dongguk University Ilsan Hospital, Goyangsi, Republic of Korea

Background: Foveal thickness may be a more sensitive indicator of primary retinal pathology than retinal nerve fiber layer thickness since the fovea contains no or sparse retinal nerve fiber layer, which coalesces into axons of the optic nerve. To our knowledge, few quantitative in vivo studies have investigated foveal thickness.
Objectives: By using optical coherence tomography (OCT), we measured foveal thickness to evaluate the intrinsic retinal pathology.
Methods: Patients with NMOSD (n=72) and age-matched healthy controls (n=34) underwent time-domain OCT and visual function testing.
Results: Seventy-two NMOSD patients (99 eyes with optic neuritis and 45 eyes without optic neuritis) and 34 age-matched controls were included. Foveal thinning was observed in both non-optic neuritis (185.1 μm, $p< 0.001$) and optic neuritis eyes (185.0 μm, $p< 0.001$) relative to control eyes (205.0 μm). Compared to controls, non-optic neuritis eyes did not have peripapillary retinal nerve fiber layer thinning but showed foveal thinning ($p< 0.001$). In NMOSD, foveal thickness correlated with disease duration, while RNFL thickness correlated with high or low contrast visual acuity, extended disability status scale, and disease duration.
Conclusions: In this study, we observed foveal thinning irrespective of optic neuritis, thus we believe that subclinical primary retinal pathology prior to retinal nerve fiber layer thinning may exist in NMOSD.

Disclosure

all authors: nothing to disclose

P1089

Influence of blood vessels on peripapillary retinal nerve fiber layer thickness measurements in patients with neuromyelitis optica spectrum disorders

F.C. Oertel[1], H. Zimmermann[1], J. Mikolacjzak[1], M. Weinhold[1], E.M. Kadas[1], T. Oberwahrenbrock[1], F. Pache[1,2], F. Paul[1,2,3], A.U. Brandt[1]
[1]NeuroCure Clinical Research Center, [2]Department of Neurology, [3]Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany

Background: Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory-degenerative diseases of the central nervous system with optic neuritis (ON) as one hallmark. Due to retrograde retinal damage subsequent to ON, peripapillary retinal nerve fibre layer (pRNFL) thinning correlates with visual dysfunction.
Objective: To exclude a potential systematic error by papillary blood vessels in severely thinned RNFL and thus to improve the accuracy of pRNFL thickness measurements in longitudinal clinical trials.
Methods: Forty patients with NMOSD (28 AQP4-positive; 25 with history of ON) were included. All patients underwent pRNFL

measurements with spectral domain optic coherence tomography (OCT) and high contrast visual acuity (VA) measurement with Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Blood vessel regions in OCT scans were semi-automatically segmented with OCTSeg.
Results: A total of 77 eyes from 40 NMOSD patients were evaluated. Three eyes were excluded due to insufficient scan quality. A mean pRNFL thickness of 76.1 ± 26.6µm was found in measurements including retinal blood vessels. After exclusion of blood vessel regions, pRNFL measurements were significantly thinner (70.7 ± 26.1µm, p< 0.001). VA was associated with pRNFL including vessels (r=0.621, p< 0.001) and pRNFL without vessels (r=0.619, p< 0.001). The relative blood vessel contribution to RNFL thickness measurements amounted to 8±3% and increased with lower pRNFL (r=-0.698, p< 0.001). When only considering eyes with RNFL thickness below 60µm, the mean relative contribution was 11±3%, and RNFL-VA correlations improved for measurements excluding blood vessels (r=0.523, p=0.004) compared to measurements including blood vessels (r=0.482, p=0.009).
Conclusion: Our findings show a difference between RNFL thickness measurements with and without blood vessels. Relative contribution of blood vessels to RNFL thickness increases with thinner RNFL, which is an important confounder when using RNFL as inter-individual but also as longitudinal intra-individual outcome measure. Excluding blood vessels might improve measurement accuracy in severely affected patients, exemplified by an improved correlation with visual function.

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P1090

Retinal atrophy in CIS patients is associated with subclinical optic nerve involvement

F. London, H. Zéphir, N. Hadhoum, P. Vermersch, O. Outteryck
Centre Hospitalier Régional Universitaire de Lille, Lille, France

Background: Subclinical optic nerve involvement is frequent in relapsing remitting multiple sclerosis patients (RRMS) but is not considered in spatial dissemination of MS lesions. Retinal atrophy at the earliest clinical stage of multiple sclerosis is discussed.
Objective: To evaluate the occurrence of retinal atrophy in clinically isolated syndrome (CIS) and the role of subclinical optic nerve involvement.
Material and methods: We prospectively included 49 CIS patients between November 2013 and March 2016. Each patient underwent a brain MRI at 3 months after CIS. Brain MRI (Philips Achieva 3T, 32 array coils) included 3D-sequences (T1, FLAIR, Double Inversion Recovery, T1-gadolinium). Subclinical optic nerve T2 hypersignal were investigated with 3D-DIR and 3D-FLAIR. We defined 3 groups: clinical ON group, subclinical ON group and NON group. We perfomed OCT analysis of both eyes (4th generation, Heidelberg Spectralis) and collected the global and temporal peripapillary retinal nerve fiber layer (pRNFL) thicknesses.
Results: We recruited 20 patients with optic neuritis (40.8%) with a mean age of 30.6 ± 7 years. Clinical episode of ON was unilateral in 92% (n=18). We highlighted subclinical optic nerve involvement in 19 patients (21 optic nerves) representing 27.6% of optic nerve without clinical episode. Mean global pRNFL thickness (in µm) in NON group (99.5 ± 8.6) was close to subclinical ON group (98.3 ± 10.1; p=0.5) and significantly higher than clinical ON group (86.27 ± 22.3; p=0.001). Mean temporal pRNFL thickness (in µm) in NON group (71.39 ± 9.3) was significantly higher than subclinical ON group (65.2 ± 7.5; p=0.01) and clinical ON group (56.5 ± 11.78; p=0.0001). Mean temporal pRNFL thickness in subclinical ON group was significantly higher than in ON group (p=0.01).
Conclusion: Subclinical optic nerve involvement is very frequent at the earliest clinical stage of RRMS and seems responsible of the retinal atrophy previously reported in CIS.

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P1091

Optical coherence tomography reflectance as a potential marker of retinal axonal damage in a preclinical model of multiple sclerosis

S.-C. Huang[1], V. Castordi[1], R. Santangelo[1], S. Marenna[1], S. Maestroni[2], G. Zerbini[2], P. Rama[3], G. Comi[1], L. Chaabane[4], L. Leocani[1]

[1]Department of Neurology and INSPE-Institute of Experimental Neurology, Vita-Salute San Raffaele University, [2]Complications of Diabetes Unit, Division of Metabolic and Cardiovascular Sciences, [3]Cornea and Ocular Surface Disease Unit, Eye Repair, San Raffaele Scientific Institute, [4]Department of Neurology and INSPE-Institute of Experimental Neurology, Scientific Institute H. San Raffaele, University Vita-Salute, Milan, Italy

Background: Experimental autoimmune encephalomyelitis (EAE) is the mostly used preclinical model for multiple sclerosis (MS). Thinning of the retinal nerve fiber layer (RNFL) in EAE due to degeneration of optic nerve can be measured using optical coherence tomography (OCT). However, axonal loss may be masked by edema in the acute phase. Reflectance, which may related to changes of the cellular skeleton, is an intrinsic optical property and has been found reduced in MS patients. Also, the reflectance of RNFL showed decrease before the thickness changes in a glaucoma model. The results imply the potential of using reflectance to monitor the neuronal loss during the acute phase. Here we aimed at exploring the usefulness of reflectance as a marker of underlying structural deformation of RNFL of EAE.

Materials and methods: Five dark Agouti female rats with EAE induced through myelin oligodendrocyte glycoprotein immunization were compared to six healthy controls. They all underwent bilateral circular peripapillary OCT scans at four time points after EAE onset, occurring 10 days post immunization-p.i. (day 21, 35, 42, and 56 p.i.). RNFL thickness (RNFLT) were measured and its reflectance (NRI) calculated as signal intensity of RNFL normalized with the intensity of retinal pigment epithelium. For each rat, edema was identified as the changing rate of thickness exceeding 10.4% (95% percentile) found in controls.

We compared RNFLT and NRI among four conditions: Pre-edema, edema, post-edema, and eyes of controls.

Results and discussion: Repeated measures ANOVA showed a significant effects of group by time interactions of RNFLT and NRI (both $p < 0.001$). Post-hoc analyses revealed that NRI was significantly decreased in the pre-edema period ($p = 0.001$), when only two eyes had delayed VEPs. On the other hand, RNFL thickness was not decreased in the edema phase (when 3 VEPS were delayed, 2 absent) and only decreased in the post-edema phase ($p < 0.001$), when three eyes had delayed and one absent VEPs.

Reflectance, which in EAE precedes the occurrence of RNFL edema, might be a potential marker for detecting early sign of RNFL damage which should further be validated exploring mechanisms of axonal dysfunction preceding axonal loss and conduction block, as demonstrated by relatively spared bioelectrical conduction.

Disclosure

The authors have nothing to disclosure.

P1092

Retinal ganglion cell loss in clinically isolated syndrome is associated with subsequent MS diagnosis

H. Zimmermann[1], T. Oberwahrenbrock[1], S. Specovius[1], J. Mikolajczak[1], J. Bellmann-Strobl[1,2], K. Ruprecht[3], F. Paul[1,2,3], A.U. Brandt[1]

[1]NeuroCure Clinical Research Center, Charité - Universitätsmedizin Berlin, [2]Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité - Universitätsmedizin Berlin, [3]Department of Neurology, Charité - Universitätsmedizin Berlin, Berlin, Germany

Introduction: Retinal ganglion cell loss was found in patients with clinically isolated syndrome (CIS) in absence of optic neuritis (ON). The goal of this study was to evaluate whether ganglion cell and inner plexiform layer (GCIP) thickness in patients with CIS is associated with a subsequent MS diagnosis according to the McDonald diagnostic criteria (MDMS) or clinically definite MS (CDMS).

Methods: Forty-nine CIS patients (mean age 33.5±7.9 years, 31 female) were observed over a period of at least one year (mean follow-up period 30.2±8.9 months, range 12-46 months). All patients underwent retinal optical coherence tomography analysis of the combined ganglion cell and inner plexiform layer at baseline visit. MS diagnosis was established based on MRI and clinical presentation according to the revised McDonald 2010 criteria.

Results: Twenty-seven CIS patients were classified as MDMS (n=15) or CDMS (n=12) during follow-up. GCIP thickness at baseline in NON eyes was thinner in patients that were diagnosed with MS by the last follow-up visit (69.3±4.9 vs. 73.6±6.7 μm, p=0.014). Follow-up duration, time since onset, age and sex had no significant influence.

Conclusion: Our results indicate that low GCIP thickness in clinically isolated syndrome without optic neuritis is associated with a later MS diagnosis. However, the predictive information for individual patients is limited by the wide range of inter-individual variety of GCIP measurements.

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Neurophysiology

P1093

Visual working memory but not verbal working memory load interferes with balance performance in earliest stages of MS

G. Brecl Jakob, S. Šega, A. Horvat Ledinek, M. Baruca, U. Rot
Department of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Background: Majority multiple sclerosis (MS) patients experience balance problems during the disease course. Subtle cognitive deficits are present in almost half of the patients at the beginning of the disease. To assess motor-cognitive interference, we studied postural performance under dual-tasking in patients with clinically isolated syndrome (optic neuritis-ON) suggestive of MS.
Methods: Within 3 months from unilateral ON we prospectively included 20 patients with regained visual acuity of 0.8 or more (age 33.4±12.8; EDSS 1±1, number of MRI lesions: min 0, max>30). We also included 20 age, weight, height and education matched healthy subjects. Balance was studied by static posturography and centre of pressure (COP) measures. Posturography was performed with eyes closed and feet together in three conditions: standing, standing+Brooks´ (BR) spatial memory task and standing+2-back verbal memory task (2B). Each trial lasted 120s, middle 90 seconds were analysed. Total COP path, maximal COP velocity, medio-lateral (m-l) and antero-posterior (a-p) sway amplitudes were measured. For each cognitive task percentage change of accuracy was calculated while dual-tasking in reference to single-task performance. Repeated measures ANOVA was used to analyse data.
Results: There was no difference in COP path or maximal COP velocity between the groups (p=0.3, p=0.2), however the response to dual tasking differed between the groups for both variables (p=0.01, p=0.02). Post-hoc analyses showed patients significantly decreased COP path and maximal COP velocity while performing br (p=0.004, p=0.02), compared to standing alone. This was not the case for 2b. There were no differences in m-l sway amplitudes (p=0.2) neither in response to different dual task condition (p=0.1) observed between the groups. The same was observed for a-p sway amplitudes (p=0.9, p=0.8). There was no difference in average % change of performance on each cognitive task while dual tasking (4% for 2b and br), compared to cognitive task alone. The same was observed in healthy subjects (3% for 2b; 1% for br).
Conclusion: Our results show that visual working memory load affects postural performance in patients with ON suggestive of MS compared to healthy subjects, while this is not the case for verbal working memory. Such results suggest that disease might affect visuo-spatial and motor information integration at its earliest stages where there is little or no motor or cognitive deficits observed.

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P1094

Effect of THC/CBD oromucosal spray on spasticity in MS: an open label clinical-neurophysiological study

A. Nuara, A. Giordano, L. Ferrè, V. Martinelli, F. Martinelli Boneschi, F. Esposito, G. Comi, L. Leocani
Ospedale San Raffaele, Milan, Italy

Background: Spasticity, manifesting as muscle stiffness, spasms and pain, is a frequent symptom of multiple sclerosis (MS), with a strong impact on quality on life of patients. Cannabis derivatives and endocannabinoid system modulator (such as Sativex, a THC/CBD oromucosal spray) have been reported to relieve symptoms of spasticity in MS. Despite demonstrated symptomatic relief of MS spasticity, few studies have investigated neurophysiological baseline characteristics on predicting treatment response, as well as the neurophysiological changes induced by theraphy with cannabinoids in MS.
Objectives: To assess the clinical-neurophysiological correlates of Sativex effect on spasticity in MS and the predictive value of neurophysiological baseline features on treatment response.
Methods: 20 outpatients affected by multiple sclerosis (6M, 14F, age 31-64, EDSS 4.0-7.5) with spasticity-associated symptoms (baseline spasticity NRS$\geq$4) underwent the following clinical evaluations at baseline (T0) and after a 4-week (T4) Sativex titration period: EDSS, 10 meters walking test, Ambulation Index (AI), Modified Ashworth Scale (MAS), spasticity and pain numerical-rating-scale (NRS). Neurophysiological baseline features (resting motor threshold [RMT], Motor-evoked-potentials [MEP's] amplitude of First Digital Interosseus [FDI] at 120% of RMT, intracortical inhibition/facilitation [ICI/ICF] were collected at T0 in the whole group ad in 10 patients at T4.
Results: From T0 to T4, a significant improvement of spasticity was observed, considering both subjective (NRS 7$\pm$1.45 vs 5.15$\pm$1.38, p=0.0001) and physician-reported (MAS 3.3$\pm$1.94 2.93$\pm$1.70) spasticity. No significant changes in neurophysiological measures were observed. Grouping patients according to treatment responsiveness (NRS improvement $\geq$20%, 9 responder), no significant differences were found in neurophysiological baseline features.
Conclusion: Our findings confirm the clinical benefit of Sativex on MS spasticity. The lack of both corresponding changes in corticospinal excitability and baseline neurophysiological predictors of efficacy, suggest the involvement of other neurophysiological mechanisms underlying Sativex effect on spasticity.

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P1095

Simultaneous recording of primary and cognitive visual evoked potentials in Multiple Sclerosis. Analysis of the relationship between primary visual and visuocognitive processing impairment and correlation with neuropsychological testing

C. Cordano[1,2], L. Mazzella[3], C. Ogliastro[1], M. Cellerino[1], C. Lapucci[1], L. Vestito[4], F. Bandini[5]
[1]DINOGMI, University of Genoa, Genova, Italy, [2]Dept of Neurology, UCSF, San Francisco, CA, United States, [3]ASL 3, [4]Associazione Rinascita Vita Onlus, Genova, [5]ASL 2 Savonese, Savona, Italy

Background: The P300 (P3) wave is an event related potential (ERP) component elicited in the process of decision making. It is usually elicited using the oddball paradigm, in which low-probability target items are mixed with high-probability non-target (or "standard") items.
Methods: We performed a study of simultaneously recorded "primary" (VEPs) and "cognitive" (ERPs) visual evoked potentials in a group of Multiple Sclerosis (MS) patients who have no signs or symptoms of visual dysfunction. Two unidimensional Gabor patches (with a luminance profile of a sinusoid multiplied by a gaussian) of 1 cycle per degree of spatial frequency, differing in the orientation of the gratings (horizontal and vertical), was presented in an "odd-ball" paradigm to 30 patients with MS and 30 age-matched control subjects. We measured the latencies and amplitudes of N70, P100 and P300 components, and derived the "normalized" measures of P300-N70 latency difference (Central Processing Time - CPT70), the P300-P100 latency difference (CPT100) and the P300 amplitude responses normalized to either N70 and P100 amplitude. We evaluated the relationship between primary and cognitive processing abnormalities. Than we investigated whether or not patients with orientation-dependent VEP changes, which are thought to be due to cortical pathology, have VERPs abnormalities. Third, we investigated if individual orientation-specific VEPs and VERPs results correlate with selective neuropsychological test scores for visuoperceptual or visuospatial skills. A wide battery of neuropsychological tests was performed.
Results: We found a significant correlation ($r=066$, $p< 0.01$) only between the Stroop test and the raw and normalized (CPT) P-300 results.
Conclusions: The P300-P100 latency difference (CPT100), a visual electrophysiological measure of cognition that is not dependent on impaired transmission along the optic nerve pathways, is associated with Stroop Test in MS patients.

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P1096

Correlation between demyelination and the latency of visual evoked potentials in spinal cord homogenate model

S. Marenna, V. Castoldi, R. Santangelo, L. Camaleonti, L. Chaabane, A. Quattrini, G. Comi, L. Leocani
San Raffaele Scientific Institute - Institute of Experimental Neurology, Milan, Italy

Remyelination is a rare phenomenon of spontaneous regeneration in the central nervous system and is the response that follows demyelination. Experimental autoimmune encephalomyelitis (EAE) is a good model to study inflammation, demyelination and also the remyelination. Optic nerve involvement and visual evoked potentials (VEPs) have been already shown in EAE model induced with myelin oligodendrocyte glycoprotein (MOG) but not with spinal cord homogenate (SCH), with the potential advantage of a milder chronic-relapsing disease. We measured clinical scores daily and VEPs in 7 DA rats at 0, 7 (n=3), 14, 21, 28, 35 and 42 days post injection (dpi) with optic nerve histology at 28 and 42 dpi. A first attack at 9 dpi, peaking at around 12 dpi with complete to partial recovery, followed by a second attack at 20-23 dpi in two subjects and by full recovery with no further attacks in one. VEPs delay was already evident at 7 dpi and persisted throughout, with the exception of the subject with a single attack and full recovery, which was accompanied by bilateral partial recovery of VEPs latencies. Optic nerves at 28 dpi showed dramatic demyelination consistent with VEPs delays and clinical scores. At 42 dpi, focal lesions were found in 3 optic nerves and remyelination in 2. In the 2 subjects with relapse, VEP at 42 dpi were more delayed and demyelination more evident with only partial or no remyelination. In the single rat where the disease developed in a single acute insult and full recovery, the ensuing remyelination was more represented, bilateral and homogeneous although with thinner myelin. Percent demyelination was correlated with VEPs latency performed at the corresponding time point ($r=0,593$; $p= 0,025$). These data are consistent with the view that VEP latencies provide a tool for detecting, measuring and monitoring the extent of demyelination and remyelination in EAE, in a non invasive and quantitative manner allowing to reduce sample size in drug testing and to provide information on the underlying pathological mechanisms.

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P1097

Entropy and phase shift as electroencephalographic markers of cognitive Information Processing Speed in Multiple Sclerosis

L.J.W. Canham[1], D.G. Western[2], P. Walsh[3], N. Kane[3], L.J. Hanley[4], A. Klicknicova[5], M. Harland[5], K. Inglis[4], D.A. Cottrell[4]
[1]Neurosciences, Bristol & Avon MS Centre, North Bristol NHS Trust, [2]Engineering, University of Bristol, [3]Grey Walter Department of Neurophysiology, [4]Bristol & Avon MS Centre, North Bristol NHSTrust, [5]Experimental Psychology, University of Bristol, Bristol, United Kingdom

Aim: To identify neurophysiological properties which may serve as biomarkers of the primary cognitive deficit arising in Multiple Sclerosis, namely reduced Information Processing Speed (IPS).
Background: Cognitive Impairment affects the majority of patients with MS and translational investigation could be aided by the availability of sensitive quantitative metrics deterministically associated with the underlying cognitive phenomena of interest. Intrachannel Bicoherence of EEG signals is an accepted index of the complexity (entropy) of regional cortical processing. The use of Hilbert Transformation to illustrate meta-stable phase state transitions buried within conventional signals has also offered indices related to intelligence in health and other states. We sought to perform a novel exploration of these phenomena in a typical MS cohort and test the hypotheses they would correlate with IPS.
Method: 30 patients with MS (20F/10M,13 RR/17 PMS, EDSS 1-7, mean IQ 102 sd 12, mean Age 42 range 24-66) were recruited and underwent neuropsychometric assessment with the Minimal Assessment of Cognitive Function In MS and resting state EEG (10:20 montage, 250Hz sample, nasal reference, 0.1-70Hz band-pass). Bicoherence in the 8-38Hz range and Hilbert Transform of the 8-12Hz alpha band in the midline and adjacent channels was examined.
Results: An anti-correlation between bicoherence of the parietal channels overlying the precuneal regions and performance on the Symbol Digit Modalities Test (SDMT Rs-.40 $p< 0.05$) and Paced Auditory Serial Addition Test (PASAT Rs-.44 $p< 0.05$) was observed. Conversely positive association between phase slip rates and performance on these tests (SDMT Rs .47 $p< .005$, PASAT Rs.48 $p< .005$) over the frontal regions was evident.
Conclusions: Increased Bicoherence (reduced entropy) over the key information integration regions and slower frontal neurophysiological cognitive frame rate in patients with slower clinical IPS support our hypotheses and suggest further exploration is warranted.

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Multimodal evoked potentials predict NEDA in patients starting first line treatment for multiple sclerosis

M. Pisa[1], M. Bianco[2], S. Guerrieri[1], G. Di Maggio[1], M. Romeo[2], L. Moiola[2], V. Martinelli[2], G. Comi[2], L. Leocani[1]
[1]Institute of Experimental Neurology - San Raffaele Hospital, Milano, [2]San Raffaele Hospital, Milan, Italy

Introduction: EPs have good predictive value on disability progression but no data are available about predictive value of EPs on NEDA evolution (No Evidence of Disease Activity) which is the goal for MS treatments.
Methods: 96 MS patients underwent multimodal EP (VEP-BAEP-SEP-MEP) at first-line treatment initiation. All patients received a 2.5±0.8 years clinical and neuro-radiological follow-up; 59 of them received a 7±1,4 years follow-up. Each EPs was assessed with an abnormality score (0 to 3); maximum possible multimodal EP score (GEPs) was 36. Patients were defined NEDA if no MRI or clinical activity and no confirmed disability progression occurred during the follow-up.
Results: A total of 35 patients (36.5%) reached NEDA criteria at follow-up. Mean EP score was 4.09 in NEDA patients (n=35) and 7.44 in patients with active disease (n=61, 63.5%), which is significantly higher (Mann-Whitney; p=0.026). Considering single modalities only VEP reached a statistically different percentage of abnormalities (Chi-square; p=0.004) between the two groups. A logistic regression was performed to ascertain the effects of GEPs, MRI lesion load, EDSS and disease duration on the likelihood that participants have NEDA evolution. The model correctly classified 77.1% of cases ($p< 0,0001$) with significant contribution of GEPs and EDSS. Similar results were obtained to predict first treatment failure (81.3%, p=0.01). Using the same controlling variables GEPs correlated with EDSS at follow-up (partial correlation coefficient=0.37; $p< 0.0001$).

The small number of NEDA patients (4/59) at the 7 years follow-up limited regression analyses which weren't statistically significant. However, GEPs correlated with EDSS at 7 years (partial correlation coefficient =0.41; p=0.002).
Discussion: Multimodal evoked potentials give significant information on disease progression at the early stages of the disease and EPs score should be included in treatment decision making process.

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P1099

Gait pattern in patients with different multiple sclerosis phenotypes

I.P. Dujmovic Basuroski[1,2], S. Radovanovic[3], V. Martinovic[4], J. Dackovic[2], G. Maric[5], S. Mesaros[1,2], T. Pekmezovic[5], J. Drulovic[1,2]
[1]Department of Neurology, University of Belgrade School of Medicine, [2]Clinic of Neurology, Clinical Centre of Serbia,

[3]Institute for Medical Research, University of Belgrade, [4]University of Belgrade School of Medicine, [5]Institute for Epidemiology, University of Belgrade School of Medicine, Belgrade, Serbia

Background: Gait pattern was reported to be impaired in multiple sclerosis (MS) patients even at the early disease stages, but gait pattern characteristics in patients with different MS phenotypes have not been fully elucidated.
Aim: We analyzed spatio-temporal gait pattern characteristics in MS patients with relapsing-remitting (RR) and primary-progressive (PP) MS in comparison with healthy controls (Co).
Patients and methods: The study comprised 70 (52 RR, 18 PP) MS patients (29 male, 41 female; mean age±SD, 37.2±10.5 years; median disease duration 5.3 years) and 40 sex- and age-matched healthy Co. In MS patients, neurological disability was assessed using the Expanded Disability Status Scale (EDSS). Median EDSS score in RRMS and PPMS patients was 3.0 (range, 0-5.0) and 4.5 (range, 3.0-6.0), respectively. Gait pattern measurements were performed using a GAITRite electronic walkway of 5.5 m active area. All subjects performed a standardized self-paced basic, simple walking task (task A), a dual-motor task (task A+ task B: holding a glass fully filled with water, aiming not to spill the water), a dual-motor/mental task (task A+ task C: serial "7" subtraction), and a triple combined motor/mental task (task A+ task B+ task C). Analyzed spatio-temporal gait parameters were: cycle time (CT), stride length (SL), swing time (ST) and double support time (DST).
Results: With each task performed, CT and DST in the total MS group were significantly longer and SL significantly shorter than in Co while ST was similar in the total MS patient group and Co. Patients with PPMS had significantly longer CT and DST and significantly shorter SL than both RRMS and Co at each of the tasks. At the dual motor task, ST was significantly longer in PPMS than in RRMS or Co while ST was similar in RRMS and PPMS at all other measurements. EDSS score correlated significantly with CT, DST and SL but no significant correlation was found with ST. In the total MS group, the simple walking paradigm and the triple motor/mental paradigm differed significantly in all studied gait parameters.
Conclusion: Patients with RRMS and PPMS differ in gait pattern characteristics, reflecting the differences in their functional capacity. Additionally, differences in gait pattern between MS patients and healthy people might partly contribute to the increased risk of falling in the MS population.

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Sensitivity of optical coherence tomography, full-field visual evoked potentials and multifocal visual evoked potentials combination to assess the visual system in Multiple Sclerosis

S. Guerrieri, G. Di Maggio, M. Pisa, F. Vitali, R. Santangelo, S. Medaglini, L. Moiola, U. Del Carro, V. Martinelli, G. Comi, L. Leocani
San Raffaele Scientific Institute, Milan, Italy

Introduction: In Multiple Sclerosis (MS) Optical Coherence Tomography (OCT) is used to measure Retinal Nerve Fiber Layer (RNFL) thickness as marker of axonal loss, while Visual Evoked Potentials (VEPs) as indicator of demyelination. We explored whether a multimodal visual system evaluation could be useful to assess MS patients in clinical practice.
Methods: 200 MS patients (16 Clinically Isolated Syndromes-CIS, 126 Relapsing Remitting-RRMS, 38 Secondary Progressive-SPMS, 20 Primary Progressive-PPMS, mean age 40.3 years, mean disease duration 8.19 years, median EDSS 2.0) underwent neurophysiological evaluation with OCT, full-field (ff-VEPs) and multifocal (mf-VEPs) VEPs. OCT was evaluated considering normative data provided by manufacturer; ff-VEPs and mf-VEPs were interpreted according to our lab data; for mf-VEPs cluster analysis was also performed. Sensitivities were compared using McNemar test.
Results: In eyes without Optic Neuritis (nON, n=274), OCT, ff-VEPs and mf-VEPs combination was more sensitive than each single technique (75.2% vs 28.8%, 52.2% and 66.1% respectively, $p< 0.001$). The same advantage (91.1% vs 63.3%, 75.6% and 82.2% respectively, $p< 0.001$ for OCT and ff-VEP, $p=0.008$ for mf-VEP) was found considering eyes with previous ON (>3 months - cON, n=90). In eyes with recent ON (< 3 months - aON, n=36) the combination of the three techniques was only superior to OCT (94.4% vs 58.8%, $p< 0.001$); both ff-VEPs and mf-VEPs showed alone a good diagnostic power (83.3% and 86.1% respectively). When comparing single techniques, both ff-VEPs and mf-VEPs were superior to OCT in nON eyes (28.8% vs 52.2% and 66.1% respectively, $p< 0.001$), with mf-VEPs more sensitive than ff-VEPs ($p< 0.001$). In cON eyes no statistical difference was found between OCT and ff-VEPs (63.3% vs 75.5%, $p=0.071$), with mf-VEPs more sensitive than OCT (82.2% vs 63.3%, $p=0.002$) but not than ff-VEPs. In aON eyes both ff-VEPs and mf-VEPs were superior to OCT (52.8% vs 83.4%, $p=0.003$ and 86.1%, $p=0.008$ respectively), with no difference among them.

Including cluster analysis mf-VEPs were found more sensitive than ff-VEPs also in cON eyes (87.8% vs 75.2%, p=0.013), but not in aON eyes, although reaching 94.4% sensitivity in this category.
Conclusions: These results support a routine multimodal approach to the visual system in MS, especially when examining nON and cON eyes. Among functional techniques, mf-VEPs show higher sensitivities than ff-VEPs if cluster analysis is performed.

Disclosure

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P1101

VEPs and OCT to explore the correlation between demyelination and axonal loss in a preclinical model of Multiple Sclerosis

V. Castoldi[1], S.-C. Huang[1], S. Marenna[1], R. Santangelo[1], S. Maestroni[2], D. De Battista[1], C. Chirizzi[1], M. Cursi[1], G. Comi[1], G. Zerbini[2], L. Chaabane[1], L. Leocani[1]
[1]San Raffaele Scientific Institute - INSPE, Institute of Experimental Neurology, [2]San Raffaele Scientific Institute, DRI - Diabetes Research Institute, Milano, Italy

Background: Experimental Autoimmune Encephalomyelitis (EAE) is a disease model of Multiple Sclerosis (MS) induced by injecting myelin oligodendrocyte glycoprotein (MOG). Although correlation between visual evoked potential (VEP) latencies and retinal neuroaxonal thinning measured with optical coherence tomography (OCT) is known in MS patients, the relationship between the two phenomena in preclinical models still needs further exploration. We investigated the correlation between the extent of VEPs and OCT abnormalities in MOG-EAE.
Methods: 24 Dark Agouti (DA) rats were tested: 12 immunized with MOG (EAE) and 12 healthy (H) with daily monitoring of body weight and EAE score. VEPs, OCT and histology were performed in selected animals at 21 (n=3), 34 (n=4) and 47 (n=5) days post injection (dpi). VEPs and thickness of retinal nerve fiber layer (RNFL) and ganglion cell/inner plexiform layer (GCL/IPL) measured with OCT were obtained in H at all time points. VEP latencies and retinal layers >2 Z-score of H were considered abnormal. For the correlation analysis, Spearman's correlations coefficient was used.
Results and conclusions: VEPs at 21 dpi were delayed in 4/6 EAE. At 34 dpi, 3/8 EAE eyes did not respond to visual stimuli and 2/8 eyes presented slow VEPs. At 47 dpi VEPs were absent in 5/10 EAE eyes and the remaining EAE eyes presented delayed latencies, suggesting that axonal loss and/or demyelination occurred in EAE, starting at early stages of the disease. RNFL of EAE was thinner at all time points, whereas atrophy of ganglion cell layer/inner plexiform layer (GCL/IPL) was not evident until 47 dpi. In EAE, VEP latency was negatively correlated with GCL/IPL thickness (rho=-0.633, p=0.011), whereas a trend was found with RNFL (rho=-0.449, p=0.093). At histology, EAE ONs presented severe demyelination, axonal loss and infiltrating microglia at 47 dpi, which were less evident at 21 and 34 dpi. The correlation between the severity of VEPs delays, detected even earlier than neuroaxonal loss evident at OCT, suggests that demyelination and axonal loss are associated in MOG EAE. The better correlation of GCL/IPL with respect to RNFL is consistent with the knowledge that the latter measure could be confounded by edema reported in the acute phases of optic neuritis. Moreover, these results confirm suggest the usefulness of both methods to monitor demyelination and neurodegeneration in vivo in EAE, providing quantitative measures for preclinical drug development.

Disclosure

All the authors of this poster have nothing to disclose.

P1102

Brain tDCS as a disease-modifying treatment of MS: A pilot study in a chronic EAE model

R. Santangelo, V. Castoldi, A. Finardi, M. Cursi, L. Camaleonti, G. Comi, R. Furlan, L. Leocani
Ospedale San Raffaele, Milan, Italy

Introduction: Transcranial direct current stimulation (tDCS) is a non invasive technique based on the application of weak, constant direct current inducing increase or decrease of neural excitability in apolarity dependent manner. Excitotoxicity and synaptic abnormalities are considered as an important mechanism underlying neurodegeneration in multiple sclerosis, as from models of experimental acute encephalomyelitis (EAE). We aimed at exploring the possibility that inhibitory tDCS could exert a neuroprotective role in EAE.
Methods: A total of 30 C57BL/6 female mice, subdivided in two sub-experiments with identical procedures, were immunized at time 0 with myelin oligodendrocyte glycoprotein (MOG) 35-55 derived peptide. They were randomized into 3 groups to receive cathodal or anodal tDCS at 250 mA, or sham (same manipulations but with no current flow) under volatile anaesthesia for a total 30 min (in on/off intervals of 10') in two cycles of 5 days each (10-14 and 17-21 days post injection -dpi). Clinical EAE scoring was quantified daily up to 26 d.p.i. by personnel blinded to the type of treatment. To account for variability in EAE onset across experiments, the time course of clinical scores in treated subgroups was aligned with respect to the time course of that of the corresponding sham subgroup.
Results and conclusions: Both active groups showed a tendency towards lower EAE score than the sham group, significant for cathodal t-DCS only (repeated measures ANOVA: Time p< 0.0001; Group: p=0.027), which was associated with a delay in

EAE onset with respect to sham (anodal: 3.4± 1.5; cathodal: 3.7 ± 1.15; p=0.0077 log rank; kaplan-meyer curve). Although preliminary, these data are promising towards further exploration of the use of t-DCS in reducing clinical expression of EAE .If further validated, these results may have a potential therapeutic impact, particularly in the disease stages characterized by dominant neuro-inflammation, such as in relapsing remitting MS.

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P1103

Attenuation of the melanopsin-mediated sustained pupillary constriction response in MS: A putative pathophysiologic signature for interrogating the integrity of the retino-hypothalamic tract in MS

E. Kildebeck[1,2], S. Beh[1], A. Conger[1], D. Conger[1], L. Balcer[3], P. Calabresi[4], S. Saidha[4], R. Rennaker[2], E. Frohman[1], T. Frohman[1]
[1]UT Southwestern Medical Center, Dallas, [2]UT Dallas, Richardson, TX, [3]New York University School of Medicine, New York, NY, [4]Johns Hopkins Hospital, Baltimore, MD, United States

Objective: Test the hypothesis that the melanopsin-mediated sustained pupillary constriction response can be attenuated in the context of damage to retinal architecture.
Background: We can objectively investigate the relationship between retinal architecture and a corresponding tissue-specific neurophysiologic signature: the blue light-induced, melanopsin-mediated pupillary constriction response. Also, retinal ganglion cell neurons expressing melanopsin project to the suprachiasmatic nucleus (SCN), known as the body´s circadian clock. Understanding how retinal damage in MS changes the melanopsin-mediated pupillary response may help elucidate the impact of damage on transmission to the hypothalamus. This can potentially alter homeostatic networks associated with fatigue, cognition, mood regulation, autonomically-mediated immune system regulation, satiety, sexual behavior, neuroendocrine reflex arcs, and thermodysregulation in MS patients.
Methods: We developed a novel device capable of stimulating the retina with a restricted range of blue light in 10nm bins from 400-500nm in order to determine if blue light-induced persistent constriction responses are of variable magnitude in different MS patients when employing discrete blue light stimuli. This melanopsin-mediated response following cessation of a blue light stimulus was compared to the photoreceptor-mediated pupillary constriction following cessation of a red light stimulus. OCT was used to characterize the relation of pupillary responses to changes in retinal architecture, specifically the thickness of the retinal ganglion cell layer and inner plexiform layer (GCL+IPL).
Results: A significant correlation between GCL+IPL thickness and duration of the melanopsin-mediated pupil constriction phase response establishes this unique response as a potential pathophysiologic signature and biomarker for understanding the relationship between structure and function of the visual system in MS.
Conclusions: Retinal damage in MS correlates with deficits in a unique blue light-specific pupillary response. We can profile individual MS patients for the stimulus characteristics of greatest response for them, and potentially fabricate glasses or other devices capable of delivering therapeutic ´epochs´ of blue light stimulation specifically optimized for each patient. Such treatment may be germane to improving a vast array of the body´s homeostatic states; and specifically those that cause significant morbidity in MS.

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P1104

The strength of association between brain MRI and cognitive measures in multiple sclerosis depends on patients characteristics

T. Uher[1], M. Vaneckova[2], J. Krasensky[2], J. Blahova Dusankova[1], L. Sobisek[3], Z. Seidl[2], M.P. Sormani[4], R.H.B. Benedict[5], E. Havrdova[1], B. Benova[1], K. Kucerova[1], T. Kalincik[6,7], D. Horakova[1]
[1]Neurology, [2]Radiology, Charles University in Prague, 1st Faculty of Medicine and General University Hospital in Prague, [3]Department of Statistics and Probability, University of Economics in Prague, Prague, Czech Republic, [4]Department of Health Sciences, University of Genoa, Genoa, Italy, [5]Department of Neurology, University of Buffalo, Buffalo, NY, United States, [6]Neurology, University of Melbourne, [7]Neurology, Royal Melbourne Hospital, Melbourne, VIC, Australia

Background: Although, majority of the previous studies showed relationship between MRI pathology and cognitive performance

(CP) in multiple sclerosis (MS) patients, it is not clear whether this association is different according to patients characteristics.
Objective: To investigate, if sub-populations of MS patients show different strength of association between MRI and cognitive measures.
Methods: Of the 1253 patients enrolled in the study, 1052 patients with complete cognitive, MRI and clinical data were included. Brain MRI (T2 lesion volume [T2-LV], brain parenchymal fraction [BPF], gray and white matter, thalamic and corpus callosum fractions) and neuropsychological assessment (brief international cognitive assessment for MS [BICAMS] and paced auditory serial addition test) were performed. Spearman´s correlation and regression analysis adjusted for age, gender, education, depression, treatment status, expanded disability status scale (EDSS) were used to investigate the associations between MRI measures and CP in various MS subpopulations.
Results: Median of EDSS was 2.5, average disease duration was 10.0 years and 82% of patients were on disease-modifying treatments. Cognitive impairment was present in 27% of patients. A weak correlation among cognitive domains and MRI measures was observed in younger patients (age⩽30 years; Spearman´s coefficient range [rho]=.08-.20), short disease duration (< 2 years; rho=.08-.17), low EDSS (⩽1.5; rho=.09-.14), low T2-LV (lowest quartile; < .59 ml; rho=.06-.10) and high BPF (highest quartile; >86.66; rho=.05-.08). A stronger correlation among cognitive domains and MRI measures were observed in older patients (age>50 years; rho=.29-.33), longer disease duration (>15years; rho=.24-.38), higher EDSS (⩾5.0; rho=.21-.27), greater T2-LV (highest quartile; >5.33 ml; rho=.16-.23) and lower BPF (lowest quartile; < 83.71; rho=.18-.27). Significant interactions (p⩽.01) among majority of MRI measures and T2-LV or BPF in adjusted regression models with the dependent variable being CP confirmed our results.
Conclusions: Weak correlations between brain MRI and cognitive measures occur predominantly in patients with a low disease burden. This indicates that impact of MRI brain pathology on CP is greater in more advanced disease. This may have an important implication for clinical practice, interpretation of research findings, investigation of the role of brain reserve and designing of clinical trials.

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P1105

Early cerebellar cognitive profile in multiple sclerosis: from saccadic impairment to grey matter alterations

A. Moroso[1,2], A. Ruet[1,2], D. Lamargue-Hamel[2], F. Munsch[2], M. Deloire[1], P. Coupé[3], J.-C. Ouallet[1], S. Cubizolle[1], N. Moscufo[4], D. Meier[4], V. Planche[2], T. Tourdias[1,2], C. Guttmann[4], V. Dousset[1,2], B. Brochet[1,2]
[1]Bordeaux Hospital University Center, [2]Neurocentre Magendie, INSERM U862, Bordeaux, [3]LaBRI, UMR 5800, PICTURA, Talence, France, [4]Center for Neurological Imaging, Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Background: Cerebellar damages occur early in multiple sclerosis (MS) and could be responsible for cognitive impairment. However, symptoms are difficult to evaluate at this stage of the disease. Eyetracking is a reliable and simple mean to evaluate both subtle cerebellar symptoms and cognitive impairment associated with morphological alterations in the cerebellum.
Objectives: To compare cognitive pattern and posterior cerebellar grey matter (GM) damages in patients with and without cerebellar symptoms as determined by saccadic abnormalities, within the first year after a clinically isolated syndrome (CIS), and healthy subjects (HS).
Methods: Twenty-eight patients and 12 HS underwent an eyetracking protocol. Cerebellar impairment was defined by registration of saccadic intrusions and/or at least 10% of dysmetria at oculomotor (OM) recording. Visually-guided (VGS), memory-guided (MGS) and antisaccade (AS) paradigms were used to assess respectively attention, working memory and inhibition and compared to classical neuropsychological assessment. GM volume in posterior cerebellar lobules (VI to VIIIb) was estimated using 3T magnetic resonance imaging including 3D T1 weighted images.
Results: Sixteen patients fulfilled saccadic criteria for cerebellar impairment. Patients with cerebellar symptoms (PwC) performed worse on memory-guided saccade latencies and error rate and had impaired working memory, executive functions and information processing speed (IPS) z scores compared to patients without cerebellar symptoms (PwNC). IPS was correlated with AS error rate in all patients and VGS error rate and MGS final eye position ratio in cerebellar patients. PwNC had increased GM volume than HS and PwC in most of the cerebellar posterior lobules. Left Crus I GM volume was correlated with visually guided saccades gain (R=0.69; p=0.003) only in PwC subgroup.
Conclusion: Eyetracking and especially memory-guided saccade paradigm is a sensitive and reliable tool to assess cognitive dysfunctions in early MS and differentiates cerebellar from non-cerebellar patients. In CIS patients, cerebellar symptoms provide a specific cognitive profile with more working memory, executive

functions and IPS impairment. GM alterations seemed more pronounced in PwC than in PwNC suggesting a potential susceptibility to early neurodegeneration.

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P1106

Gray and white matter damage differently correlated with cognition in adult multiple sclerosis patients with different age of disease onset

L. Vacchi[1], M.A. Rocca[2], B. Colombo[3], M. Rodegher[3], L. Moiola[3], A. Ghezzi[4], G. Comi[3], A. Falini[5], M. Filippi[2]

[1]Ospedale San Raffaele - Vita-Salute San Raffaele UniversityDepartment of Neurology and INSPE, [2]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, [3]Department of Neurology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, [4]MS Center, Ospedale di Gallarate, Gallarate, [5]Department of Neuroradiology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Background: Age of MS onset may influence clinical status during adulthood.

Aims. To explore the relationship between the patterns of brain gray matter (GM) atrophy and white matter (WM) microstructural abnormalities and cognitive performances in adult MS patients according to their age of disease onset.

Methods: 3D T1-weighted and diffusion tensor (DT) MRI scans were acquired from 41 pediatric-onset (PO), 42 age-matched (AOA) and 35 disease duration-matched (AODD) adult-onset MS patients. Fifty-eight healthy controls were also studied. Whole-brain voxel-wise methods were used to define the regional distribution of damage in the brain GM and WM, using tract-based spatial statistics (TBSS) and voxel based morphometry (VBM). Between-group comparisons were adjusted for age or disease duration, as appropriate. Correlations with cognitive performances were estimated (age-adjusted analyses).

Results: Comparable cognitive performances were observed in POMS *versus* AOA or AODD patients. In POMS patients, atrophy of frontal and subcortical areas correlated with poor memory performance. Moreover, decreased FA in the main WM tracts and increased MD in the main supra-tentorial tracts correlated with deficits at the main cognitive domains. In AOA-MS and AODD-MS patients, decreased FA and an increased MD in the corpus callosum, cingulum, corona radiata, internal and external capsule, superior longitudinal fasciculus and posterior thalamic radiation correlated poor performance at the attentive domain only.

Conclusions: Although POMS had similar cognitive performance, the relationship between cognitive abnormalities and brain structural damage was more distributed than in patients with similar age and disease duration. This suggests the role of structural maturational aspects in the proper development of cognitive skills and the possible presence of different MS pathogenic mechanisms during childhood that may alter brain structural development, in particular WM connections.

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Prof. Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory boards for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer´s Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

P1107

The brief international cognitive assessment in multiple sclerosis: preliminary results from a two-year follow-up study

N. McNicholas[1], K. O'Connell[2], N. Tubridy[3], M. Hutchinson[2], C. McGuigan[4]

[1]Department of Neurology, St. Vincent's University Hospital / University College Dublin, [2]Department of Neurology, St. Vincent's University Hospital / University College Dublin, [3]Department of Neurology, St. Vincent's University Hospital / University College Dublin=, [4]Department of Neurology, St. Vincent's University Hospital / University College Dublin, Dublin, Ireland

Background: Cognitive impairment (CI) is common amongst people with multiple sclerosis (MS), resulting in a significant impact on quality of life, irrespective of disability. Although its burden is now well-recognised, it remains a neglected area in clinical practice. The brief international cognitive assessment in multiple sclerosis (BICAMS) was developed as a screening tool of CI, for use in a clinical setting. It consists of the symbol digit modality test (SDMT), California verbal learning test (CVLT-2) and brief visuospatial memory test (BVMTR), and takes 15 minutes to administer. It has been validated in 10 different populations to-date.

Aim: The aim of this study was to test BICAMS as a dynamic marker of CI over time.

Methods: 33 of 67 MS subjects and 24 of 66 control participants, who were involved in the original validation study at our department were re-administered BICAMS at a second time-point (mean 2.17years, (standard deviation [SD] 2.52weeks) for patients; mean 2.12years (SD 4.72weeks) for controls. Baseline age, sex, and years of education were recorded in both groups - with MS subtype, disease duration and EDSS in the patient cohort. A t-test was used to examine between group differences in mean scores and mean change over time on the individual tests, $p< 0.05$ considered significant.
Results: Baseline characteristics showed mean age of 44.4 years (SD 10.86) in patients, and 46.4 years (SD 11.74 years) in controls, and mean education of 13.6 years (SD 2.22) in patients, 14.25 years (SD 2.98) in controls. 69.7% of patients and 62.5% of controls were female. Significant differences were seen in mean scores between patients and controls in each of the three parameters tested. SDMT patient mean score: 50.94, controls: 57.875, p 0.0291. CVLT-2 patient mean score: 47.667, controls: 56.458, p 0.0051. BVMTR patient mean score: 16.64, controls: 20.29, p 0.0063. No difference was seen between mean scores at T0 and T1 in any individual test for either patient or control groups, and testing was administered by a different neurologist at T1 and T0, reflecting low inter-rater variability.
Conclusion: Our study shows differences in mean scores between patients and controls persist over time, supporting its use in screening for CI. There was no significant cognitive change over time, which may be an effect of the small sample size and short follow-up period. Further work is needed to assess the role for BICAMS in monitoring cognition over time.

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P1108

Cognitive impairment is a marker of disease progression in multiple sclerosis patients: a 7-year follow-up study

M. Pitteri[1], C. Romualdi[2], S. Ziccardi[1], R. Magliozzi[1,3], S. Monaco[1], M. Calabrese[1]
[1]Department of Neurosciences, Biomedicine and Motor Sciences, University of Verona, Verona, [2]Department of Biology, University of Padova, Padova, Italy, [3]Division of Brain Sciences, Department of Medicine, Imperial College London, London, United Kingdom

Introduction: Cognitive impairment (CI) affects a large proportion of multiple sclerosis (MS) patients and can reflect disease progression. The factors associated with CI in MS have not been fully elucidated; in particular, the prognostic value of CI combined with advanced MRI metrics (cortical thickness, CTh) has not been explored yet.
Aims: We evaluated the role of CI as a marker of cortical thinning development in the long term with the ultimate aim to identify MS patients at high risk of developing disease progression since the early phase of the disease. A secondary aim was to follow-up the disability progression.
Methods: We studied 78 MS patients who underwent cognitive assessment at baseline and who had been followed-up for a median of 7 years (range: 4-13). At baseline, 71 were RR and 7 SP (Age: mean 37.8±10.5; Gender: 50 F; disease duration: mean 8.5±7.5). Patients were under immunomodulatory therapy during the course of this retrospective study. We divided MS patients in three groups, according to the number of failed tests (we considered the cut-off scores based on the 5th percentile): 1) cognitive normal (CN; 0 failed tests), 2) mild CI (up to 2 failed tests), and 3) severe CI (3 or more failed tests). All images were acquired using a 1.5T Philips Achieva MRI scanner.
Results: At baseline, 39 patients were CN, 26 mCI, and 13 sCI. Global cortical thinning was higher in mCI (mean Δ-CTh= 16.7%±6.5%, $p< 0.001$) and in sCI (mean Δ-CTh=33.6%±7.1%, $p< 0.001$) than in CN (mean Δ-CTh=3.6%±1.7%) patients, whereas no difference was observed among the three groups in terms of Δ-White Matter Lesion Volume (WMLV; p=0.360). CI was the only significant predictor (β=-0.148, $p< 0.001$) of Δ-CTh. Strong correlation was observed between number of pathological tests and Δ-CTh (r_s=0.879, $p< 0.001$), but not with Δ-WMLV (r_s=-0.234, p=n.s.). Six CN (15%), 14 mCI (54%), and 12 sCI (92%) showed disability progression at follow up, $\chi^2(2,78) = 26.49$, $p < .001$.
Conclusions: We showed that CI in MS patients can be a prognostic marker of more aggressive and neurodegenerative disease and can be a predictor of disease progression 7 year later from the time of diagnosis. We suggest that comprehensive neuropsychological assessment should be carried out since the time of diagnosis, because it can play a crucial role in defining and predicting the clinical course of the disease in the long term and may contribute in improving the clinical decision-making.

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P1109

Vocational status in patients with relapsing remitting MS: what are the most contributing factors?

M. Filser[1], S. Ullrich[2], C. Lassek[3], I.-K. Penner[1,4]
[1]COGITO Center for Applied Neurocognition and Neuropsychological Research, [2].05 Statistikberatung,

Düsseldorf, [3]Neurological Group Practice, Kassel/Vellmar, [4]Neurology, University Hospital Düsseldorf, Düsseldorf, Germany

Background: Since the majority of patients with multiple sclerosis (MS) is affected by the disease at younger ages the ability to work and to hereby remain independent are crucial prerequisites for quality of life (QoL). There is evidence from a former study that at early stages, cognitive functionality plays a major role in the context of working ability.
Objective: To evaluate on a large sample of consecutively screened relapsing remitting MS (RRMS) patients which factors exert the strongest influence on vocational status. Design/**Methods:** All data were collected as part of a large multi-centre study across 65 centres in Germany. In each centre patient related data (age, education, vocational status, disease duration, medication, duration of medication) were recorded as well as cognitive functionality assessed by the Brief International Cognitive Assessment for MS (BICAMS) battery comprising Symbol Digit Modalities Test (SDMT), Brief Visual Memory Test revised (BVMT-R) and Verbal learning and Memory Test (VLMT, as German equivalent of the CVLT-II).
Results: 826 RRMS patients, 632 female, mean age 41,53 (SD=10,55), 750 under medication were included. To evaluate which factors best predict patients´ working ability, a logistic regression analysis was conducted and revealed significant effects for SDMT, age, education, and disease duration (DD) while VLMT, BVMT-R, duration of medication and medication in general were not influencing factors.
Conclusions: These results clearly demonstrate that besides age, education and DD the ability to process information quickly and to keep information for a short period of time in working memory is highly relevant for patient's ability to work. Thus, regular screening by the SDMT is recommended not only for detecting decline as early as possible but also for offering therapeutic strategies targeting on this highly relevant cognitive domain.

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P1110

Corpus callosum atrophy and cognitive impairment in multiple sclerosis

M.Y. Pérez Martín[1], M. González Platas[1], S.L. López Gallardo[1], L. Miceli Sopo[1], A. Jiménez Sosa[2]
[1]Service of Neurology, [2]Unit of Research, Complejo Hospitalario Universitario de Canarias, La Laguna, Spain

Background: Atrophy of the corpus callosum, was often associated with different cognitive variables such as processing speed, verbal fluency, interhemispheric disconnection deficit or presence of fatigue.
Objectives: Investigate the relationship between total and regional corpus callosum (CC) atrophy and cognitive performance in patients with MS.
Method: 112 patients with MS were included; mean age 41±10 years, 74 women, schooling 12±3 years, mean disease duration 9±6 years, 104 Relapsing-Remitting forms and Expanded Disability Status Scale (EDSS) score 2.0 (median). All participants underwent brain magnetic resonance and comprehensive cognitive testing. Total and regional CC atrophy was measured with the corpus callosum index (CCI).
Results: Controlling for age and schooling, CCI was associated to information processing mesaures (Symbol Digit Modalities Test (p>0,001), Verbal Tracking Test (p=0,02), and Spatial Location (p=0,02)), verbal and visual memory (total recall of Selective Reminding Test (p>0,001), Logic Memory Test (p=0,01), Complex Figure Test (p=0,004) and 10/36 Spatial Recall Test (p< 0,001)), categorical fluency (p< 0,001), visuoperceptive organization (Hooper Visual Organization Test: p=0,01) and cognitive flexibility (Wisconsin Card Sorting Test: p=0,005). Anterior CC segment was associated to verbal, visual and working memory, Splenium was associated to attention, visuoperceptive organization and naming, and médium segment was associated to processing speed, memory and executive functions.
Discussion: Atrophy of the CC is related with cognitive dysfunction in MS. Regionally, different cognitive processes are associated to the three portions of CC suggesting a relative cognitive specialization. Naming, depending anterior areas, show association with splenium size suggesting a posterior areas intervention that help run this function.

Disclosure

Nothing to disclose

P1111

Cognitive changes in multiple sclerosis patients treated with subcutaneous adrenocorticotropic hormone for acute relapse

K.A. Kunker, A.S. Drake, L.N. Irwin, A. Khan, M. Bucello, B. Weinstock-Guttman, R.H.B. Benedict
Neurology, University at Buffalo, State University of New York, Buffalo, NY, United States

Background: Few studies have focused on cognitive changes occurring during multiple sclerosis (MS) relapses as measured by neurocognitive tests. In the few published studies, cognitive processing speed as measured by the Symbol Digit Modalities Test (SDMT) declined from baseline, and nearly normalized following conventional steroid therapy. In some studies, this effect was accompanied by changes in patient report outcomes (PROs), but not so in others. To date, there is no study on the effects of subcutaneous adrenocorticotropic hormone (ACTH) self-injection on cognitive outcomes.
Methods: The SDMT and the MS Neuropsychological Screening Questionnaire (MSNQ) were administered at baseline, during relapse but prior to therapy, and at 3-month follow-up. There were two groups of participants: [a] 14 patients with cognitive relapse as indicated by patient, caregiver, or clinician perceived decline and confirmed by a drop of 3 points on SDMT, and [b] 14 stable

MS controls. Patients were treated for relapse with 5 days of 80 units/day ACTH self-injection. Follow-up SDMT and MSNQ scores were obtained 90 days later. Patients who recovered 3 or more points on the SDMT were categorized as ACTH responders (n = 7). Data were analyzed by mixed-factor ANOVA with a significance threshold of $p < 0.05$.

Results: Relapsing and stable patients differed on SDMT and MSNQ, with only relapsing patients declining at relapse, and showing statistically significant recovery. Within the relapsing group, the responder analysis revealed a significant interaction, or trend, on three MSNQ items: item 3 (slowed problem solving, $p = 0.026$), item 1 (easily distracted, $p = 0.056$) and item 7 (need instructions repeated, $p = 0.096$). Perceived worsening of impairment was observed at time of relapse in both groups, but only responders reported perceived improvement at 3 months.

Conclusions: These findings suggest a recovery from cognitive relapse in patients treated with subcutaneous ACTH self-injection. PRO changes are found concordant with changes noted on the SDMT. These results may have significant implications for future trial design examining cognitive relapse and recovery, and for ascribing clinical meaningfulness to changes in SDMT and self-reported measures of cognition. Future studies are warranted.

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P1112

Emotional modifications in multiple sclerosis: a neuropsychological study

L. Pfaff[1], D. Gounot[1], J.-B. Chanson[2], J.-P. Armspach[1], J. De Seze[2], F. Blanc[1,2]
[1]CNRS, ICUBE, FMTS, University Of Strasbourg, [2]Neurology, Hôpitaux Universitaires de Strasbourg, STRASBOURG, France

Background: Emotions are essential for human being. They help us to make decision to better manage our personal and social life (Sanders, 2012). In Multiple Sclerosis (MS), emotional disorders are frequent, generally identified by difficulty to recognize facial expression (Henry & all 2011). However, interaction between emotional disorder and other cognition or psychological disorders remains little documented. Furthermore, emotions have been considered into the recognition component, rarely into the experience dimension.

Objective: Explore emotion in MS with regard to his two neurosciences dimension that are emotion recognition and emotional experience and to compare this data with cognitive, psychological, and disease aspect.

Methods: 25 women with relapsing-remitting MS (EDSS=1,64 ± 1,57) and 27 Healthy Controls (HC) matched for age, sex and education were evaluated by a comprehensive neuropsychological battery and psychological scales (EHD, Hamilton, TAS 20, Fatigue Scale). Facial emotion recognition was assessed using the Florida Affect Battery (FAB). Emotion Experience was assessed using emotional scene stemming from the IAPS, differing in valence (positive, negative, neutral), and arousal (ranging from calm to excited). Participants had to estimate their experience by seeing every image and scoring the valence and the arousal sensation.

Results: Compared to control, MS patient showed significantly less correct answer at the Emotional FAB ($p=0.017$). The subjective evaluation in front of positive, negative or neutral scene does not differ between MS patients and HC, for the aspect of valence or arousal.

MS group showed significantly higher score in Depression, Anxiety, Fatigue and Alexithymia Scales, was significantly slower in processing speed, and had lower short-term memory. For MS group, *emotion recognition* at the FAB was correlated with several executive functions, processing speed, and divided attention and *emotional experience* with flexibility capacity. No correlations were found between psychological or diseases characteristic for emotion recognition and emotion experience.

Conclusion: Patient with MS present difficulty to identify emotion but their emotional experience are preserved. These difficulties are correlated with processing speed and executive functions, but are independent from other psychological disturbance or disease characteristics. Further studies should include fMRI data to better understand these interconnexions.

Disclosure

nothing to disclose

P1113

Modifying the SDMT to reduce working memory: A pilot study

V. Patel[1,2], L. Walker[3,4], A. Feinstein[1,2]
[1]Psychiatry, Sunnybrook Health Sciences Centre, [2]University of Toronto, Toronto, [3]Neuroscience, Ottawa Hospital Research Institute, [4]University of Ottawa, Ottawa, ON, Canada

Background: Information processing speed is a hallmark cognitive deficit in multiple sclerosis (MS). The Symbol Digit Modalities Test (SDMT) is considered the most sensitive indicator of processing speed.

Objective: To modify the SDMT by reducing the working memory component and focusing primarily on processing speed.

Methods: Two computerized versions of the SDMT (c-SDMT) were developed. In the fixed version the symbol-digit key is kept constant throughout the 8 trials of the test, whereas in the variable version a different key is presented for each trial. Each trial consisted of 9 symbols and digits. A total sample of 78 MS and 68 healthy control (HC) subjects, matched in age, gender, years of

education and premorbid IQ, were recruited. Forty MS and 33 HC subjects were administered the fixed c-SDMT, and 38 MS and 35 HC subjects the variable version.
Results: MS subjects performed significantly slower than HC subjects on both the fixed (mean [SD]: 15.19 [5.61] vs. 12.14 [1.73] seconds, t=-2.997, p=0.004) and variable (15.11 [3.48] vs. 13.08 [2.26] seconds, t=-2.967, p=0.004) c-SDMT respectively. There were no differences in mean time between the fixed and variable tests for MS and HC subjects (t=0.078, p=0.938 and t=-1.907, p=0.061 respectively). While the HC group demonstrated changes over time in performance speed on both the fixed (repeated measures ANOVA, F=12.281, p< 0.001) and variable (F=4.161, p=0.001) c-SDMT, the MS group did so only on the former (F=13.812, p< 0.001).
Conclusions: MS subjects no longer show an improvement in serial performance on the SDMT when the working memory component is substantially reduced. This suggests that purer measures of processing speed may be relatively resistant to practice effects in people with MS.

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P1114
Cognitive profile clusters of patients with CIS and early relapsing remitting MS

V. Chavarro, E. Freitag, J. Behrens, C. Finke, M. Scheel, S. Papazoglou, K. Ruprecht, J. Bellmann-Strobl, A.U. Brandt, F. Paul
Charité - Universitätsmedizin Berlin, Berlin, Germany

Background: Cognitive impairment is observed in more than half of patients with Multiple Sclerosis and recent studies suggest that cognitive deficits are detectable as early as the first neurological event. Characterizing cognitive profiles could identify patients who would benefit from rehabilitation and prevention strategies at the earliest phases of the disease.
Objective: To investigate cognitive profiles among patients within 6 months of the first neurological event.
Methods: We included 132 patients after a first clinical event. From these, 110 patients were diagnosed with Clinically Isolated Syndrome (CIS), average age 32.6 years (SD=8.6), 65% females, and 22 patients were diagnosed with Relapsing Remitting Multiple Sclerosis (RRMS), average age 32.7 years (SD=10.1), 73% females, according to the 2010 McDonald criteria. Primary outcome measures were scores of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) normalized for age and education to the German population. Z-scores between patients with CIS and RRMS were compared with t-tests. We performed a within-groups linkage cluster analysis for the entire cohort to detect distinct cognitive profile clusters.
Results: There was no difference between RRMS and CIS patients' performance on any of the cognitive domains. We identified three meaningful cognitive profile clusters. Clusters did not differentiate RRMS from CIS patients. Cluster 1 (N=97) performed average or slightly above average on all cognitive domains (BRB-N total z-score = 0.846). Cluster 2 (N=22) performed significantly lower on concentration and attention (BRB-N concentration/attention z-score = -1.442) but had normal performance on the remaining cognitive domains, and a total BRB-N z-score = -0.255. Cluster 3 (N=12) performed below average on all cognitive domains, and their BRB-N total z-score =-0.898.
Conclusion: Cognitive performance at the first neurological event does not differ between patients diagnosed with CIS and RRMS, but distinct cognitive profiles delineate three patient groups. The majority of patients (74%) perform slightly above average on all cognitive domains. A small group (17%) perform below average only on tests of concentration and attention. Another small group (9%) perform worse than average on all cognitive domains. Further work should address how these different profiles relate to neuroimaging findings and disease progression.

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P1115
Temporal lobe integrity underlies cognitive impairment in pediatric onset multiple sclerosis (MS)

C. Schwarz[1], L. Ijaz[2], M. Shaw[1], E. Bartlett[2], L. Krupp[1], C. Delorenzo[2], L. Charvet[1]
[1]Neurology, NYU Langone Medical Center, New York, [2]Stony Brook Medicine, Stony Brook, NY, United States

Pediatric onset multiple sclerosis (POMS, referring to those diagnosed before the age of 18 years) is marked by demyelination in the context of ongoing neurodevelopment. Approximately one-third of those with POMS are estimated to have cognitive impairment. However, the risk factors and trajectory remain relatively unknown. We studied cognitive performance in a sample of

POMS participants compared to age-matched healthy controls, linking to neuroimaging measures of structure and function. Cognitive functioning was assessed using the Pennsylvania Computerized Neurocognitive Battery (CNB), an approximately 1.5 hour battery assessing a range of cognitive domains. Participants then underwent MRI scanning. MRI sequences included a T1-weighted anatomical scan and 64-direction diffusion tensor imaging (DTI). Regions of interest were automatically determined using Freesurfer analysis software. These labels were used to calculate region-wise mean DTI fractional anisotropy (FA), a measure of white matter integrity. Participants were 18 consecutively-recruited POMS patients along with 24 healthy controls matched for age (18.5±4.4), gender (69%), and years of education (12.3±3.0). The POMS group did not differ from the controls on most measures across the battery. However, the POMS sample did perform more poorly on tasks of motor praxis (MP, p=0.006) and visual abstract reasoning (Conditional Exclusion Test or CET, p=0.007). Further, performance on both tasks was significantly correlated with temporal lobe FA (Motor Praxis, r=0.62, p=0.01 and visual abstract reasoning, r=0.59, p=0.02). In summary, a consecutively-recruited POMS sample was not distinguished from matched controls on most cognitive measures. However, relative impairments were found for motor praxis and visual abstract reasoning, which corresponded to decreased temporal lobe FA. This decrease in FA suggests that there is white matter fiber disruption, such as demyelination, cellular infiltration, axonal loss and/or disorganization in the temporal lobe in the POMS sample, which may be involved in the relative impairment in motor praxis and visual abstract reasoning. Decreased temporal lobe FA is also consistent with previous findings in POMS samples. Standard neuropsychological domains may not be sensitive to detecting early impairment in POMS.

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P1116

The rivermead behavioural memory test: a useful tool for the assessment of prospective memory in multiple sclerosis patients

M. López-Góngora, L. Querol, N. Vidal, A. Escartin
Neurology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

Background: and **Objective:** Frequently, multiple sclerosis (MS) patients complain of memory problems that may include difficulties to remember to perform certain actions at the right time in the future. This ability is known as prospective memory. One of the tests that has been used to assess this type of memory is the Rivermead Behavioural Memory Test (RBMT), nevertheless, it is not frequently used in the assessment of MS patients.
The aim of the present work is to study the RBMT as a tool to evaluate prospective memory in MS patients.
Method: We included MS patients with no history of alcohol or drug dependence, or medical or psychiatric disorder that could affect cognitive performance. Patients who had presented a relapse or who were treated with corticosteroid in the previous month, were not included. All patients underwent a neuropsychological assessment that included the RBMT and the Brief Repeatable Battery of Neuropsychological Tests (BRB-N). Patients also answered a depression questionnaire. All patients were assessed by the neurologist in order to obtain the Expanded Disability Status Scale (EDSS) score. The same procedure was repeated one and seven years later.
Results: A total of 96 patients (68 females) with a mean age of 36,9 years(SD=9,15), were included. Time of evolution of the disease was 6,7 years(SD=6,4) and median EDSS score was 2,0.

The Pearson correlation coefficient showed a positive and significant correlation($p< 0.05$) between the RBMT and the subtests of the BRB-N in the three assessments, except for the 2 seconds version of the Paced Auditory Serial Addition Test where the correlation in the 2nd and 3rd assessments was not significant(p=0.078; 0.070).

A negative significant correlation was observed between the RBMT and the EDSS in the three evaluations.

The correlations between the RBMT and the depression questionnaire were not significant at the 2nd and 3rd evaluations.

In general, the higher correlations were observed between the RBMT and the visual and verbal memory tests and the symbol digit modalities test (SDMT) in all three evaluations (baseline, one and seven years).
Conclusions: In a follow-up period of 7 years, the results of the present study show a positive and significant correlation between the RBMT and the memory subtests of the BRB-N and with the SDMT that has shown to be a useful tool assess cognitive impairment in MS. These data support the use of the RBMT to assess prospective memory in MS.

Disclosure

Authors have nothing to disclose.

P1117

Functional and structural correlates of computerized processing speed in multiple sclerosis

M. Shaw[1], E. Bartlett[2], C. Schwarz[1], M. Kasschau[1], L. Ijaz[2], L. Krupp[1], C. Delorenzo[2], L. Charvet[1]
[1]Neurology, NYU Langone Medical Center, New York, [2]Stony Brook Medicine, Stony Brook, NY, United States

Cognitive impairment affects more than half of all individuals with multiple sclerosis (MS), although its cause remains unclear. Cognitive processing speed is the earliest and most common area to be affected. Recent technological advances have allowed for the development of computer-based assessments of cognitive processing speed that are sensitive, reliable, and resistant to practice effects. We sought to identify the physiological mechanism underlying cognitive processing speed impairment in MS using these

advanced measurement approaches, in combination with neuroimaging measures. Relapsing-Remitting MS (RRMS) (n=20, 19.3±2.7 years of age, 55% female) and healthy control (n=26, 20.0±3.9 years of age, 69% female) participants completed the Cogstate Brief Battery information processing tasks and an MRI scan. MRI sequences included a T1-weighted anatomical scan and 64-direction diffusion tensor imaging (DTI). Regions of interest delineation and cortical thickness estimations were automatically performed using Freesurfer analysis software. Regional labels were also used to calculate region-wise mean DTI fractional anisotropy (FA), a measure of white matter integrity The Cogstate information processing measures successfully differentiated between RRMS and HC cohorts, with a z score of -0.93±1.01 for MS and -0.35±0.61 for HC, p=0.03. Further, information processing speed was differentially associated with frontal lobe FA (r=-0.550, P=0.02) in the RRMS sample and insular cortical thickness (r=-0.481, p=0.02) in the HC sample. Studies looking at both region-wise and tractography-based FA have reported frontal lobe FA reductions to be associated with cognitive impairment in RRMS. We have shown that computer-based information assessments of cognitive processing speed are not only sensitive in RRMS samples, but are also able to predict variability in frontal lobe FA in the RRMS brain.

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P1118

Cerebral atrophy in relapsing-remitting multiple sclerosis and its relation to cognitive performance

T. Kunchev, S. Mehrabian, M. Raycheva, L. Traykov
Department of Neurology, Alexandrovska University Hospital, Sofia, Bulgaria

Background: Cognitive impairment (CI) is present in up to 70% of all patients with multiple sclerosis (MS). Magnetic resonance imaging (MRI) studies have shown that atrophy measures are better predictors of CI than white matter lesion volume in MS.
Objective: The objectives of this study are to investigate the global cortical atrophy (GCA) and medial temporal lobe atrophy (MTLA) in patients with relapsing-remitting multiple sclerosis (RRMS) and to explore the relationship between atrophy and cognitive performance.
Methods: Twenty two patients (mean age 38.8 ±10.1) underwent clinical, detailed neuropsychological and neuroimaging (MRI) examination. GCA and MTLA were assessed by visual MRI atrophy rating scales. The patients were classified in two groups: patients with cognitive impairment (CI) and cognitive preserved (CP) patients.
Results: Twelve (54.5%) MS patients were classified as having CI. GCA was significantly more pronounced in the group of patients with CI (p=0.001) in comparison with CP patients. Interestingly, MTLA was also significantly more prominent in the CI group than in CP patients (p=0.01). Verbal and non-verbal memory scores, as well as semantic verbal fluency were significantly correlated to MTLA. Several executive functioning measures were highly correlated to GCA, in addition to verbal and non-verbal memory. MOCA appeared to be a more sensitive neuropsychological scale for general cognitive functioning associated with cerebral atrophy in comparison with MMSE.
Conclusion: Our results showed that visual MRI atrophy rating scales could be a feasible and facile method for evaluation of MS patients in relation to cognitive impairment. GCA and MTLA were related to specifically impaired cognitive domains even in patients with mild RRMS.

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P1119

Deficit awareness and the role of executive functions and processing speed in memory and learning in patients with multiple sclerosis: An exploratory study

F. García-Vaz[1,2], E. Antonietti[3], V. Meca-Lallana[4], J. Vivancos[4]
[1]Neurology, Hospital Universitario La Princesa, [2]University Complutense of Madrid, Madrid, Spain, [3]University of Padova, Padova, Italy, [4]Hospital La Princesa, Madrid, Spain

Background: Slowed processing speed has been appointed as the core cognitive deficit in multiple sclerosis (MS) and can negative affect other cognitive domains whereas executive function (EF) training has demonstrated improvement for global cognitive functioning.
Objectives: We aimed to study two aspects in multiple sclerosis. First, to analyse the relation between memory (ML) and PS and EF tests performance. Secondly, self-awareness of cognitive symptoms in MS patients.
Methods: A sample of 33 MS patients (21 female) aged between 30 and 60 y.o. (mean 49,2 y.o.) was recruited from the clinic. A battery of neuropsychological tests was administered to assess PS, EF and ML (Trail Making Test (TMT), STROOP, Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modality Test (SDMT), Spanish version of California Verbal Learning Test (TAVEC), the 10/36 Spatial Recall Test (SRT) and verbal fluency tasks). 24 patients and their families also completed the Prefrontal Symptoms Inventory (IPS) and the Inventory of Memory Failures for Daily Living (MF30). T-test analysis for related samples was executed for questionnaires and neuropsychological measures comparison, establishing significance level on .05. A multiple linear regression was calculated to predict memory performance based on measures of PS and EF.
Results: A significant regression equation was found for F (1,23) =17.220, p< .000 with an R^2 of .428 participants short term visual

memory predicted is equal to 22.971-.160 TMT A direct score. The model for verbal short-term auditory memory was F (1,26) = .548, p< .05, with an R^2 of .162 resulting short-term verbal memory predicted equal to 13.653-0.059 TMT A direct score. Significant findings were obtained for verbal and visual long-term memory. ISP and MFE-30 scores showed no significant differences when compared self-report to family results at any of the subscales, a significant regression equation was found for F (1,23) = 25.627, p< .000 with a R^2 of .538, participants´ predicted memory failures in daily living is equal to 5.978+.807 score in attention subscale from ISP.

Conclusions: The results of this exploratory study suggest that: (i) visual and verbal memory test performance could be at least partially predicted by processing speed measures; (ii) cognitive deficit awareness is preserved for this sample of MS patients compared to family report; (iii) attention subscale from ISP could be used as a predictor of memory failures in daily living.

Disclosure

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Biomarkers

P1120

Elevated kappa free light chain in cerebrospinal fluid in Korean patients with multiple sclerosis

J.-W. Hyun[1], W. Kim[2], S.-Y. Huh[3], G. Kim[1], Y. Kim[1], I.H. Jeong[1], S.-H. Kim[1], H.J. Kim[1]
[1]Research Institute and Hospital of National Cancer Center, Goyang, [2]The Catholic University of Korea College of Medicine, Seoul, [3]Kosin University College of Medicine, Busan, Republic of Korea

Introduction: Kappa free light chain (KFLC) in cerebrospinal fluid (CSF) has been proposed as a diagnostic marker in western patients with multiple sclerosis (MS). We aimed to evaluate the diagnostic value of KFLC and lambda free light chain (LFLC) in Korean patients with MS.

Methods: KFLC and LFLC were measured by turbidometry in cerebrospinal fluid (CSF) samples of 219 patients with MS (n = 86) and other neurological diseases (n=133, OND, Guillain-Barre syndrome, headache, etc) from three referral MS centers in Korea. Among these patients, serum and CSF paired samples were tested in 161 patients with MS (n = 63) and OND (n = 98). Kappa index was calculated by the ratio of CSF/serum KFLC/albumin. This was repeated for Lambda index using LFLC values. Upper normal limit was calculated by mean value plus two standard deviation. Oligoclonal bands (OCB) were assessed by isoelectric focusing technique and the ratio of CSF/serum IgG/albumin over 0.7 was defined as high IgG index. We compared diagnostic values of KFLC, Kappa index, OCB and high IgG index for diagnosis of MS.

Results: CSF KFLC (2.59 ± 0.48 vs. 0.62 ± 0.12 mg/L, p< 0.001) and Kappa index (36.2 ± 7.3 vs. 10.9 ± 2.6, p< 0.001) were significantly higher in MS than OND. Diagnostic sensitivity, specificity, positive and negative predictive values for MS were estimated 45.4%, 85.7%, 67.2% 70.8% in CSF KFLC, 40.4%, 87.8%, 67.6%, 69.4% in Kappa index, 32.0%, 86.7%, 60.6%, 66.4% in OCB, 42.9%, 92.8%, 79.4%, 71.7% in high IgG index. In MS patients with OCB, CSF KFLC was significantly higher than those without OCB (5.28 ± 1.56 vs. 1.12 ± 0.37 mg/L, p< 0.001). Kappa index was also higher in MS patients with OCB than those without OCB, although it did not reach statistical significance (53.1 ± 17.5 vs. 28.3 ± 6.9, p=0.11). Patients without OCB were positive CSF KFLC in 10 patients and Kappa index in 15 patients. In MS patients with high IgG index, CSF KFLC and Kappa index were significantly higher than those without high IgG index (4.94 ± 1.22 vs. 0.56 ± 0.12 mg/L, 72.9 ± 14.2 vs. 8.6 ± 1.8, p< 0.001, respectively). Seven patients with normal IgG index demonstrated positive CSF KFLC and Kappa index. In contrast, CSF LFLC (0.46 ± 0.08 vs. 0.39 ± 0.04 mg/L) and Lambda index (5.48 ± 0.71 vs. 5.04 ± 0.42) were not significantly different between MS and OND.

Discussions: These findings suggest that CSF KFLC and Kappa index can be used as an additional diagnostic biomarker for MS, which complement OCB and IgG index.

Disclosure

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P1121

Elevated cerebrospinal fluid -CRMP5 as a biomarker of damage to astrocyte foot process and growth corn in AQP4-IgG-seropositve NMOSD

S. Nishiyama[1], T. Misu[2], I. Nakashima[1], T. Takahashi[1], K. Fujihara[3], M. Aoki[1]
[1]Department of Neurology, [2]Department of Multiple Sclerosis Therapeutics, Tohoku University Graduate School of Medicine, Sendai, [3]Department of Multiple Sclerosis Therapeutics, Fukushima Medical University, Fukushima, Japan

Background: NMOSD is an autoimmune neurologic disease characterized by severe optic neuritis and transverse myelitis, and associated with AQP4-IgG binding membranous AQP4 in the foot process of astrocyte. Collapsin response mediator protein 5 (CRMP5) is a membranous protein located on the filopodia in the foot process of astrocyte. It has been reported that anti-CRMP5 antibody-positive patients developed NMOSD-like symptoms, suggesting that CRMP5 could be an autoimmune target and a biomarker of astrocytic damage. However, the clinical and pathological implications of CRMP5 in the cerebrospinal fluid (CSF-CRMP5) in AQP4-IgG-seropositive NMOSD are unknown.

Methods: We conducted a cross-sectional study in 52 patients with inflammatory neurologic diseases (20 with AQP4-IgG-seropositive NMOSD, 3 with MOG-IgG-seropositive NMOSD, 23 with MS, 2 with Neuro-Behcet´s disease, and 4 with Neurosarcoidosis) who were diagnosed as neurological inflammatory demyelinating diseases and control patients with 7 non-inflammatory neurologic diseases(NIDC). CSF-CRMP5, GFAP, and MBP were measured by sandwich ELISA kits. The data were analyzed by Graphpad Prism 5.
Results: CSF-CRMP5 in the AQP4-IgG-seropositve NMOSD was signinficantly elevated (0.0975±0.1552 pg/mL, p=0.0298) than in MS (0.00435±0.0209). CSF-CRMP5 was not detected in MOG-IgG-seropositve NMOSD, Neuro-Behcet´s disease, Neurosarcoidosis, and NIDC patients. CSF-CRMP5 was mildly correlated with CSF-GFAP, but not related with CSF-MBP.
Conclusion: Elevated CSF-CRMP5 levels in AQP4-IgG-seropositve NMOSD could reflect damages to astrocytic foot process and growth corn caused by AQP-IgG. CSF-CRMP5 might serve as a biomarker of diagnosis and disease activity in AQP4-IgG-seropositive NMOSD.

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Masashi Aoki: nothing to disclose

P1122

Sema4A as a biomarker for the selection of treatment of MS

Y. Nakatsuji[1], T. Koda[1], T. Okuno[1], Y. Miyazaki[2], M. Niino[2], T. Fukazawa[3], K. Takata[4], A. Namba[1], K. Yamashita[1], M. Shimizu[1], M. Kinoshita[4], S. Sakoda[5], A. Kumanogoh[1], H. Mochizuki[1]
[1]Neurology, Osaka University Graduate School of Medicine, Suita, [2]Hokkaido Medical Center, [3]Sapporo Neurology Clinic, Sapporo, [4]Osaka General Medical Center, Osaka, [5]National Hospital Organization Toneyama National Hospital, Toyonaka, Japan

Backgrounds: Although interferon-beta (IFN-β) is the first-line therapy in relapsing-remitting multiple sclerosis (RRMS), one-third of patients are poor responders to IFN-β therapy. Currently, other disease-modifying drugs (DMDs) such as Fingolimod, Natalizumab, and BG12 become available. However, the problem is that there are no suitable biomarkers for the selection of treatment of MS. We previously reported that immune semaphorin Sema4A is increased in the sera of MS patients and those with high Sema4A do not respond well to IFN-β therapy. We also reported that recombinant Sema4A inhibits the therapeutic effect of IFN-β in experimental autoimmune encephalomyelitis (EAE). However, it remains unknown whether other DMDs are effective for patients with high Sema4A or not.
Objective: The purpose of this study is to investigate whether patients with high Sema4A respond to Fingolimod or not.
Methods: Fifty-six patients with MS who have been treated with Fingolimod were investigated. The levels of serum Sema4A were assayed with a sandwich ELISA, and the association between Sema4A levels and clinical characteristics including responsiveness to Fingolimod treatment was analyzed. We also investigated the efficacy of Fingolimod in EAE mice given Sema4A-Fc.
Results: The serum Sema4A titer was 2877 ± 5469. The ratio of patients with high Sema4A levels (≧2500) was 30.3%. The levels of Sema4A were not changed by Fingolimod treatment. Fingolimod reduced the relapse rates of patients both with low and high Sema4A. Fingolimod also ameliorated the severity of mice with EAE given Sema4A-Fc.
Conclusions: Fingolimod is more suitable for patients with high Sema4A levels than IFN-β

Disclosure

There is nothing to disclose.

P1123

Immunological profile of peripheral blood mononuclear cells (PBMCs) as a tool to understand the development of anti-drug immune responses in multiple sclerosis

M. Adriani[1], C. Mbogning[2], S. Hässler[2], P. Dönnes[3], P. Nytrova[4], P. Blair[1], L. Magill[1], P.E. Jensen[5], P. Creeke[6], K. Wolffram[7], Z. Bocskeis[8], F. Deisenhammer[9], A. Fogdell-Hahn[10], P. Broët[2,11], H. Perdry[2,11], C. Mauri[1], E. Jury[1], on behalf of the ABIRISK Consortium
[1]Department of Rheumatology, University College London, London, United Kingdom, [2]Inserm U 1178 Hôpital Paul-Brousse, Villejuif, France, [3]SciCross AB, Skövde, Sweden, [4]Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic, [5]Department of Neurology DMSC, Rigshospitalet, Region H, Copenhagen, Denmark, [6]Neuroimmunology Unit, Centre for Neuroscience and Trauma, Blizard Institute, Barts and The London School of Medical center and Dentistry, Queen Mary University of London, London, United Kingdom, [7]Department of Neurology, Medical Faculty, Research Group for Clinical and Experimental Neuroimmunology, Heinrich-Heine-University, Düsseldorf, Germany, [8]Sanofi R&D, Paris, France, [9]Clinical Department of Neurology, Innsbruck Medical University, Innsbruck, Austria, [10]Department of Clinical Neuroscience, Center for Molecular Medicine (CMM), Karolinska University Hospital, Stockholm, Sweden, [11]University Paris-Sud, Paris, France

Between 5 and 30% of multiple sclerosis (MS) patients treated with Interferon beta (IFNβ) develop neutralizing antibodies against the drug (nADA) leading to reduced drug bioactivity and therapeutic responses. To investigate the cellular and immunological mechanisms contributing to anti-IFNβ responses we

analyzed the expression of 332 cell surface markers on B-cell, T-cell and myeloid CD14+ cell populations using the LegendScreen™ (BioLegend®) platform. The antigen-specific fluorescence intensity for each subset was examined in 20 IFNβ-treated patients (11 nADA+ and 9 nADA-), 15 IFNβ-treatment-naïve patients and 10 matched healthy controls. Data was analyzed using a mixture model approach and 4 class clustering for each cell subpopulation. Markers that clustered with 'gold standard negative' markers and were expressed by < 5% of the relevant cell subset in at least 90% of the samples were removed from further analysis. Differentially expressed markers (DEMs) between patient groups were determined using unpaired t-test analysis [$p < 0.05$; False discovery rate (FDR) < 0.2]. Phenotypic markers associated with MS disease were identified by comparing healthy donors and IFNβ-treatment-naïve MS patients. The immune signature associated with IFNβ-treatment was characterized by comparing IFNβ-treated and untreated MS patients. Finally, in order to define the immune signature associated with the development of nADA we compared nADA+ and nADA- IFNβ-treated MS patients and excluded markers that had been identified as part of the IFNβ-treatment signature and/or not significantly altered when the nADA+ IFNβ-treated patients were compared to IFNβ-treatment-naive patients.

In summary, using the LegendScreen™ platform we have identified the disease, IFNβ-treatment and nADA+ associated immune signature on PBMC cell subtypes from patients with MS. We are currently validating these signatures on a second independent cohort of IFNβ-treated patients and investigating the functional role of the DEMs.

Disclosure

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P1124

Functional and structural MRI predictors of disability worsening in multiple sclerosis: a 4-year follow-up study

F. Pirro[1], P. Valsasina[1], E. Pagani[2], A. Meani[3], M. Copetti[4], F. Martinelli-Boneschi[5], M. Rodegher[5], G. Comi[5], A. Falini[6], M. Filippi[1,5], M.A. Rocca[1,5]
[1]Neuroimaging Research Unit, INSPE, San Raffaele Scientific Institute - Milan (Italy), Milano, [2]San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, [3]Neuroimaging Research Unit, INSPE, San Raffaele Scientific Institute, Milano, [4]Biostatistics Unit, IRCCS-Ospedale Casa Sollievo Della Sofferenza, San Giovanni Rotondo, Foggia, Italy, Foggia, [5]Dept. of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, [6]Dept. of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, Milano, Italy

Aims: We assessed the value of conventional, diffusion tensor imaging (DTI) and resting state (RS) functional connectivity (FC) MRI measures in predicting clinical deterioration over a four year period in multiple sclerosis (MS).
Methods: Baseline brain MRI brain scans were obtained from 258 MS patients (132 relapsing remitting [RR], 63 secondary progressive [SP], 19 primary progressive [PP] and 44 benign [B] MS), who were followed-up with clinical visits and rating of the Expanded Disability Status Scale (EDSS) score for a median period of 3.8 years. T2 and T1 lesion volumes, normalized white (WM), grey (GM) and deep GM volumes, DTI metrics from the main brain WM tracts and RS FC scores of the sensorimotor and default mode (DMN) networks were obtained. Multivariable analyses, adjusted for baseline EDSS and follow-up duration, were performed to identify the predictors of neurological deterioration at follow up.
Results: At follow-up, 90 MS patients (35%) showed significant worsening of disability. The multivariable model with EDSS score deterioration as dependent variable, identified decreased RS FC of the left postcentral gyrus ($p=0.03$), average RS FC of the sensorimotor network ($p=0.02$), baseline GM atrophy ($p=0.001$), reduced fractional anisotropy of the right cingulum ($p=0.003$) and decreased RS FC in the right middle temporal gyrus of the DMN ($p=0.01$) as predictors of disability worsening (C-index=0.78).
Conclusions: In addition to the well-know role of structural damage to the WM and GM, RS FC abnormalities in the sensorimotor network and DMN contribute to identify MS patients with a worse clinical outcome over time.

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M.Filippi serves onscientific advisory boards for Teva Pharmaceutical Industries; has received compensationfor consulting servicesand/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer´s Drug

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P1125

Stability of anti-JCV antibody index in multiple sclerosis: a 6-year longitudinal study

H. Hegen, M. Auer, G. Bsteh, F. Di Pauli, F. Deisenhammer, T. Berger
Medical University of Innsbruck, Innsbruck, Austria

Background: Risk of progressive multifocal leukoencephalopathy with natalizumab treatment is associated with the presence of anti-JC virus (JCV) antibodies.
Objective: To determine the predictive value of baseline anti-JCV antibody index for long-term stability of anti-JCV antibody status in MS patients.
Methods: MS patients from the MS centre of Medical University of Innsbruck, who had serum sampling for a time period of 4-6 years at intervals of 6±3 months, were included in this retrospective, longitudinal study. Anti-JCV antibody serological status and index were determined by 2-step second-generation anti-JCV antibody assay.
Results: 154 patients were included in this study. Median follow-up time was 63.7 months, with median 11 samples available per patient. At baseline, 111 (72.1%) patients were anti-JCV antibody positive. Baseline anti-JCV antibody index significantly correlated with age (R=0.22, p=0.005); there was no difference with respect to sex, disease duration or previously used disease-modifying treatment. During follow-up anti-JCV antibody status changed from negative to positive or vice versa in 17% of patients. In seronegative patients at baseline, baseline anti-JCV antibody index was significantly lower in those remaining seronegative at follow-up compared to those converting to seropositivity (median 0.16 vs. 0.24, p=0.002). In seropositive patients at baseline, index was higher in those remaining seropositive compared to those reverting to seronegativity (2.6 vs. 0.45, $p< 10^{-7}$). Baseline anti-JCV antibody index >0.70 predicted stable positive serostatus (sensitivity 94.8%, specificity 94.7%) and < 0.20 stable negative serostatus (sensitivity 61.3%, specificity 97.6%).
Conclusions: In MS patients, anti-JCV antibody index remained relatively stable over 6-year follow-up with annual serostatus change of approximately 3%. Anti-JCV antibody index appears to be a good predictor for future serostatus change.

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P1126

Decreased soluble IFNß receptor (sIFNAR2) in multiple sclerosis patients: a potential serum diagnostic biomarker

B. Oliver-Martos[1], M.J. Pinto-Medel[1], J. Pavia[2], I. Hurtado-Guerrero[1], J.L. Rodriguez-Bada[1], P. Urbaneja[1], M. Suardíaz[1], L.M. Villar[3], M. Comabella[4], X. Montalban[4], J.C. Alvarez-Cermeño[5], L. Leyva[1], Ó. Fernández[6]
[1]UGC neurociencias, Hospital Regional Universitario de Málaga. IBIMA, [2]Departamento de Farmacología y Pediatría, Universidad de Málaga, Málaga, [3]Departamento de inmunología, Hospital Ramón y Cajal, Madrid, [4]Hosp. Vall d'Hebron-Barcelona, Barcelona, [5]Neurologúa, Hospital Ramón y Cajal, Madrid, [6]UGC Neurocincias, Hospital Regional Universitario de Málaga. IBIMA, Málaga, Spain

Background: The subunit IFNAR2 of the IFNß receptor (IFNAR) has a soluble isoform (sIFNAR2), generated by alternative splicing, which lacks the transmembrane and cytoplasmic domain and that can be detected in serum. This soluble isoform has been understudied in multiple sclerosis despite it could modulate the activity of both endogenous and systemically administered IFN beta and its function in MS is still unknown. We have previously described that serum sIFNAR2 levels were significantly lower in untreated-MS patients than in healthy controls (HC), and in the current study, our aim is to address sIFNAR2 levels in a new cohort of MS patients and HC, as well as in patients with clinically isolated syndrome (CIS) and with other inflammatory neurological disorders (OIND), in order to assess its ability as diagnostic biomarker.
Methods: The cross-sectional study included 148 MS patients (84 treatment-naive and 64 treated), 87 CIS, 42 OIND, and 96 HC. Longitudinal study included 94 MS patients pre-treatment and after 1 year of therapy with IFNβ, GA o Natalizumab. sIFNAR2 serum levels were measured by a quantitative ELISA, previously developed and validated in our laboratory. Non parametric tests were used to compare sIFNAR2 levels between groups.
Results: Naive MS patients showed significantly lower sIFNAR2 levels than HC (p< 0.0001) and OIND patients (p< 0.0001) and showed no differences with CIS patients. CIS patients had also significant lower levels than HC (p< 0.0001) and OIND (p< 0.0001). The optimal cut-off value of sIFNAR2 to discriminate between MS and OIND patients was 122.02 ng/ml. The sensitivity and specificity for this threshold were 70.1%, and 79.4%, whereas positive and negative predictive values were 88.4% and 64.4%. In the longitudinal study, sIFNAR2 increased significantly in IFNß-treated patients

along the first year of therapy in contrast to Glatiramer acetate and Natalizumab-treated patients who showed non significant changes.
Conclusions: Differences in sIFNAR2 serum levels observed between naive MS patients and HC or OIND patients suggest that sIFNAR2 could be a potential diagnostic biomarker for MS

Disclosure

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P1127

Olfactory threshold and odour identification are markers of disease activity in relapsing-onset multiple sclerosis

G. Bsteh[1], A. Lutterotti[1,2], L. Brendli[1], M. Vedovello[1], M. Reindl[1], T. Berger[1]
[1]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria, [2]Department of Neurology, University Hospital Zurich & University of Zurich, Zurich, Switzerland

Background: It has been previously reported, that olfactory threshold is impaired in early, active multiple sclerosis (MS) and that impaired odour identification is associated with disease duration. However, prospective longitudinal data on this matter are lacking.
Objective: To prospectively investigate the course of different qualities of olfactory function in relapsing-onset MS (ROMS) and correlate these with clinical data to assess a potential association with course of disease.
Methods: In this prospective, 5-year-follow-up study, 28 patients with ROMS were included. Olfactory function was measured by the Sniffin' Sticks test which quantifies three different qualities of olfactory function (threshold, discrimination and identification). Results were correlated with age, sex, duration of disease, relapses, expanded disability status scale (EDSS), depression, smoking, quality of life and cognitive function quantified by the single-digit modality test (SDMT). Mixed effect linear regression models were calculated to address for confounders.
Results: Olfactory threshold and odour identification both decreased over the 5-year observation period, while odour discrimination remained stable. Threshold decreased stronger and was significantly lower in patients with 3 or more relapses (4.3±1.9 vs. 6.0±1.7; p=0.031). On the other hand, odour identification was significantly lower in patients with an EDSS of 2,5 or higher (11.2±2.3 vs. 13.5±1.4; p=0.004) and with cognitive dysfunction (11.2±2.8 vs. 13.4±1.5; p=0.039). These findings remained significant in mixed effect linear regression models correcting for age, sex, disease duration, smoking habit and depression.
Conclusions: We report the first prospective, longitudinal study on the development of olfactory function over time in ROMS. We found evidence that olfactory threshold is a marker of disease activity, while odour identification is associated with male sex, longer disease duration, higher disability and cognitive dysfunction. While these results definitely have to be interpreted cautiously, olfactory threshold and identification might be useful as safe and easily obtainable parameters for monitoring both inflammation and neurodegeneration in MS.

Disclosure

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P1128

Nitrotyrosine, neuronal and inducible nitric oxide synthetase in serum and cerebrospinal fluid of patients with multiple sclerosis: potential markers of oxidative stress

E. Andreadou[1], E. Kemanetzoglou[1], V. Constantinides[1], M. Zoga[2], F. Boufidou[2], C. Nikolaou[2]
[1]1st Department of Neurology, [2]Department of Medical Biopathology, National and Kapodistrian University of Athens, Aeginition Hospital, Athens, Greece

Objective: Oxidative injury has been implicated in tissue damage in multiple sclerosis (MS). High levels of nitric oxide (NO) play an important role in cytotoxicity. NO although not toxic itself, it reacts with superoxide to form peroxynitrite. Peroxynitrite cannot be detected directly but it nitrates tyrosine residues to form nitrotyrosine (NT), which is considered its foot-print. The activated

microglia is responsible for the release of NO through activation of nitric oxide synthetase (NOS) in the form of endothelial NOS, neuronal NOS (nNOS), inducible NOS (iNOS) and mitochondrial NOS. The aim of our study was to compare the levels of NT, nNOS and iNOS in patients with clinically isolated syndrome (CIS) relapsing remitting (RRMS) and progressive (PMS) MS and to examine the correlation of their levels with demographic and clinical variables.

Methods: In this study, 33 CIS, 40 RRMS, 32 PMS patients and 18 aged matched control subjects were included. Clinical data collected were age, disease duration, medication and Expanded Disability Status Scale score. NT, nNOS and iNOS levels were measured in serum and CSF using the enzyme-linked immunosorbent assay (ELISA). A non-parametric Kruskal-Wallis test was used for multiple comparisons (significant p value < 0.05). For comparisons of patients with controls the non-parametric Mann-Whitney U test with Bonferroni correction was used.

Results: Mean age of the patients was 36,05 ± 8,79 years, disease duration 53,96 months and EDSS score ⩽4. NT serum levels were elevated in CIS and PMS patients, compared to controls (p=0,004 and p=0,0001 respectively), as were in PMS compared to RRMS (p=0,002) patients. iNOS serum levels were also increased in CIS (p=0,006) and PMS (p=0,002) patients regarding controls. iNOS CSF levels were high in PMS compared to controls (p=0,002), CIS (p=0,0001) and RRMS (p = 0,001) patients. NT serum/CSF value was smaller for controls than PMS patients (p=0,006). Finally, iNOS serum/CSF was consistently less in PMS patients than controls (p=0,001), CIS (p=0,001) and RRMS patients (p=0,003).

Conclusion: CIS and RRMS patients did not differ regarding the studied parameters, whereas NT levels were higher in PMS, suggesting that NT may be used as a marker of disease progression. This implies that measurement of NO-related metabolites may help in the detection of possible disease activity and even the prediction of therapeutic response, offering optimum clinical monitoring for the patient.

Disclosure

Nothing to disclose

P1129

Brain-derived neurotrophic factor polymorphism methylation in multiple sclerosis patients: a marker of disease progression

V. Nociti[1,2], M. Santoro[3], D. Quaranta[1], F.A. Losavio[1], C. De Fino[1], R. Giordano[4], N. Palomba[4], P.M. Rossini[1], F.R. Guerini[3], M. Clerici[5], D. Caputo[3], M. Mirabella[1]

[1]Neurosciences, Catholic University, Rome, [2]Neurosciences, [3]Don C. Gnocchi Foundation, Milan, [4]Catholic University, Rome, [5]Pathophysiology and Transplantation, Milan University, Milan, Italy

Background and aims: Multiple Sclerosis (MS) is considered an autoimmune disease, but the exact cause is unknown. Moreover no prognostic factors have been identified.Brain-Derived Neurotrophic Factor (BDNF) serum levels, its Val66Met polymorphism and its methylation levels have been linked to neurological diseases. We verified the presence of possible correlations between the methylation status of the CpG site adjacent to the BDNF-Val66Met polymorphism and the severity of the disease.

Materials and methods: Blood samples was collected from 209 MS patients; genetic analyses were performed to identify the Val66Met polymorphism and its methylation levels.At the time of observation, 126 (60%) of the subjects were affected by relapsing-remitting MS whereas secondary progressive MS was present in 83 (40%) individuals. The course of the disease was assessed by means of a survival analysis in which the outcome event was defined as reaching an EDSS score of 6.Results were analyzed via a regression analysis using the following variables: age;gender;clinical relapses; MRI relapses;annualized relapse rate;annualized MRI relapse rate; treatment; BDNF polymorphism and gene methylation

Results: The Val/Val genotype was carried by 122 subjects (58%); 81 (39%) carried the Val/Met genotype and 6 (3%) the Met/Met genotype.Since the group of patients homozygous for the Met allele was very small, we conducted further analysis considering subjects carrying (Met+) or not carrying (Met-) the Met allele. The mean percentage of methylation was 80.9±17; median=81.The percentage of methylation of subjects carrying the Val/Val (mean=74.6±10.8), Val/Met (mean=94.5±10.7) and Met/Met (mean=28.5±2.7) genotypes was significantly different ($F_{2,206}$=160.2; p< 0.001).Stratification according to the percentage of the BDNF methylation showed that patients falling below the median (median methylation=81%) were at a higher risk of reaching an EDSS score of 6.

Conclusions: Lower levels of BDNF gene methylation are correlated with a higher rate of progression toward a severe disease. Patients with a more aggressive disease could need higher levels of serum BDNF to sustain the plastic adaptations needed to deal with more extensive SNC damages. This could be achieved by a hypomethylation of the gene that would lead to a higher transcription and translation rate of this neurotrophic factor. These patients, having a more severe prognosis, are also likely to need a quicker and more aggressive therapy.

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P1130

Neurofilament light in serum: A potential biomarker for monitoring treatment efficacy in RRMS

L. Novakova[1], M. Axelsson[2], C. Malmeström[2], H. Zetterberg[3], K. Blennow[3], J. Lycke[2]
[1]Clinical Neuroscience, Sahlgrenska Academy at University of Gothenburg, Gothenburg, [2]Clinical Neuroscience, [3]Psychiatry and Neurochemistry, Sahlgrenska Academy at University of Gothenburg, Göteborg, Sweden

Background: Neurofilament light (NFL) is a biomarker of axonal damage and is the best studied biochemical biomarker of disease activity and treatment response in patients with relapsing remitting multiple sclerosis (RRMS). Development of the bioassay made it possible to determine NFL levels in healthy controls. However, until recently, NFL has only been determined in cerebrospinal fluid (CSF). This has limited the usefulness of NFL as a biomarker in clinical care of MS.
Objective: Determine the correlation between serum and CSF NFL levels and investigate the response from natalizumab treatment on serum NFL levels.
Methods: 74 pairs of serum and CSF samples were obtained simultaneously from patients with relapsing forms of MS. They were collected from 31 patients in a prospective manner prior to and once again after 6 or 12 months of natalizumab treatment. In 12 patients, samples were only obtained prior to treatment and not at follow up. CSF NFL levels were determined using the UmanDiagnostics NF-light enzyme-linked immunoassay (ELISA), previously described.Serum NFL levels were determined using the NF-Light kit from UmanDiagnostics transferred onto the Simoa platform using a homebrew kit (Quanterix Corp, Boston, MA, USA), as previously described (Gisslén M et al., EBioMedicine. 2015 Nov 22;3:135 -40).
Results: The correlation between serum and CSF NFL was r=0.977 ($p< 0.001$). Natalizumab treatment during 6 or 12 months reduced mean CSF levels from 2442 ng/L (range 230 - 27 310) to 481 ng/L (200-1 510), $p< 0.001$). The corresponding reduction in serum was 35 pg/mL (range 8 - 394) to 13 pg/mL (range 4 - 33), $p< 0.001$.
Conclusion: Serum NFL has high potential to become a new biomarker in RRMS for monitoring disease activity and the effects on axonal damage from disease modifying treatments.

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P1131

MSDx complex-1: A circulating biochemical marker of neurodegeneration in Multiple Sclerosis?

R.C. Nayak[1], V. White[1], T. Vollmer[2], H. Justin[2], T. Schreiner[2]
[1]MSDx Inc, Tucson, AZ, [2]Rocky Mountain MS Center, University of Colorado - Anschutz Medical Campus, Aurora, CO, United States

Objective: To develop a plasma marker of neurodegeneration in MS.
Background: We have discovered an extremely large (400-1000KD) protein complex in plasma that may be suitable for monitoring neurodegeneration in MS. The proteins in this complex are from basement membranes suggesting that it is generated by proteolysis associated with leukocyte entry into the CNS.
Methods: Plasma was obtained from the Barrow Neurology Institute (Phoenix, AZ)and the Rocky mountain MS center (Aurora, CO). We designed a synthetic peptide that binds to this complex and created a competitive peptide binding assay to measure the levels of this protein complex in plasma. Gadolinium enhancing lesions, T2 lesion number and third ventricular width was obtained from analysis of clinical care MRIs. Results were analyzed statistically with Fisher´s exact test and single regression analyses.
Results: We found this complex to be elevated in RRMS compared to healthy controls. Twenty-five apparently healthy controls (aHC) and 154 subjects with MS were studied. In aHC the mean level was 2.18 ng/mL (range 0.04 - 14.78 ng/mL Relapsing Remitting MS (RRMS) subjects (n=140) had a mean level of 12.9 ng/mL (range 0.83 - 90.85 ng/mL). In nine Primary Progressive MS (PPMS) subjects the mean level was 39.6 ng/mL (range 2.16 - 89.05 ng/mL). Five Secondary Progressive (SPMS) subjects had a mean level of 23.42 ng/mL (range 5.85 - 61.55 ng/mL). The complex levels are reduced in DMT treated subjects compared to currently untreated subjects. In a small set of subjects with gadolinium enhancing lesions and less than 10 years duration of RRMS (n=6) we found a strong correlation with T2 lesion number (rsquared=0.9925)and third ventricular width (rsquared=0.8933).
Conclusions: A strong correlation between MSDx complex-1 and measures of neurodegeneration has been found, warranting an expanded study of the correlation of this marker with measures of neurodegeneration

Disclosure

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P1132

Potential biomarkers for different clinical subtypes of multiple sclerosis

E. Tahir Turanli[1], T. Avsar[1], E. Everest[1], Z. Ozturk[1], E. Sahin[1], D.C. Oran[1], M. Tutuncu[2], S. Saip[2], U. Uygunoglu[2], A. Siva[2]
[1]Molecular Biology and Genetics, Istanbul Technical University, [2]Neurology, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey

Heterogeneous clinical presentation, course, and treatment responses of multiple sclerosis (MS) require specific diagnostic and prognostic biomarkers. In a previous study of our group,

cerebrospinal fluid (CSF) proteomic analysis of a prospective cohort (N=179) revealed 151 differentially expressed proteins and corresponding affected pathways including sodium reabsorption and notch signalling pathways in different clinical MS subtypes (Avsar, 2015). Current study aimed to confirm and quantify differential expressions of identified proteins separately, and explore related other proteins from the affected pathways from a subset of patients of the same MS cohort. CSF levels of proteins were evaluated by enzyme-linked immunosorbent assay (ELISA) in 30 clinically isolated syndrome (CIS), 30 relapsing-remitting MS (RRMS), 24 primary progressive MS (PPMS) patients, and 20 non-MS controls comprised of patients with non-inflammatory neurologic disorders and other neuro-inflammatory diseases. Phosphatidylinositol 3-kinase (PI3K), and E3 ubiquitin-protein ligase (NEDD4) proteins levels, involved in sodium reabsorption pathway, were significantly increased in CSF samples of CIS patients compared to controls (292.3 μg/ml and 23.4 μg/ml, respectively, 95% CI, 92%, $p< 0.01$). Notch, nicastrin (NCT), numb-like protein (NUMBL), and presenilin enhancer 2 (PSENEN) proteins from the notch signalling pathway were also evaluated. NUMBL level was decreased in CIS (1621.9 μg/ml, 95% CI, 95%, $p< 0.01$) and RRMS (1469.8 μg/ml, 95% CI, 95%, $p< 0.001$) compared to controls and PPMS in CSF samples. CSF PSENEN level was decreased in CIS, RRMS, and PPMS patients compared to controls (1874.7 μg/ml, 2584 μg/ml, 2348.1 μg/ml, 95% CI, 96%, $p< 0.0001$, $p< 0.0001$, $p< 0.05$ respectively). As a result of our initial screening of CSF sodium reabsorption and notch pathways; PI3K, NEDD4, NUMBL and PSENEN proteins appeared as potential biomarkers for differentiating CIS patients from other clinical forms of MS, which require further scrutiny.

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P1133

Luminex analysis of immunoglobulin A, M, and G subclasses in the cerebrospinal fluid and serum in Multiple Sclerosis and other neurological diseases

A. Pachner, D.B. Royce, F. Gilli
Geisel School of Medicine at Dartmouth, Lebanon, NH, United States

Background/Goals: To test the hypothesis that measurement of IgG subclasses, IgA, and IgM in the cerebrospinal fluid (CSF) provides more useful information than standard CSF assays in multiple sclerosis (MS) and other neurological diseases.
Materials/Methods: Serum and CSF samples from the Dartmouth Neurological specimen bank were obtained on 56 patients. Patients were chosen based on their diagnosis of MS (n=26), other neuroinflammatory and neuroinfectious diseases (n=9), idiopathic intracranial hypertension patients felt to be negative controls (n=5), and a variety of other unselected neurological diseases (OND), some of which had not been confidently diagnosed at the time of the lumbar puncture. CSF cell count, differential, protein, IgG index, Q(albumin), and oligoclonal bands were obtained as standard CSF assays (SCSFA) in the clinical laboratory. Luminex technology was used to assess concentrations of IgG1, IgG2, IgG3, IgG4, IgA, and IgM in the CSF and serum.
Results: IgA analysis did not significantly add benefit relative to the other Luminex analytes or to SCSFA. Elevated IgMs were correlated with particularly inflammatory disease in the MS patients. In 5 of 16 OND patients, the Luminex panel provided evidence of intrathecal Ig production with normal or near normal SCSFA in patients with likely neuroinflammatory syndromes.
Discussion: Luminex technology is increasingly being used to quantitate potential biomarkers in the CSF and other body fluids because it is fast, relatively inexpensive, customizable, and requires small volumes. In our hands assessing IgG subtypes and IgM was helpful diagnostically in both MS patients and in OND patients. In a significant number of OND patients in our study, the Luminex assay provided evidence of immune dysfunction in the nervous system, not detectable by SCSFA, that led to improved diagnosis and therapy.

Disclosure

Dr. Pachner, Ms. Royce and Dr. Gilli have nothing to disclosure.

P1134

Factors that changes carriership status of oligoclonal immunoglobulin gamma bands in cerebrospinal fluid in MS during follow up time, -registry based study

V.D. Karrenbauer[1,2], J. Hillert[1,2], A. Manouchehrinia[1]
[1]Dep of Clinical Neuroscience, Karolinska Institutet, [2]Karolinska University Hospital, Stockholm, Sweden

Objective: To determine if oligoclonal immunoglobulin bands (OCB) status changes during longitudinal follow up and which factors influences that in treatment naïve and treated MS patients.
Background: Nordic MS population carries OCBs in CSF in 90-95% of cases. Qualitative and quantitative changes of OCBs in CSF might occur due to immunomodulatory treatment. Oligolonal bands in CSF are risk factor of CIS conversion to MS.
Methods: We used data from clinically definite MS patients with known OCB-status registered in the Swedish MS register. Date of birth, sex, date of first relapse, diagnosis date and dates for lumbar punctures, data on first and second line immunomodulatory treatment was collected. Multivariate logistic regression model was used to investigate the influence of time length between first relapse and lumbar puncture dates for risk to carry OCBs in CSF; the same method was used to evaluate influence of duration of first and second line disease modifying treatment for risk to OCB status changes from OCB+ to OCB-.
Results: 4,728 relapsing remitting (RR) patients were included. Overall, 475 (10%) were OCB negative. Cohort included 72.9% females. Median EDSS was 2.5. Statistics is still ongoing to meet the project objectives.
Conclusions: This study reveals factors relevant for OCB status changes during follow up time in treatment naïve and treated MS patients.

Disclosure

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P1135

Anti-EBNA1 antibody titres at presentation predict failure of thalamic growth in pediatric multiple sclerosis (MS)

G. Fadda[1], R.A. Brown[1], B. Aubert-Broche[1], C. Yea[2], J. O'Mahony[2], R.A. Marrie[3], E.A. Yeh[2], D.L. Arnold[1], D.L. Collins[1], B. Banwell[4], A. Bar-Or[1], on behalf of the Canadian Pediatric Demyelinating Disease Network

[1]Montreal Neurological Institute, Montreal, QC, [2]The Hospital for Sick Children, Toronto, ON, [3]University of Manitoba, Winnipeg, MB, Canada, [4]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background: The risk of developing MS increases with seroconversion and with increasing anti-Epstein Barr Nuclear Antigen 1 (EBNA1) antibody titres. Anti-EBNA1 titres have also been associated with greater subsequent focal inflammatory disease activity in adults with established MS. We recently reported that the thalamus is one of the most affected CNS structures in children with MS. Whether and how trajectories of thalamic growth may be related to anti-EBNA1 antibodies in MS is unknown.

Objectives: To examine whether anti-EBNA1 antibody titres are associated with the failure of thalamic growth in pediatric-onset MS.

Methods: We prospectively studied 60 children from the time of presentation with an incident acquired demyelinating syndrome (ADS) with serial co-registered brain MRI and serum sampling; 25 were subsequently (median follow-up 4.2 years) ascertained to have MS; the other 35 remained monophasic (monoADS). We used normative growth trajectory data (NIH Study of Normal Brain Development) as a frame-of-reference for expected brain growth. We measured anti-EBNA1 titres using ELISA, then used linear mixed effect modeling to study the association of anti-EBNA1 titres at presentation and growth trajectories of whole brain and brain-normalized thalamus. We used receiver operator characteristic (ROC) analysis and leave-one-out validation to predict growth at individual level.

Results: At the group level, increasing anti-EBNA1 titres predicted slower subsequent thalamic growth in children with MS (-6.97×10^{-04} z-score/year/anti-EBNA Unit, $p< 0.0001$) but not monoADS ($p = 0.602$), reflecting an MS-specific association ($p = 7.0\times10^{-4}$). The association between anti-EBNA1 titres and brain growth trajectory was not significant in either group. The anti-EBNA1 titre was a good predictor of failure of normal thalamic growth also at the level of individual children with MS, with an area under the ROC curve of up to 0.88. Anti-EBNA titers tended to be stable in individual children over time, such that their measurement at times that followed initial ADS presentation also predicted subsequent thalamic growth.

Conclusions: Our findings suggest that early anti-EBNA1 measurements may identify individual pediatric MS patients who will experience a more severe disease trajectory, and may benefit from more aggressive therapy. Whether these antibodies have pathogenic effects on trajectories or are merely markers of disease trajectories remains to be elucidated.

Disclosure

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C. Yea has nothing to declare
J. O'Mahony has nothing to declare
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P1136

Cerebrospinal fluid chitinase 3-like 1 levels in patients with radiologically isolated syndromes

C. Matute-Blanch[1], L.M. Villar[2], E. Evdoshenko[3], G. Makshakov[3], V. Nazarov[4], S. Lapin[4], L. Midaglia[1], À. Vidal-Jordana[1], J. Drulovic[5], A. García-Merino[6], A. Saiz[7], U.K. Zettl[8], I. Schroeder[8], L. Ramió-Torrentà[9], E. Quintana[10], D. Galimberti[11], X. Montalban[1], M. Comabella[1]

[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, Barcelona, [2]Department of Neurology & Immunology, Hospital Ramón y Cajal, Madrid, Spain, [3]MS Center (City Clinical Hospital 31), [4]First Pavlov Saint-Petersburg State Medical University, Saint Petersburg, Russian Federation, [5]Neurology Clinic, Clinical Centre of Serbia, Belgrade, Serbia, [6]Hospital Universitario Puerta de Hierro, Madrid, [7]Neurology Department, Hospital Clinic and Institut d´Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [8]Department of Neurology/Neuroimmunological

Section, University of Rostock, Rostock, Germany, [9]MS & Neuroimmunology Unit, Hospital Universitari de Girona Dr. Josep Trueta, [10]MS & Neuroimmunology Unit, Hospital Universitari de Girona Dr. Josep Trueta & IDIBGI, Girona, Spain, [11]Fondazione Ca'Granda, IRCCS Ospedale Policlinico, University of Milan, Milan, Italy

Background: Recent studies point to a prognostic role for chitinase 3-like 1 (CHI3L1) in patients with multiple sclerosis (MS), particularly at the time of the first neurological event or clinically isolated syndrome (CIS) where cerebrospinal fluid (CSF) CHI3L1 levels were found to be associated with the conversion to MS. In this study, we investigated a potential prognostic role of CHI3L1 in patients with radiologically isolated syndromes (RIS).
Methods: Forty-six RIS patients (mean age: 36.8 years; 65.2% females) recruited from 9 European MS centres were included in the study. All RIS patients (i) fulfilled the 2009 Okuda criteria; (ii) had a lumbar puncture performed in proximity to the RIS diagnostic MRI (⩽6 months); and (iii) had at least 1 year of follow-up. A group of 20 CIS patients (35.2 years; 75.0% females) and 21 relapsing-remitting MS (RRMS) patients (42.3 years; 61.9% females) were also included for comparison purposes. CSF CHI3L1 levels were measured by enzyme-linked immunosorbent assay (ELISA). Univariable and multivariable Cox regression models were used to investigate the association between CSF CHI3L1 levels and conversion to CIS.
Results: Mean follow-up time of RIS patients was 2.6 years; 21.7% of patients converted to CIS with a mean conversion time of 2.0 years. A total of 73.9% of RIS patients were positive for IgG oligoclonal bands. CSF CHI3L1 levels were similar between patients with RIS (208.8 ng/ml), CIS (199.3 ng/ml), and RRMS (210.9 ng/ml). A lack of association was observed between CSF CHI3L1 levels and time to CIS in univariable (p=0.475 for CHI3L1) and multivariable Cox regression models including age at RIS and IgG oligoclonal bands as covariates (p=0.515 for CHI3L1; p=0.312 for IgG oligoclonal bands; p=0.873 for age at RIS).
Conclusions: These results do not suggest a prognostic role of CHI3L1 in patients with RIS. Further studies in independent cohorts of RIS patients may be required to confirm the lack of association between CSF CHIL1 levels and conversion to CIS in these patients.

Disclosure

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X Montalban has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Phramaceuticals, Almirall and Roche.
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P1137

Search of biomarkers in patients with progressive multiple sclerosis

M. Comabella[1], J. Sastre-Garriga[1], D. Pareto[2], E. Borràs[3], M. Tintoré[1], J. Río[1], S. Malhotra[1], E. Sabidó[3], Á. Rovira[2], X. Montalban[1]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, Vall d'Hebron University Hospital, [2]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, [3]Department of Experimental and Health Sciences, Universitat Pompeu Fabra - Institute of Evolutionary Biology (CSIC-UPF), Barcelona, Spain

Background: An important proportion of multiple sclerosis (MS) patients suffer from a progressive course of the disease, with sustained neurological deterioration. Long-term follow-up of progressive MS patients with prospectively acquired clinical, radiological, and biological information is crucial to establish a disease prognosis. Here, we aimed to identify prognostic biomarkers associated with brain atrophy and disease progression in a cohort of patients with progressive MS followed for a period of time longer than 10 years.
Methods: Patients with progressive MS who between the years 1998 and 2001 participated in a single-center, double-blind placebo-controlled clinical trial of interferon-beta 1b were included in the study. The percentage brain volume change between baseline and follow-up MRI studies was calculated using SIENA. Progression rate variables were created by dividing the EDSS changes by the time on follow-up. Protein-based biomarkers were

determined using a targeted quantitative proteomics approach in cerebrospinal fluid (CSF) samples (N=28) collected during the trial. To identify mRNA-based biomarkers, a transcriptomic approach using gene expression microarrays was conducted in peripheral blood mononuclear cells (PBMC) obtained at baseline in the trial (N=42).

Results: Regarding protein-based biomarkers, LYVE1 (lymphatic vessel endothelial hyaluronan receptor 1) showed the highest differential expression between patients with and without brain atrophy and was less abundant in the CSF of MS patients with higher brain atrophy ($p=2.2x10^{-4}$). CSF CD163 levels were reduced in patients with higher brain atrophy ($p=0.02$) and higher long-term disability progression ($p=0.004$). As for mRNA-based biomarkers, the highest differential expression in PBMC from MS patients with and without brain atrophy corresponded to the anti-apoptotic gene BAG3 (BCL2 associated athanogene 3), which was up-regulated in patients with higher brain atrophy ($p=2.5x10^{-9}$). Regarding clinical progression, CUZD1 (CUB and zona pellucida-like domains 1) was up-regulated in patients with higher long-term disability progression ($p=1.2x10^{-9}$).

Conclusions: Although validation in independent cohorts of patients is needed, these findings point to LYVE1, CD163, BAG3, and CUZD1 as attractive biomarkers associated with brain atrophy and long-term disability progression in patients with progressive MS.

Disclosure

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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.

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J Rio has received speaking honoraria and personal compensation for participating in advisory boards from Bayer-Schering Healthcare, Biogen-Idec, Genzyme, Merck-Serono, Novartis, Teva, and Sanofi-Aventis.

A Rovira serves on scientific advisory boards for NeuroTEC and on the editorial board of the American Journal of Neuroradiology and Neuroradiology, has received speaker honoraria from Bayer Schering Pharma, Sanofi-Aventis, Bracco, Merck Serono, Teva Pharmaceutical Industries Ltd. and Biogen Idec, receives research support from Bayer Schering Pharma, and serves as a consultant for 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.

Immunomodulation/Immunosuppression

P1138

The German MS Register: update on immunotherapy

A. Stahmann[1], K. Buckow[2], D. Ellenberger[3], D. Heymann[4], M. Mai[4], T. Meißner[2], U. Zettl[5], for the German Multiple Sclerosis Register of the German National MS Society (DMSG)

[1]MS Forschungs- und Projektentwicklungs-gGmbH, Hannover, [2]Medical Informatics, University Medical Center Göttingen, [3]Medical Statistics, University Medical Centre Göttingen, Göttingen, [4]German Multiple Sclerosis Society, Hannover, [5]Klinik und Poliklinik für Neurologie, Universitätsklinikum Rostock, Rostock, Germany

Background: Disease-modifying drugs (DMD) serve to alter the long-term course of MS by reducing the inflammatory aspects of the disease. Currently, Immunotherapy is available for relapsing-remitting (RRMS) and secondary progressive (SPMS) forms of MS, none of the licensed drugs has proven efficacy in primary progressive MS (PPMS) and thus current S2e-guidelines in Germany do not foresee DMD treatment. Conversely, a recent study by Petersen et al. (2014) based on claims data by health insurance funds showed high numbers of PPMS-patients receiving DMD-treatment (1). Data from the German MS-Register were analysed in an attempt to verify these findings based on clinical data.

Methods: In 2014 the German MS-Register established new data set and register infrastructure. Currently 65 out of 165 participating centres in the register already use the new dataset and infrastructure, and further are currently migrating. This analysis is based on data sets collected from 2014 until 04/2016. A total of 3132 patients were enrolled in the new database. Data related to DMD-treatment and course of disease was available for 2744 of them. Proportion of patients receiving treatment are given for each disease course along with 95%-Clopper-Pearson confidence intervals. Global test for differences between courses are done with Chi^2-test.

Results: The number of patients receiving DMD-treatment differed substantially between RRMS, SPMS and PPMS ($p< 0.001$): 85.1% of patients with RRMS (95%-CI: [83.4-86.6%]; n=1981) received DMD-treatment, while 53.2% of SPMS patients (95%-CI: [48.8-57.6%]; n=511) were treated with DMDs. 32.3% of the PPMS patients (95%-CI: [25.0-40.2%]; n=155) received DMD treatment.

Conclusions: The updated results show that a high proportion of MS patients receive DMD treatment which is in line with previous analyses and other investigations. The amount of PPMS patients receiving DMD treatment in conflict with the guidelines, is lower than in our older analyses from 2009 but is still high and confirms the findings of the population based analysis (1). The reduction in comparison to our analysis in 2009 [59% of PPMS patients received DMD treatment] could indicate a stronger adherence to the guidelines. This might be influenced by health insurance funds claiming damages if treatment is not in line with the guidelines.

Reference

1. Petersen G, et al. Epidemiologie der Multiplen Sklerose in Deutschland. Nervenarzt. 2014;85(8)

Disclosure

Buckow, Ellenberger, Mai, Meißner and Stahmann: nothing to disclose.

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The German MS Society, National Association yearly publishes the received grants and sources of funding: www.dmsg.de - The consented guidelines by the association of self-help organizations and the DMSG-guidelines for co-operation with (pharmaceutical) companies apply.

P1139

Impaired pro-inflammatory capabilities and Th1/Th 17 cell activation by slan dendritic cells after fingolimod in multiple sclerosis

K. Thomas[1], U. Hainke[2], T. Sehr[2], J. Eisele[2], T. Ziemssen[2]
[1]Center of Clinical Neuroscience, University 'Hospital Dresden, [2]Center of Clinical Neuroscience, University Hospital Dresden, Dresden, Germany

Growing evidence has demonstrated the relevance of sphingolipids and its metabolic pathways in dendritic cell (DC) metabolism and immunity. Regarding their extraordinary properties as antigen presenting cells, DCs are key players in balancing tolerogenic versus encephalitogenic responses in multiple sclerosis (MS) pathophysiology. The aim of this study was to evaluate direct effects of fingolimod on major pro-inflammatory DC - slanDC - versus common DC subsets in MS.

DCs and monocytes of MS patients were investigated prior and after treatment initiation with fingolimod up to 24 months regard cell frequency and activation/maturation profile. Additionally, in vivo impact of fingolimod on pro-inflammatory cytokine release of IL1-beta, IL-6, IL-12, IL-23 and TNF-alpha as well as maturation and activation profile was assessed by ELISA and FACS-analysis ex vivo in fingolimod-treated patients. Modulation of DC depending programming of naïve CD4+ T cells, T cell proliferation and phagocytotic activity were investigated.

Absolute cell number of slanDCs and CD1+DCs increased during fingolimod, monocytes frequency kept stable. CD83 and CD86 was up-regulated, whereas HLADR was decreased in DCs of fingolimod treated patients. Interestingly, in vitro analyses with fingolimod and fingolimod-phosphate presented contradictory results of surface marker expression. Pro-inflammatory cytokine release was decreased in analyzed slanDCs, CD1+DCs and monocytes in vivo and in vitro. APC potential of major pro-inflammatory slanDCs was markedly impaired to induce pro-inflammatory interferon-gamma producing Th1 or IL-17 releasing Th17 cells as well as T cell proliferation by fingolimod. In comparison, effects on further DC populations on T cell regulatory potential was less pronounced. Fingolimod inhibited significantly phagocytotic capacity in slanDCs and monocytes.

Additionally to previous studies on animal models, we provide further evidence, that fingolimod impacts pro-inflammatory capabilities and T cell regulatory potential of the major DC populations and monocytes by in vitro experiments and in treated patients. These results indicate, that fingolimod could modulate essential DC-mediated pro-inflammatory pathways in MS pathogenesis and highlight antigen-presenting cells as interesting target in sphingosine-1-receptor-directed therapies.

Disclosure

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U. Hainke. T. Sehr and J. Eisele have nothing to disclose.
T. Ziemssen is on the scientific advisory board for Bayer Healthcare, Biogen Idec, Novartis, Merck-Serono, Teva, Genzyme, and Synthon; has received speaker honorarium from Bayer Healthcare, Biogen Idec, Genzyme, MSD, GSK, Novartis, Teva, Sanofi, and Almirall; and has received research support from Bayer Halthcare, Biogen Idec, Genzyme, Novartis, Teva, and Sanofi.

P1140

Teriflunomide (Aubagio®) effect on gray matter pathology in multiple sclerosis is associated with the change in humoral response to Epstein-Barr virus

R. Zivadinov[1,2], B. Weinstock-Guttman[3], J. Hagemeier[1], C. Kolb[3], N. Modi[1], J. Carl[1], N. Bergsland[1], D. Ramasamy[1], J. Durfee[1], M. Ramanathan[4]
[1]Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, [2]MR Imaging Clinical and Translational Research Center, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, [3]Jacobs Multiple Sclerosis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, [4]Department of Pharmaceutical Sciences, State University of New York, Buffalo, NY, United States

Background: Teriflunomide (Aubagio®) has been shown to reduce brain atrophy progression, compared to placebo over 2 years. Most recently, it was demonstrated that MS patients treated with teriflunomide over 12 months showed similar volume changes in gray matter (GM), compared to age- and sex-matched healthy controls (HCs). We hypothesized that the effect of teriflunomide on GM pathology may be related to the change in humoral response to Espstein-Barr virus (EBV).
Objective: This study aimed to explore whether the effect of teriflunomide on GM volume loss in relapsing MS patients over 12 months is associated with the change in humoral response to EBV.
Methods: This was a prospective, observational, single-blinded, longitudinal study of 30 relapsing MS patients, who started de-novo treatment with teriflunomide, and 20 age- and sex-matched HCs. Subjects were assessed at baseline, 6 and 12 months with clinical, MRI and EBV examinations. MRI outcomes included percent change from baseline to 6, 6 to 12 and baseline to 12 months in whole brain volume using SIENA, in cortical volumes using the SIENAX multi-time point algorithm, and in deep GM volumes using the FIRST methods. Serum samples were analysed for IgG antibodies against EBV viral capsid antigen (VCA) and nuclear antigen-1 (EBNA-1) and their quartiles were determined on whole study sample.
Results: At baseline, MS subjects with the highest quartile of anti-EBV VCA showed significantly decreased caudate (p=0.002) and total deep GM (p=0.027) volumes and increased T1 lesion volume (LV) (p=0.014). The median decrease in EBV titre over the follow-up, after teriflunomide initiation, was 5.3% in MS patients, while no changes were observed in HCs. In correlation

analysis, MS patients who showed the highest decrease in EBV VCA titre from baseline to follow-up, developed less GM and cortical atrophy ($p< 0.05$). MS patients who showed the highest decrease in EBV EBNA-1 titre from baseline to follow-up, developed less hippocampal atrophy ($p< 0.05$). Over the 12-month follow-up, the percent change in whole brain was -0.38% in HCs and -0.50% in MS patients, p=0.378. The percentage change in cortical volume was -0.31% in HC vs. -0.80% in MS, p=0.302.
Conclusions: These findings suggest that the effect of teriflunomide on slowing down whole brain and GM atrophy may be mediated by its effect on altering humoral response to EBV.

Disclosure

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Noopur Modi, Jill Carl, Jesper Hagemier, Niels Bergsland, Deepa Ramasamy, Jacqueline Durfee have nothing to disclose.
Bianca Weinstock- Guttman has participated in speaker´s bureaus and served as a consultant for Biogen Idec, Teva Neuroscience, EMD Serono, Novartis, Genzyme & Sanofi, Mylan Inc., and Acorda Therapeutics, Inc. Dr. Weinstock-Guttman also has received grant/research support from the agencies listed in the previous sentence as well as Questcor Pharmaceuticals, Inc., and Shire. She serves in the editorial board for BMC Neurology, Journal of International MS, Journal of Multiple Sclerosis.
Murali Ramanathan is on the editorial board for AAPS Journal, receives publishing royalties from Pinnacle, Summit and Zenith, received research support from Serono, Novartis, Pfizer, Biogen, Department of Defense, National Multiple Sclerosis Society

P1141
Selective depletion of MOG-reactive B lymphocytes by modular T cell targeting

K. Thomas[1], C. Weiß[1], M. Bachmann[2], M. Cartellieri[2], T. Ziemssen[1]
[1]Center of Clinical Neuroscience, [2]Department of Immunology, University Hospital Dresden, Dresden, Germany

Growing evidence suggests that myelin-specific B cells are crucially involved in the inflammatory and destructive processes in the central nervous system in multiple sclerosis pathophysiology. Up to now, general (CD20) but not antigen-specific depletion is used in B-cell targeted therapies. Chimeric antigen receptors (CAR) are synthetic surface receptors providing artificial antigen specificity to genetically engineered T cells. As part of this project, we tried to develop specific B cell receptor constructs with inducible retargeting of genetically engineered T cells to deplete antigen specific B cells.

An universal (Uni) modular targeting platform was developed, which allows an inducible retargeting of (Uni)CAR engineered T cells against a specific target structure. The platform consists of genetically engineered T cells expressing a CAR with specificity towards a short amino acid sequence derived from the human La protein (anti-La(5B9)scFv), and a targeting module (TM) with a binding moiety against the desired target fused to the epitope recognized by the anti-La(5B9)scFv. On the basis of the modular CAR T cell system, a TM was designed including the human myelin-oligodendrocyte-glycoprotein (MOG) epitope that is recognized by MOG-specific B cells.

The TM was successfully expressed in eukaryotic chinese-hamster-ovary (CHO)-cells and purified from cell culture supernatant. Specific binding of the TM to B cells of different MOG-specific heavy chain knock in mice was evaluated. Positive binding of TM was demonstrated. Furthermore, redirecting and mediated lyses of UniCAR T cells against MOG-specific B cells could be demonstrated.

Here we present first data of antigen-specific cytotoxicity to B cells using the TM linked UniCAR platform. Using a selective TM may help to provide antigen-specific depletion and flexible modulation in the therapeutic setting of B cell depleting treatment strategies. Further and more detailed studies have to elucidate distinct effects in vivo and its impact on disease progression.

Disclosure

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C. Weiß, M. Bachmann and M. Cartellieri have nothing to disclose.
T. Ziemssen is on the scientific advisory board for Bayer Healthcare, Biogen Idec, Novartis, Merck-Serono, Teva, Genzyme, and Synthon; has received speaker honorarium from Bayer Healthcare, Biogen Idec, Genzyme, MSD, GSK, Novartis, Teva, Sanofi, and Almirall; and has received research support from Bayer Halthcare, Biogen Idec, Genzyme, Novartis, Teva, and Sanofi.

P1142
A comparison of neurologists‘ and MS nurses‘ with MS patients‘ preferences for the characteristics of disease modifying drugs for decision making

I.E.H. Kremer[1], S.M.A.A. Evers[1,2], P.J. Jongen[3,4], T. van der Weijden[5], M. Hiligsmann[1]
[1]Health Services Research, Maastricht University, Maastricht, [2]Center for Economic Evaluations, Trimbos Institute, Utrecht, [3]MS4 Research Institute, Nijmegen, [4]Community & Occupational Medicine, University Medical Center Groningen, Groningen, [5]Family Medicine, Maastricht University, Maastricht, The Netherlands

Purpose: The choice between disease modifying drugs (DMDs) for the treatment of multiple sclerosis (MS) becomes more often a shared decision between the patient and the neurologist and MS nurse. This study assessed which characteristics of DMDs are most important for the healthcare professionals in selecting a DMD for a patient. Subsequently, their preferences were compared to the patients' preferences to detect any differences that may need attention in the communication about DMDs between patients and neurologists and MS nurses.
Methods: A best-worst scaling (BWS) was conducted among 27 neurologists and 33 MS-specialized nurses experienced making decision on DMD use in MS. Twenty-seven DMD characteristics were evaluated in 17 choice tasks of 5 characteristics each,

by asking respondents to choose the most and least important characteristic in the decision. Hierarchical Bayes analysis was used to obtain mean relative importance scores (RIS) per DMD characteristic between 0 and 100. A RIS of 3.7 per characteristic would indicate that all characteristics are equally important in the decision. The results were compared with results of an earlier conducted BWS among 185 MS patients using t-tests or non-parametric tests on the characteristics' RIS.

Results: According to the neurologists and MS nurses, the effect of the DMD on disease progression and quality of life were most important (median RIS (interquartile range): 9.8 (9.3-10.1) and 9.5 (8.9-9.9), respectively), in line with the patients' preferences (median RIS: 9.8 (9.3-10.1) and 9.5 (8.8-10.0)). For thirteen attributes significant differences in RIS were found between patients and the healthcare professionals. The absolute differences in median RIS for safety (2.5), uncertainty about long-term consequences (1.0), influence on lifestyle (1.3), and insurance coverage (1.1) were relatively large, while the other nine attributes had absolute median differences of 0.7 or less.

Conclusions: Neurologists, MS nurses and MS patients overall agree about which DMD characteristics most influence the decision, but safety and uncertainty about long-term consequences are, on average, more important for neurologists and MS nurses compared to patients, while patients valued the influence on lifestyle and insurance coverage higher. Improvement in the communication between patients and neurologists and MS nurses regarding these aspects of DMDs could result in a better shared decision.

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Hiligsmann, M.: nothing to disclose

P1143

Ofatumumab is a fully human anti-CD20 antibody achieving potent B-cell depletion through binding a distinct epitope

P. Smith, A. Kakarieka, E. Wallstroem
Novartis Pharma AG, Basel, Switzerland

Background: Anti-CD20 therapies have shown significant clinical efficacy in MS patients. Ofatumumab is a human IgG1 anti-CD20 antibody that depletes circulating peripheral B cells. Novartis is currently initiating two Phase 3 clinical trials in relapsing MS.

Objective: Elucidate the characteristics of ofatumumab to potentially differentiate from other anti-CD20 antibodies.

Methods: Ofatumumab binding to human CD20 protein was determined using overlapping 15-mer peptide Pepscan-based ELISA. Binding EC_{50} values were determined using peripheral blood mononuclear cells (PBMCs) via flow cytometry. Dissociation rates were measured via ^{125}I-labeled antibodies in the presence of azide/2-deoxyglucose to prevent internalisation. Ofatumumab-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) was performed with ^{51}Cr-labeled B cells incubated with whole blood. Complement dependent cytotoxicity (CDC)-mediated B-cell lysis was quantified via incubation with fresh-frozen pooled human serum. Immunogenicity of ofatumumab and rituximab chimeric anti-CD20 antibody was studied *in silico* for potentially immunogenic T-cell epitopes (Epibase™ profiling).

Results: Ofatumumab binds to two distinct epitopes within the large and small extracellular loops of CD20 protein. This binding motif is towards the N-terminal. Ofatumumab bound to human (EC_{50}=287ng/mL) PBMCs and stained B cell-rich regions within lymphoid tissues. Strong differences in off-rates were observed between ofatumumab and rituximab. Rituximab dissociated rapidly whereas a slow off-rate and long residence time of ofatumumab resulted in long-lasting effector function and potent B-cell depletion. In vitro whole blood assays showed superiority of ofatumumab over rituximab in lysing CD20-expressing cells, primarily due to enhanced CDC activity. ADCC activity was similar. Ofatumumab binding to target cells did not directly induce apoptosis. *In silico* profiling showed that ofatumumab has a low number of epitopes capable of inducing an anti-antibody response.

Conclusions: Ofatumumab binds a distinct CD20 epitope on B cells in blood and lymphoid tissues. The slow CD20-binding dissociation and enhanced CDC-mediated lysis (vs rituximab) results in potent effector functions. B-cell depletion is mediated by a combination of CDC and ADCC. These characteristics, together with low potential for anti-antibody response, makes ofatumumab suitable for testing in clinical trials as a low-dose subcutaneous treatment for relapsing MS.

Disclosure

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All the authors are employees of Novartis Pharma AG, Switzerland.

P1144

International evaluation of the new BETACONNECT autoinjector for patients with MS undergoing treatment with interferon beta-1b

F. Patti[1,2], I. Kleiter[3,4], M.L. Martínez Ginés[5], S. Groicher[6], C. Norenberg[7], J.-P. Bugge[8]
[1]Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, [2]Multiple Sclerosis Center, University of Catania, Catania, Italy, [3]Department of Neurology, St. Josef Hospital, Ruhr University, [4]Ruhr University Bochum, Bochum, Germany, [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain, [6]Department of Neurology, Klinikum Wels-Grieskirchen, Wels, Austria, [7]Bayer Pharma AG, Wuppertal, [8]Bayer Pharma AG, Berlin, Germany

Background: Adherence to injectable disease-modifying therapies (DMTs) can be improved through the use of drug delivery devices. BETACONNECT® is a novel electronic autoinjector for the administration of interferon beta-1b that performs injections in 4 phases. It also records the time, date, speed, depth, volume and status of injections and includes injection reminders.

Objectives: The primary objective is to investigate adherence among patients using BETACONNECT®. Secondary objectives include assessments of satisfaction with the autoinjector; symptoms of depression, anxiety and fatigue; quality of life and cognition.

Methods: BETAEVAL is an observational cohort study that enrolled patients from 11 countries in Europe with relapsing-remitting MS (RRMS) or clinically isolated syndrome currently undergoing treatment using BETACONNECT®. Follow-up visits are planned at 4, 12, and 24 weeks after enrollment. Injection data will be recorded electronically through the BETACONNECT®. Data on adherence (calculated by >80% compliance with prescribed interferon beta-1b dosages) will be presented with the final results after completion of the study. Interim results on patient satisfaction are presented here.
Results: Recruitment is complete (N=500, current analyses based on 443). Mean (SD) age was 44.1 (11.4) years. 64.3% were women. 96.2% were diagnosed with RRMS. Mean (median, range) EDSS at baseline was 2.2 (2, 0-6.5). 68.0% of patients were using autoinjectors prior to entry, including 20.3% using BETACONNECT®. At enrollment, satisfaction with the previous injection devices was high (mean [SD] 7.5 [2.2] out of 10). Device satisfaction was higher after 4 weeks (8.2 [2.1], nominal P< .0001). Mean (SD) intensity of injection related pain was 4.7 (2.6) out of 10 with the prior method of injection and decreased to 4.0 (2.4) with BETACONNECT® (nominal P< .0001). Prophylactic analgesics were used by 22.7% and 23.1% of patients prior to and during the study, respectively. Most participants strongly agreed that BETACONNECT® was user-friendly (initial: 92.5%, Week 4: 90.3%). They felt confident using it (75.3%, 77.0%), and preferred it over their previous method (73.9%, 74.3%).
Conclusion: Satisfaction with BETACONNECT® was higher than with previous methods in this interim analysis. Patients also reported a high perception of user-friendliness, confidence with using the device and a preference over their previous injection methods. Injection site pain was lower with BETACONNECT.

Disclosure

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P1145

Assessment of lymphopenia in patients with multiple sclerosis treated with dimethyl fumarate in a real clinical setting

R. Alroughani[1], S. Ahmed[2], R. Behbehani[3], J. Al-Hashel[2]
[1]Amiri Hospital, [2]Ibn Sina Hospital, [3]Al-Bahar Ophthalmology Center, Kuwait, Kuwait

Background: Dimethyl fumarate (DMF), a disease-modifying therapy for multiple sclerosis (MS), causes lymphopenia in a fraction of patients. Since lymphocytes contribute to MS pathology, lymphopenia may be a biomarker for response to the drug or for serious adverse events such as infections.
Objectives: To evaluate absolute lymphocyte counts (ALCs) in MS patients treated with DMF in a real clinical setting.
Methods: Using the national MS registry, a retrospective study was conducted to identify MS patients who received DMF. Patients included in the analyses received at least 3 months prescription and had ALC values available at baseline (within 3 months prior to DMF initiation) and at least twice 3 months post DMF initiation. Grades of lymphopenia were assigned according to the common terminology criteria for adverse events: grade 1 ALC < lower limit of normal to 800/mm^3, grade 2 ALC < 800-500/mm^3, and grade 3 ALC < 500-200/mm^3.
Results: A total of 54 patients met the inclusion criteria; of whom 66.7% were females. Mean age and mean disease duration were 32.3±11.4 years and 6.9±6.8 years respectively. Most patients (74.1%) received prior disease modifying therapies. The mean ALCs decreased from 2190 to 1510/mm^3 (~30% decrease) over a mean duration of 11.7±5.86 months. Among patients who had at least 2 follow-up ALCs, lymphopenia was seen in 22.2% of patients. Grade 1 and 2 ALCs were observed in 11.1% and 7.4% of patients respectively while 3.7% of the patients had grade 3 lymphopenia necessitating interruption or discontinuation of DMF.
Conclusions: ALC profiles in DMF-treated patients were generally stable throughout the observational period. The proportion of patients, who developed severe lymphopenia, was similar to figures reported in clinical trials. Further studies are needed to assess the time of ALC recovery in severely lymphopenic patients.

Disclosure

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P1146

Induction therapy of relapsing secondary multiple sclerosis using generic cladribine

K. Rejdak[1,2], K. Mitosek-Szewczyk[3], K. Prus[1], O. Trzciniecka[1], D. Baker[4], K. Schmierer[4,5], Z. Stelmasiak[1]
[1]Neurology, Medical University of Lublin, Lublin, [2]Medical Research Center, Warsaw, [3]Child Neurology, Medical University of Lublin, Lublin, Poland, [4]Blizard Institute (Neuroscience), Queen Mary University of London, [5]Barts Health NHS Trust, Emergency Care and Acute Medicine Neurosciences Clinical Academic Group, London, United Kingdom

Background: Evidence suggests Cladribine is an effective, safe and convenient disease modifying induction therapy for people with multiple sclerosis.
Objective: To report our experience using subcutaneous Cladribine as a treatment for people with relapsing secondary progressive MS (SPMS).
Methods: Study was performed at the Department of Neurology, Medical University of Lublin and received local ethics approval. Cladribine (Biodribine) was offered to 45 patients with SPMS (30 women and 15 men; aged 42 years [25-56]; EDSS = 6 [2-7], disease duration= 10 years [5-15]; median, range). Cladribine was

given subcutaneously at a dose of 0.07 mg/kg/day for 4-6 days[1]. Treatment courses were given every 5 weeks for a total of five courses (total dose: 1.4 - 2.1 mg/kg). Blood samples were collected before treatment initiation, before each subsequent treatment course, and three months after the last dose. Patients were followed-up for initial 28 weeks of treatment course, and there was extended follow up of up to 5 years to record relapses, disability progression and adverse events.

Results: All patients completed the follow-up period. Cladribine induced a gradual decline in the total lymphocyte count from 1.8±0.5 (x10*9/L; mean±SD) at baseline to 1.5±0.5 after the 1st, 1.3±0.5 after the 2nd; 1.0±0.4 after the 3rd; 1.0±0.4 after the 4th, and 0.9±0.3 after the 5th doses, respectively. Lymphocyte count then remained stable for 3 months after follow up (0.9±0.4). The total white cell count was also reduced however remained within the normal range throughout the observation period (6.4±1.6 x10*9/L at baseline, and 5.5±2.7 at last follow up). Other blood counts remained unaffected. In seven cases mild infections occurred during the follow-up period. No serious adverse events, relapses or disability progression were observed.

Conclusion: Cladribine induction therapy was safe and well tolerated in people with SPMS followed up for 28 weeks. Extended follow-up is underway to collect further data on safety and efficacy.

Reference

1 Stelmasiak Z, et al. Mult Scler 2009;15:767-70.

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P1147

Effectiveness and safety of dimethyl fumurate treatment in multiple sclerosis patients in clinical practice

R. Alroughanii[1], S. Ahmed[2], R. Behbehani[3], J. Al-Hashel[2]
[1]Amiri Hospital, [2]Ibn Sina Hospital, [3]Al-Bahar Ophthalmology Center, Kuwait, Kuwait

Background: Dimethyl Fumurate (DMF) has been recently approved as a disease modifying therapy for the treatment of Multiple Sclerosis (MS). Post-marketing studies are important to confirm the findings of pivotal clinical trials.

Objective: To evaluate the effectiveness and safety of DMF in a cohort of relapsing MS patients in a clinical practice setting.

Methods: Using the national MS registry, we retrospectively identified patients who had been prescribed DMF. Data of relapsing MS patients with EDSS ⩽ 6 and at least 6 months follow-up were analyzed. Patients with progressive MS were excluded. Primary outcome measure was the proportion of relapse-free patients at last follow-up. Secondary outcome measures included the mean change in the expanded disability status scale (EDSS) scores at last follow-up and the proportion of patients with MRI activity (new T2/flair or gadolinium-enhancing lesions) at 6 months.

Results: Of 134 patients identified, 119 patients were eligible and included in the analysis. Women represented 59.7% of the studied cohort. Mean age and mean disease duration were 33.5 ±11.1 years and 8.3 ±7 years respectively. 75.6% of the patients received prior disease modifying therapies. Mean duration of DMF exposure was 12.4 ±5.5 months. The proportion of relapse-free patients increased significantly from 51.2% to 91.6% ($p < 0.0001$) while the mean EDSS score decreased from 2.8±1.8 at baseline to 2.1±1.6 at last follow up visit. Among patients (n=90) who had MRI follow-up after 6 months, 14.4% of patients had MRI activity compared to 61.1% at baseline ($p < 0.0001$). Although no serious adverse events were reported, 13.4% (n=16) of patients discontinued DMF. The most common adverse events leading to discontinuation were gastrointestinal upset (n=6), persistent lymphopenia (n=2), and tolerability (n=2).

Conclusion: In clinical practice, DMF appeared to be effective in reducing disease activity and progression of disability throughout the observational period. DMF was well tolerated with no serious adverse events. Our results are in parallel with what was seen in clinical trials.

Disclosure

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P1148

Impact of fingolimod treatment on T cell migration to the central nervous system: a four-year observational study

A. Mathias[1], S. Perriot[1], M. Canales[1], C. Gaubicher[1], B. Engelhardt[2], M. Schluep[3], R. Du Pasquier[1,3]
[1]Laboratory of Neuroimmunology, Center of Research in Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois, Lausanne, [2]Theodor Kocher Institute, University of Bern, Bern, [3]Service of Neurology, Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Background: Fingolimod (FTY), one of the treatments used in multiple sclerosis (MS), is active through the retention of B and T cells in peripheral lymph nodes, reducing access of activated T cells to the central nervous system (CNS). Strikingly, FTY has been associated with the reactivation of herpes viruses and five cases of progressive multifocal leukoencephalopathy (PML). One hypothesis is that the reactivation of these viruses in the CNS would be related to a suboptimal immune surveillance induced by FTY.

Objective: To assess the role of FTY on the tissue trafficking profile and function of T cells *ex vivo* in a four-year observation period.
Methods: We enrolled 29 MS patients under FTY, 14 under natalizumab (NTZ), and 11 under other treatments. Blood draws were done before treatment onset (T0) and after 6, 12, 24 and 48 months (T6, T12, T24, T48, respectively). The *ex vivo* expression of homing molecules to: 1. the CNS (CD49d, CD29, CD11a); 2. the skin (CCR4, CCR10); and 3. the gut (CD49d, β7) was assessed using flow cytometry, gating on CD4+ and CD8+T cells. Adhesion profiles of CD3+ T cells were measured *in vitro* with integrin ligands (VCAM-1, ICAM-1, MAdCAM-1; specific ligands of VLA-4, LFA-1 and α4β7, respectively) in a selected number of patients before and after 12 and 48 months (n=6-10 patients per group).
Results: We demonstrate first that FTY sustains a reshuffling of the T cell migration profile over the whole treatment duration. Indeed, FTY doubles the frequency of VLA-4 (CD49d+CD29+) and LFA-1 ($CD11a^{high}$)-expressing CD4+ and CD8+ T cells, and almost triples the frequency of skin-related CCR4+CCR10+CD4+ T cells. However, under FTY, there is a decrease of T cells able to migrate to the gut (α4β7). These phenomena are directly related to the retention of T_N and T_{CM} in secondary lymphoid organ. However, and of high interest, we observed, already at T12, a drop in CD3+ T cell adhesion to VCAM-1 (p=0.027) and to MAdCAM-1 (p=0.008) but not to ICAM-1 (p=0.57), after FTY onset. This profile strikingly resembles what was detected in NTZ-treated MS patients.
Conclusions: Despite the elevated relative frequency of CNS-related T cells expressing VLA-4, the function of this integrin is impaired under FTY. Thus, the dysfunction of VLA-4 integrin, a major player for T cells entrance into the CNS to perform immune surveillance, could contribute to explain the occurrence of CNS viral infections such as PML.

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Du Pasquier R. has served on scientific advisory boards for Biogen Idec, Genzyme, Merck Serono, Novartis, and Teva, and has received funding for travel or speaker honoraria from Biogen Idec, Teva, Merck Serono, and Genzyme.
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P1149

Efficacy and safety of ozanimod from the 2-year blinded extension of RADIANCE: a randomized, double-blind, placebo-controlled Phase 2 trial in relapsing multiple sclerosis

J.A. Cohen[1], K. Selmaj[2], D.L. Arnold[3,4], G. Comi[5], A. Bar-Or[6], A. Olson[7], J. Kopicko[7], M. Cravets[7], P. Frohna[7]
[1]Mellen Center for MS Treatment and Research, Cleveland Clinic, Cleveland, OH, United States, [2]Department of Neurology, Medical University of Lodz, Lodz, Poland, [3]NeuroRx Research, [4]McGill University, Montreal, QC, Canada, [5]Vita-Salute San Raffaele University, Neurology, San Raffaele Scientific Institute, Milan, Italy, [6]Department of Neurology and Neurosurgery, Montreal Neurological Institute, Montreal, QC, Canada, [7]Clinical Development, Receptos Inc., San Diego, CA, United States

Background: Ozanimod (OZ) is an oral, selective sphingosine 1-phosphate receptor modulator ($S1P_{1R/5R}$) in clinical development to treat relapsing MS.
Objectives: Characterize 1-year (48 Week) and 2-year (96 Week) efficacy and safety of low (LD, 0.5 mg) and high (HD, 1 mg) dose OZ in the ongoing blinded extension.
Methods: RADIANCE is an ongoing combined Phase 2/3 trial. Results of the 24-wk, placebo (PBO)-controlled, Phase 2 demonstrated efficacy of both LD and HD with good safety and tolerability (Lancet Neurol 2016). Patients originally randomized to OZ continued their assigned dose (LD, n=85; HD, n=81) and PBO patients were randomized 1:1 to LD (n=41) or HD (n=42).
Results: 224 of 249 patients (90%) entering the extension completed the Wk 96 visit; 5 patients discontinued due to an AE. By the end of Extension Year 1, the original PBO-treated pts had accumulated similar clinical benefits as the OZ-treated patients, so the data were pooled. The LD and HD groups showed a dose-dependent trend on reducing mean±SD Gadolinium-enhancing (GdE) lesions at Wk 48 (0.4±1.6 and 0.1±0.5) and Wk 96 (0.3±1.3 and 0.1±0.5), and new/enlarging T2 lesions at Wk 48 (1.3±3.7 and 0.7±3.8) and Wk 96 (1.8±4.4 and 0.6±1.2), respectively. The proportion of patients GdE lesion-free were comparable at Wk 96 for both doses (91% and 89%, respectively). Effect on unadjusted annualized relapse rate was maintained in the LD and HD groups: Wk 48 (0.26 and 0.15) and Wk 96 (0.3 and 0.19). No evidence of disease activity (no GdE or new/enlarging T2 lesions at Wk 48/96, and no relapse or increase in EDSS by Wk 48/96) was achieved in the LD (44% and 39%) and HD (62% and 47%) during years 1 and 2, respectively.
The AE profiles were comparable across groups. 20 patients experienced serious AEs, none considered related to OZ. The most common AEs continued to be minor infections and headache, with a single AE of bradycardia reported in a LD patient. No events of $\geqslant 2^{nd}$ degree AV block or cases of macular edema were reported. Alanine aminotransferase ⩾3x upper limit of normal occurred in 16 patients (6.4%), with 12/16 continuing to receive study drug, and none satisfying Hy's law.
Conclusions: Both doses of ozanimod demonstrated efficacy over 48 and 96 weeks on MRI and clinical measures of MS disease activity in patients continuing ozanimod and those switching from PBO. The tolerability and safety results suggest a favorable risk-benefit profile that support the ongoing Phase 3 RADIANCE and SUNBEAM trials.

Disclosure

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Mr. Jeff Kopicko is an employee of Celgene.
Mr. Matt Cravets is an employee of Celgene.
Mr. Paul Frohna is an employee of Celgene.

P1150

Efficacy of alemtuzumab is durable over 6 years in patients with active relapsing-remitting multiple sclerosis and an inadequate response to prior therapy in the absence of continuous treatment (CARE-MS II)

E.J. Fox[1], R. Alroughani[2], D. Brassat[3], S. Broadley[4], J.A. Cohen[5], H.-P. Hartung[6], E. Havrdova[7], C. Oreja-Guevara[8], K.W. Selmaj[9], B. Singer[10], P. Vermersch[11], S. Wray[12], D.H. Margolin[13], K. Thangavelu[13], M. Chirieac[13], A.J. Coles[14], on behalf of the CARE-MS II Investigators
[1]Central Texas Neurology Consultants, Round Rock, TX, United States, [2]Amiri Hospital, Sharq, Kuwait, [3]Purpan Hospital and Mixed Unit of Research 1043, University of Toulouse, Toulouse, France, [4]School of Medicine, Gold Coast Campus, Griffith University, Southport, QLD, Australia, [5]Cleveland Clinic, Cleveland, OH, United States, [6]Heinrich-Heine University, Duesseldorf, Germany, [7]First Medical Faculty, Charles University in Prague, Prague, Czech Republic, [8]University Hospital San Carlos, Madrid, Spain, [9]Medical University of Łódź, Łódź, Poland, [10]MS Center for Innovations in Care, Missouri Baptist Medical Center, St. Louis, MO, United States, [11]University of Lille Nord de France, Lille, France, [12]Hope Neurology, Knoxville, TN, [13]Sanofi Genzyme, Cambridge, MA, United States, [14]University of Cambridge School of Medicine, Cambridge, United Kingdom

Background: In patients with active relapsing-remitting multiple sclerosis (RRMS) and an inadequate response (⩾1 relapse) to prior therapy at baseline (BL), alemtuzumab significantly reduced the annualised relapse rate (ARR), reduced the risk of confirmed disability worsening (CDW), and increased the proportion of patients with confirmed disability improvement (CDI) compared with subcutaneous interferon beta-1a over 2 years (CARE-MS II; NCT00548405). In an extension study (NCT00930553), efficacy has been shown to be durable through 5 years in the absence of continuous treatment.
Goal: To evaluate 6-year efficacy and safety of alemtuzumab in patients with an inadequate response to prior therapy.
Methods: CARE-MS II patients received 2 treatment courses of alemtuzumab 12 mg (Month 0: 5 days; Month 12: 3 days); patients who completed CARE-MS II could enter the extension, with as-needed alemtuzumab retreatment for relapse or MRI activity. Another disease-modifying therapy could be provided per investigator discretion. Assessments: ARR, proportion of patients free from 6-month CDW (⩾1-point EDSS increase [⩾1.5-point if BL EDSS=0]), 6-month CDI (⩾1-point EDSS decrease [BL score ⩾2.0]), no evidence of disease activity (NEDA), and adverse events (AEs).
Results: Through 6 years, 344/393 (88%) who enrolled in the extension remained on study. A low ARR was maintained through the extension (Year 6: 0.15). Through 6 years, 72% of patients were free from 6-month CDW, and 43% achieved 6-month CDI. Mean EDSS increased from BL by 0.10 over Years 0-6; the proportion of patients with improved or stable EDSS remained high (77% at Year 6). In each year, most patients achieved NEDA (60% at Year 6). These efficacy results were achieved with 50% of patients receiving no additional treatment after their initial 2 courses of alemtuzumab. The overall rate of AEs decreased over time. Thyroid AEs peaked at Year 3 and subsequently declined. Infusion-associated reactions decreased with additional treatment courses. The serious AE rate was low, including rate of serious infections, throughout the extension.
Conclusion: Alemtuzumab efficacy was maintained over 6 years in patients who had an inadequate response to prior therapy. 50% of patients received no additional treatment after the initial 2 courses of alemtuzumab. Based on these findings, alemtuzumab may provide a unique treatment approach with durable efficacy in the absence of continuous treatment for RRMS patients.

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P1151

The efficacy of natalizumab versus fingolimod for patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis of randomized and observational study data

G. Tsivgoulis[1], A.H. Katsanos[2], D. Mavridis[3], N. Grigoriadis[4], E. Dardiotis[5], I. Heliopoulos[6], P. Papathanasopoulos[7], C. Kilidireas[8], G.M. Hadjigeorgiou[5], K. Voumvourakis[1], HELANI (Hellenic Academy of Neuroimmunology)
[1]Second Department of Neurology, University of Athens, Athens, [2]Department of Neurology, [3]Department of Hygiene and Epidemiology, University of Ioannina Medical School, Ioannina, [4]Department of Neurology, University of Thessalonica, Thessaloniki, [5]Department of Neurology, University of Thessaly, Larissa, [6]Department of Neurology, Democritus University of Thrace, Alexandroupolis, [7]Department of Neurology, University of Patras Medical School, Patras, [8]First Department of Neurology, University of Athens, Athens, Greece

Background: The efficacy of Natalizumab (NTZ) and Fingolimod (FGD) in patients with relapsing remitting multiple sclerosis (RRMS) has never been directly compared in randomized clinical trials (RCT). We sought to evaluate the comparative efficacy of NTZ to FGD using data from both eligible placebo-controlled RCTs (indirect meta-analysis) and observational studies (pairwise meta-analysis).
Methods: We calculated odds ratios (ORs) in each study protocol to evaluate the comparison of the reported dichotomous outcomes, while we expressed the unadjusted mean differences of reported continuous outcomes between subgroups as standardized mean differences (SMDs). The mixed-effects model was used to calculate the pooled point estimates in each subgroup and the overall estimates in all occasions. We also compared the baseline characteristics of RRMS patients treated with NTZ or FGD in the corresponding RCTs, and estimated the indirect effect sizes with their corresponding 95%CI.
Results: We identified 3 RCTs (2498 patients) and 5 observational studies (2576 patients). Baseline characteristic analyses in the included studies suggest that NTZ treated patients had a more aggressive disease profile at baseline (more active lesions on brain MRI) compared to those treated with FGD. In the indirect meta-analysis NTZ was found to be associated with a greater (p=0.005) reduction in the 2-year annualized relapse rate (ARR) compared to FGD ($SMD_{indirect}$=-0.24; 95%CI:-0.44--0.04), while no differences between the two therapies were found in the proportion of patients who remained relapse-free (ORindirect=1.20; 95%CI:0.84-1.71) and those with disability progression ($OR_{indirect}$= 0.76; 95%CI:0.48-1.21) at 2 years. In the subgroup analysis of observational data no significant differences between NTZ and FGD were found in the 2-year ARR (SMD=-0.05; 95%CI:-0.26-0.16), and disability progression at 1 (OR: 1.37; 95%CI:0.95-1.98) and 2 years (OR: 1.08; 95%CI:0.77-1.52). However, NTZ-treated patients had a higher (p=0.020) probability of remaining relapse-free at 2-years compared to those treated with FGD (OR: 2.19; 95%CI:1.15-4.18). They tended (p=0.09) also to have a higher likelihood to be relapse-free at 1 year (OR:1.61; 95%CI:0.94-2.78).
Conclusion: Randomized and observational data suggest that NTZ is probably more effective than FGD in terms of relapse reduction in patients with RRMS. However, head-to-head RCTs are required to independently confirm this preliminary observation.

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P1152

Safety and efficacy of dimethyl fumarate in multiple sclerosis - an observational study

A. Miclea[1], R. Hoepner[1], V.I. Leussink[2], H.-P. Hartung[2], R. Gold[1]
[1]Neurology, St. Josef Hospital, Ruhr University, Bochum, [2]Neurology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

Background: Dimethyl fumarate (DMF) was recently approved for treating patients with relapsing remitting multiple sclerosis (RRMS) based on two phase III clinical trials demonstrating its efficacy. This prompts the need to obtain real world data comparing DMF with other first line immunotherapies.
Methods: By retrospective analysis of medical records at two German MS centres, 644 RRMS patients treated with DMF were identified. All were included in a safety analysis and a subgroup of patients with available efficacy data during previous MS therapies (n=352) was further analysed for annualised relapse rate and disability progression assessed by the Expanded Disability Status Scale.
Results: In the overall population studied, DMF reduced annualised relapse rate and disability progression by 33%. Patients who had been switched from interferons or glatiramer acetate to DMF benefited more, whereas those pretreated with more potent immunotherapies did not respond as well. In contrast, the subgroup of patients with no disease activity prior to DMF worsened, revealing an increase in annualised relapse rate and disability progression. Interestingly, patients with a lymphocyte count ⩾2000/µl after 0.52 years (mean, SD 0.2) of DMF treatment did not benefit

compared to those with lower lymphocyte counts. In total, 22.2% of the patients withdrew from DMF due to side effects with gastrointestinal discomfort (12.7%) and lymphopenia (5.3%) as most frequently reported reasons.
Conclusion: Our study corroborates that DMF is an overall safe and effective drug reducing relapse rate as well as disability progression in RRMS patients. Further prospective studies are warranted to establish additional parameters predicting DMF response, especially in patients switching from other first line medications.

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P1153

Effect of oral versus injectable disease-modifying therapies on the epigenome-wide DNA methylation and gut microbiota in multiple sclerosis patients

P. Casaccia[1], Y. Zhu[1], E. Cekanaviciute[2], J. Debelius[3], Y. Bencosme[1], S. Mazmanian[4], R. Knight[3], R. Kanner[2], S. Singh[2], B. Cree[2], S. Baranzini[2], I. Katz-Sand[1], MS Microbiome Consortium
[1]Icahn School of Medicine at Mount Sinai, New York, NY, [2]University of California, School of Medicine, San Francisco, [3]University of California, San Diego, [4]California Institute of Technology, Pasadena, CA, United States

The gut microbiota has been proposed as a key modulator of immune dysregulation in many inflammatory diseases, including MS. The purpose of this study is to address whether currently available immunomodulatory drugs for relapsing multiple sclerosis (RRMS) might differentially impact microbiota composition. Similarly, it is not currently known whether modulation of immune responses and differential treatment effectiveness among patients could in part be related to baseline or induced differences in microbiota. We collected biological samples (blood, stool) as from carefully phenotyped RRMS patients who are either untreated or treated with glatiramer acetate or dimethyl fumarate (DMF) for at least 3 months. Immunoprofiling of blood samples using flow cytometry revealed that both DMF and GA differentially regulated T cell populations with a more prominent effect of DMF than GA in reducing Th2 and Th17 cell numbers. This effect was associated with changes of the DNA methylation profile of T cells, as determined by the Illumina Infinium MethylationEPIC BeadChip array. Analysis of patients' fecal microbiome using 16S rRNA amplicon sequencing did not identify global difference at community level. However, several bacterial genera were differentially regulated in GA or DMF treated compared to untreated patients. Interestingly, while GA re-balanced microbial abundances (with an equal number of taxa being downregulated or upregulated), DMF strongly reduced the vast majority of the differentially changed bacteria. More importantly, a common group of bacteria were reduced in both GA or DMF treated patients, suggesting a possible contribution of these bacteria to the effect of the therapeutic agents on MS disease development. We are currently working to test this hypothesis in mouse models of MS. Our ultimate goal is to provide a better understanding of the relationship between current MS treatments and the gut microbiota with the hope to develop adjuvant treatments modulating currently available therapeutic choices for MS.

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P1154

Can dimethyl-fumarate be a good treatment choice after natalizumab discontinuation?

G. Farina[1], M. Pitteri[1], R. Magliozzi[1,2], M. Castellaro[1,3], V. Camera[1], C. Romualdi[4], A. Bertoldo[3], S. Monaco[1], M. Calabrese[1]
[1]Neurology B, Dept. of Neurological and Movement Sciences, University of Verona, Verona, Italy, [2]Division of Brain Sciences, Department of Medicine, Imperial College London, London, United Kingdom, [3]Department of Information Engineering, [4]Department of Biology, University of Padova, Padova, Italy

Background: Several studies demonstrated the impressive efficacy and the good tolerability profile of Natalizumab (NTZ) in Multiple Sclerosis (MS) patients. Although the long-term safety of NTZ therapy is burdened by the risk of progressive multifocal leukoencephalopathy (especially in anti-JCV seropositive patients treated for more than two years) the NTZ discontinuation enlightened the risk of disease reactivation. Previous data indicated that Fingolimod does not exert clinical activity quickly enough to stop MS reactivation after a break from NTZ.
Aim: In this study we wanted to explore the efficacy of Dimethyl-fumarate (DMF) in controlling MS reactivation after NTZ discontinuation.
Patients and methods: 37 relapsing-remitting MS patients having high titre of JCV-Ab and more than 2 years of treatment, were shifted from NTZ to DMF after a mean of 1 month washout period. An increasing dose scheme as the following was used: 120 mg BID for 1 week, then 240 mg BID.
Expanded Disability Status Scale (EDSS) was evaluated monthly for a mean follow-up period of 9.8
(±3; range 5.5-16) months. Brain 3T MRI was obtained at the beginning of DMF and every 3 months after therapy initiation. Three patients had less than 6 months of follow up to date and therefore were excluded from the analysis.
The number of relapses, the disability (EDSS) progression and the MRI activity (new Gad+ lesions, new T2 lesions, new enlarging T2 lesions and new cortical lesions) were evaluated.

The NEDA-3 patients defined by no clinical relapses, no disability progression and no MRI activity were also calculated.
Results: Among the 34 analysed patients and after 9 months of follow up, 31 (91%) can be considered NEDA-3. One patient (2.9%) had a clinical relapse plus MRI activity while 2 patients (5.9%) showed MRI activity only. In all cases, disease activity occurred within the first 3 months of the DMF treatment. The side effects were similar to the phase 3 main clinical trials and no drop-outs were registered.
Discussion and conclusion: Although DMF does not seem to completely eliminate the possibility of disease reactivation, our results indicate that it might be a promising drug for those patients who shall discontinue NTZ. Additional data on larger sample sizes should confirm this hypothesis.

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Gabriele Farina: nothing to disclose.
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P1155

Comparative analysis of MS outcomes in natalizumab-treated patients using a novel three-way multinomial propensity score match

T. Spelman[1], F. Pellegrini[2], A. Zhang[2], M. Trojano[3], H. Wiendl[4], L. Kappos[5], R. Hyde[2], H. Koendgen[2], F. Verheul[6], F. Grand'Maison[7], G. Izquierdo[8], E. Havrdova[9], D. Horakova[9], A. Lugaresi[10], P. Duquette[11], P. Grammond[12], R. Hupperts[13], J. Lechner-Scott[14], F. Granella[15], T. Petersen[16], M. Terzi[17], E. Pucci[18], P. Sola[19], H. Butzkueven[1], MSBase Study Group and the Tysabri Observational Programme Investigators

[1]Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia, [2]Biogen, Inc., Weston, MA, United States, [3]Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy, [4]Department of Neurology, University of Münster, Münster, Germany, [5]Departments of Neurology and Biomedicine, University Hospital Basel, Basel, Switzerland, [6]Groene Hart Ziekenhuis, Gouda, The Netherlands, [7]Neuro Rive-Sud, Hôpital Charles LeMoyne, Quebec, QC, Canada, [8]Hospital Universitario Virgen Macarena, Seville, Spain, [9]Department of Neurology and Center of Clinical Neuroscience, 1st Faculty of Medicine, General University Hospital and Charles University, Prague, Czech Republic, [10]MS Center, Department of Neuroscience and Imaging, University 'G. d'Annunzio', Chieti, Italy, [11]Hôpital Notre Dame, Montreal, [12]Center de Réadaptation Déficience Physique Chaudière-Appalache, Lévis, QC, Canada, [13]Maaslandziekenhuis, Sittard-Geleen, The Netherlands, [14]John Hunter Hospital, Newcastle, NSW, Australia, [15]Department of Neuroscience, University of Parma, Parma, Italy, [16]Kommunehospitalet, Aarhus, Denmark, [17]19 Mayis University, Samsun, Turkey, [18]Neurology Unit, ASUR Marche - AV3, Macerata, [19]Department of Neuroscience, Neurology Unit, Nuovo Ospedale Civile S. Agostino/Estense, Modena, Italy

Objective: The objective of this analysis is to compare relapse and progression outcomes across a range of treatment switch scenarios following relapse on prior therapy. The analysis describes a novel application of multinomial propensity score matching across three separate switch treatment groups.
Methods: All data were sourced from the MSBase registry. Three treatment switch patient groups were specified for the comparative three-way analysis: 1) relapsing remitting MS (RRMS) patients switching from Interferonβ (IFNβ), glatiramer acetate (GA), teriflunomide (T) or dimethyl fumarate (DMF) (IFNβ/GATD) to natalizumab (NTZ); 2) switching between IFNβ/GATD perparations and 3) switching from IFNβ/GATD to fingolimod (FTY). Annualised relapse rate (ARR), time to first on-treatment relapse and time to first three month confirmed disability progression were analysed as the primary end-points.
Results: Mean ARR was significantly higher in the IFNβ/GATD to IFNβ/GATD switch group (mean 0.60, SD 0.80) relative to either the NTZ (mean 0.28, SD 0.53) or FTY (mean 0.28, SD 0.56) switch groups
($p < 0.0001$). NTZ switchers were associated with a 47% reduction in the rate of first relapse post-switch relative to patients switching between IFNβ/GATD (adjusted HR: 0.53; 95% CI 0.40, 0.69). Similarly FTY switchers were associated with a 51% reduction in the rate of first relapse relative to patients switching between IFNβ/GATD (adjusted HR: 0.49; 95% CI 0.37, 0.64). NTZ switchers were associated with a 39% decrease in the rate of disability progression relative to IFNβ/GATD switchers (aHR: 0.61; 95% CI 0.39, 0.94). Both NTZ and FTY switchers were associated with an increased rate of EDSS regression relative to inter- IFNβ/GATD switchers. Patients switching to NTZ were associated with 1.84 times the rate of EDSS regression relative to IFNβ/GATD (HR 1.84; 95% CI 1.35, 2.52) whilst FTY switchers were associated with 1.62 times the rate (HR 1.62; 95% CI 1.17, 2.26).
Interpretation: Switching to either NTZ or FTY after relapsing on prior IFNβ/GATD therapy was associated with a significant reduction in ARR and time to first relapse relative to patients switching between IFNβ/GATD products. NTZ switchers were also associated with a decrease in three-month confirmed disability progression relative to inter- IFNβ/GATD switchers. Both NTZ and FTY were associated with an increased rate of EDSS regression compared with IFNβ/GATD switchers.

Disclosure

Tim Spelman received compensation for serving on scientific advisory boards, honoraria for consultancy and funding for travel from Biogen Inc; speaker honoraria from Novartis.
Fabio Pellegrini is an employee of Biogen.
Annie Zhang is an employee of Biogen.
Maria Trojano received honoraria for consultancy and/or speaking from Biogen Idec, Genzyme-Sanofi, Merck Serono, Novartis,

and Roche; research grants from Biogen Idec, Merck Serono, Novartis, and Teva.
Heinz Wiendl received compensation for serving on scientific advisory boards for Bayer Healthcare, Biogen Idec, Genzyme, Merck Serono, Novartis, and Sanofi; speaker honoraria and travel support from Bayer Schering AG, Bayer Vital GmbH, Biogen Idec, CSL Behring, Fresenius Medical Care, Genzyme, GlaxoSmithKline, GW, Merck Serono, Novartis, and Sanofi; compensation as a consultant from Biogen Idec, Merck Serono, Novartis, and Sanofi; research support from Bayer Vital GmbH, Biogen Idec, Merck Serono, Novartis, Sanofi Germany, and Sanofi US.
Ludwig Kappos received research support from Acorda, Actelion, Allozyne, BaroFold, Bayer HealthCare, Bayer Schering, Bayhill Therapeutics, Biogen Idec, Elan, European Union, Genmab, Gianni Rubatto Foundation, GlaxoSmithKline, Glenmark, MediciNova, Merck Serono, Novartis, Novartis Research Foundation, Roche, Roche Research Foundation, Sanofi-Aventis, Santhera, Swiss MS Society, Swiss National Research Foundation, Teva Neuroscience, UCB, and Wyeth.
Robert Hyde is an employee of Biogen.
Harold Koendgen is an employee of Biogen.
Freek Verheul is an advisory board member for Teva Biogen Merck Serono and Novartis.
Francois Grand-Maison received an honorarium for organizing a CME event for Biogen Idec in 2013 and received consultation fees from Biogen Idec as well as from Novartis and Genzyme in 2013 and 2014.
Guillermo Izquierdo received consulting fees from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi, and Teva.
Eva Havrdova received speaker honoraria and consultant fees from Biogen Idec, Merck Serono, Novartis, Genzyme and Teva, as well as support for research activities from Biogen Idec and Merck Serono.
Dana Horakova received speaker honoraria and consultant fees from Biogen Idec, Merck Serono, Novartis, Genzyme and Teva, as well as support for research activities from Biogen Idec and Merck Serono.
Alessandra Lugaresi was a Bayer, Biogen, Genzyme, Merck Serono, Novartis Advisory Board Member. She received travel grants and honoraria from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla, her Institution received research grants from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla.
Pierre Duquette has received honoraria for organising CME events and has obtained funding to attend meetings from Biogen Idec, EMD Serono, TEVA Neuroscience, Novartis, and Genzyme, has received funding for investigator-initiated trials with Biogen Idec, EMD Serono and Novartis, and has received peer-review funding from CIHR and from the MS Society of Canada.
Pierre Grammond is a Novartis, Teva-neuroscience, Biogen Idec advisory board member, consultant for Merck Serono, received payments for lectures by Merck Serono, Teva-Neuroscience and Canadian Multiple sclerosis society, and received grants for travel from Teva-Neuroscience and Novartis.
Raymond Hupperts received honoraria as consultant on scientific advisory boards from Merck-Serono, Biogen-Idec, Genzyme-Sanofi and Teva, research funding from Merck-Serono and Biogen-Idec, and speaker honoraria from Sanofi-Genzyme.
Jeannette Lechner-Scott has accepted travel compensation from Novartis, Biogen and Merck Serono. Her institution receives the honoraria for talks and advisory board commitment and also clinic support from Bayer Health Care, Biogen , CSL, Genzyme Sanofi, Merck Serono, Novartis and TEVA.
Franco Granella has served on scientific advisory boards for Biogen Idec, Novartis and Sanofi Aventis and has received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, and Almirall.
Thor Petersen did not declare any competing interests.
Murat Terzi received travel grants from Merck Serono, Novartis, Bayer-Schering, Merck-Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.
Eugenio Pucci served on scientific advisory boards for Genzyme, Novartis and Biogen-Idec; he has received honoraria and travel grants from Sanofi Aventis, Novartis, Biogen Idec, Merck Serono, Genzyme and Teva; he has received travel grants from Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche.
Patrizia Sola did not declare any competing interests.
Helmut Butzkueven received honoraria for consultancy and/or speaking from Biogen Idec, Genzyme-Sanofi, Merck Serono, Novartis, and Roche; research grants from Biogen Idec, Merck Serono, Novartis, and Teva.

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Comparison of MS outcomes after Switching to Natalizumab versus staying on Interferon-beta or glatiramer

T. Spelman[1], G. Izquierdo[2], A. Lugaresi[3], R. Alroughani[4], P. Duquette[5], C. Boz[6], R. Fernández Bolaños[7], E. Pucci[8], F. Grand'Maison[9], G. Iuliano[10], T. Petersen[11], C. Oreja-Guevara[12], M. Fiol[13], M. Barnett[14], V. Van Pesch[15], S. Hughes[16], F. Pellegrini[17], A. Zhang[17], H. Wiendl[18], L. Kappos[19], R. Hyde[17], H. Koendgen[17], F. Verheul[20], M. Trojano[21], H. Butzkueven[1], on behalf of the MSCOMET (an MSBase Substudy) Investigators and the TOP Investigators.
[1]Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia, [2]Hospital Universitario Virgen Macarena, Seville, Spain, [3]MS Center, Department of Neuroscience and Imaging, University 'G. d'Annunzio', Chieti, Italy, [4]Amiri Hospital, Kuwait, Kuwait, [5]Hôpital Notre Dame, Montreal, QC, Canada, [6]Karadeniz Technical University, Trabzon, Turkey, [7]Hospital Universitario Virgen de Valme, Seville, Spain, [8]Neurology Unit, ASUR Marche - AV3, Macerata, Italy, [9]Neuro Rive-Sud, Hôpital Charles LeMoyne, Quebec, QC, Canada, [10]Ospedali Riuniti di Salerno, Salerno, Italy, [11]Kommunehospitalet, Aarhus, Denmark, [12]Hospital Clínico San Carlos, Madrid, Spain, [13]Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia, Buenos Aires, Argentina, [14]Brain & Mind Research Institute, Sydney, NSW, Australia, [15]Cliniques Universitaires Saint-Luc, Brussels, Belgium, [16]Craigavon Area Hospital, Portadown, United Kingdom, [17]Biogen, Inc., Weston, MA, United States, [18]Department of Neurology, University of Münster, Münster, Germany, [19]Departments of Neurology and Biomedicine, University Hospital Basel, Basel, Switzerland, [20]Groene Hart Ziekenhuis, Gouda, The Netherlands, [21]Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy

Background: Switching immunomodulatory therapy is a potentially useful treatment strategy in patients with Multiple Sclerosis (MS) failing first line interferonβ (IFNβ) or glatiramer acetate (GA) therapy. One key question facing people with MS and their clinicians is whether to switch therapy after a relapse or stay on their current therapy. Outcomes in patients switching to natalizumab compared with remaining on IFNβ/GA after an on-treatment relapse are not known, and this question is unlikely to be addressed in an RCT. We therefore conducted a multi-centre, international head-to-head comparison study of on-treatment relapse and treatment persistence outcomes in a cohort of patients switching to natalizumab compared with matched patients persisting on IFNβ/GA following a relapse.

Methods: Natalizumab switch patients were sourced from Tysabri Observation Programme (TOP) and were propensity matched to IFNβ/GA treated patients sourced from the MSBase registry substudy, MSComet, using a range of baseline demography and disease activity characteristics. This comparative analysis was pre-specified in both study protocols. Time to first relapse, treatment discontinuation and confirmed disability progression by treatment arm were compared using a Cox marginal model.

Results: Switching to natalizumab was associated with a 64% decrease (HR 0.36, 95% CI 0.30, 0.44;
$p < 0.001$) in the rate of on-treatment relapse, a 44% decrease in the rate of treatment discontinuation (HR 0.56, 95% CI 0.50, 0.63; $p < 0.001$) and a 39% reduction in the rate of confirmed disability progression (HR 0.61, 95 CI: 0.36, 0.51; $p=0.001$) relative to persisting on IFNβ/GA. Natalizumab was also associated with a greater mean (SD) decrease in on-treatment EDSS (-0.04 (0.98) vs 0.06 (1.08); $p=0.016$). The mean cumulative area-under the EDSS curve was decreased by 0.41 EDSS-years in the natalizumab switch arm compared to the IFNβ/GA stayer arm.

Conclusions: Following relapse on IFNβ/GA, switching to natalizumab was associated with a decrease in both time to first relapse, confirmed disability progression and discontinuation rate relative to persisting on IFNβ/GA therapy. Our results quantify the switch benefits in clinical practice to be weighed against known risks in the shared patient-physician therapeutic decision process.

Disclosure

Tim Spelman received compensation for serving on scientific advisory boards, honoraria for consultancy and funding for travel from Biogen Inc; speaker honoraria from Novartis.

Guillermo Izquierdo received consulting fees from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi, and Teva.

Alessandra Lugaresi was a Bayer, Biogen, Genzyme, Merck Serono, Novartis Advisory Board Member. She received travel grants and honoraria from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla, her Institution received research grants from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla.

Raed Alroughani received honoraria from Biologix, Biogen, Bayer, Genzyme, Genpahrm, Merck Sorono, GSK and Novartis, and served on advisory board for Bayer, Biologix, Biogen, Genzyme, Genpharm, Novartis and Merck Sorono.

Pierre Duquette has received honoraria for organising CME events and has obtained funding to attend meetings from Biogen Idec, EMD Serono, TEVA Neuroscience, Novartis, and Genzyme, has received funding for investigator-initiated trials with Biogen Idec, EMD Serono and Novartis, and has received peer-review funding from CIHR and from the MS Society of Canada.

Cavit Boz received conference travel support from Biogen Idec, Novartis, Bayer-Schering, Merck-Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Ricardo Fernández Bolaños did not declare any competing interests

Eugenio Pucci served on scientific advisory boards for Genzyme, Novartis and Biogen-Idec; he has received honoraria and travel grants from Sanofi Aventis, Novartis, Biogen Idec, Merck Serono, Genzyme and Teva; he has received travel grants from Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche.

Francois Grand-Maison received an honorarium for organizing a CME event for Biogen Idec in 2013 and received consultation fees from Biogen Idec as well as from Novartis and Genzyme in 2013 and 2014.

Gerardo Iuliano received honoraria from Biogen-Idec, Novartis, Sanofi, Serono and Teva.

Thor Petersen did not declare any competing interests

Celia Oreja-Guevara received honoraria as scientific advisory board consultant from Biogen-Idec, Bayer-Schering, Merck-Serono, Teva and Novartis; has participated in research projects by Biogen-Idec, GSK, Teva and Novartis

Marcela Fiol did not declare any competing interests.

Michael Barnett did not declare any competing interests.

Vincent Van Pesch has received travel grants and honoraria for consultancy or lectures from Bayer-Schering, Biogen Idec, Merck Serono, Novartis Pharma, Sanofi-Aventis and Teva

Stella Hughes did not declare any competing interests.

Fabio Pellegrini is an employee of Biogen.

Annie Zhang is an employee of Biogen.

Heinz Wiendl received compensation for serving on scientific advisory boards for Bayer Healthcare, Biogen Idec, Genzyme, Merck Serono, Novartis, and Sanofi; speaker honoraria and travel support from Bayer Schering AG, Bayer Vital GmbH, Biogen Idec, CSL Behring, Fresenius Medical Care, Genzyme, GlaxoSmithKline, GW, Merck Serono, Novartis, and Sanofi; compensation as a consultant from Biogen Idec, Merck Serono, Novartis, and Sanofi; research support from Bayer Vital GmbH, Biogen Idec, Merck Serono, Novartis, Sanofi Germany, and Sanofi US.

Ludwig Kappos received research support from Acorda, Actelion, Allozyne, BaroFold, Bayer HealthCare, Bayer Schering, Bayhill Therapeutics, Biogen Idec, Elan, European Union, Genmab, Gianni Rubatto Foundation, GlaxoSmithKline, Glenmark, MediciNova, Merck Serono, Novartis, Novartis Research Foundation, Roche, Roche Research Foundation, Sanofi-Aventis, Santhera, Swiss MS Society, Swiss National Research Foundation, Teva Neuroscience, UCB, and Wyeth.

Robert Hyde is an employee of Biogen.

Harold Koendgen is an employee of Biogen

Freek Verheul is an advisory board member for Teva Biogen Merck Serono and Novartis.

Maria Trojano received honoraria for consultancy and/or speaking from Biogen Idec, Genzyme-Sanofi, Merck Serono, Novartis, and Roche; research grants from Biogen Idec, Merck Serono, Novartis, and Teva.

Helmut Butzkueven received compensation for serving on scientific advisory boards and as a consultant for Biogen Idec and

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Comparative analysis of MS outcomes in dimethyl fumarate-treated patients relative to propensity matched fingolimod, interferon, glatiramer acetate, or teriflunomide

T. Spelman[1], T. Kalincik[1], M. Trojano[2], F. Grand'Maison[3], G. Izquierdo[4], E. Havrdova[5], D. Horakova[5], A. Lugaresi[6], P. Duquette[7], P. Grammond[8], R. Hupperts[9], J. Lechner-Scott[10], F. Granella[11], T. Petersen[12], M. Terzi[13], E. Pucci[14], P. Sola[15], V. Van Pesch[16], G. Iuliano[17], C. Oreja-Guevara[18], C. Boz[19], R. Bergamaschi[20], M. Slee[21], H. Butzkueven[1], on behalf of the MSBase Investigators

[1]Department of Medicine and Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia, [2]Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy, [3]Neuro Rive-Sud, Hôpital Charles LeMoyne, Quebec, QC, Canada, [4]Hospital Universitario Virgen Macarena, Seville, Spain, [5]Department of Neurology and Center of Clinical Neuroscience, 1st Faculty of Medicine, General University Hospital and Charles University, Prague, Czech Republic, [6]MS Center, Department of Neuroscience and Imaging, University 'G. d'Annunzio', Chieti, Italy, [7]Hôpital Notre Dame, Montreal, [8]Center de Réadaptation Déficience Physique Chaudière-Appalache, Lévis, QC, Canada, [9]Maaslandziekenhuis, Sittard-Geleen, The Netherlands, [10]John Hunter Hospital, Newcastle, NSW, Australia, [11]Department of Neuroscience, University of Parma, Parma, Italy, [12]Kommunehospitalet, Aarhus, Denmark, [13]19 Mayis University, Samsun, Turkey, [14]Neurology Unit, ASUR Marche - AV3, Macerata, [15]Department of Neuroscience, Neurology Unit, Nuovo Ospedale Civile S. Agostino/Estense, Modena, Italy, [16]Cliniques Universitaires Saint-Luc, Brussels, Belgium, [17]Ospedali Riuniti di Salerno, Salerno, Italy, [18]Hospital Clínico San Carlos, Madrid, Spain, [19]Karadeniz Technical University, Trabzon, Turkey, [20]Neurological Institute IRCCS Mondino, Pavia, Italy, [21]Flinders Medical Centre, Adelaide, SA, Australia

Objective: The objective of this analysis is to compare time to first relapse (TTFR), annualised relapse rate (ARR) and discontinuation outcomes in patients treated with dimethyl fumarate (DMF) pair-wise relative to a propensity matched cohort of either fingolimod (FTY), teriflunomide (TERI), interferons (IFN) or glatiramer acetate (GA).

Methods: All data were sourced from the MSBase registry. RRMS patients aged ⩾18 yrs at the time of index DMD initiation with ⩾12 mos of pre-baseline follow-up and ⩾6 mos persistence on the index DMD were eligible for the analysis. Propensity score (PS) matching was used to match patients from the DMF group to a comparable patient in the comparator treatment arms on a 1:1 basis. TTFR and time to index DMD discontinuation were analysed using a Kaplan-Meier approach and a marginal Cox model accounting for PS matched pairs. Mean ARRs will be reported by treatment arm and analysed with a Generalised Estimating Equations Poisson model offsetting for treatment exposure time. Event numbers and follow-up time were insufficient to analyse disability progression.

Results: A total of 415 DMF initiators (out of overall 434) were successfully matched to 415 FTY patients. There was no difference in risk of first relapse between DMF and FTY (HR 1.15; 95% CI 0.87, 1.51; reference = FTY). DMF was associated with increased risk of discontinuation relative to fingolimod following 6 mos of continuous therapy (HR 2.39; 95% CI 1.78, 3.20). A total of 420, 382, and 256 patient pairs were matched for DMF/IFN, DMF/GA, and DMF/TERI, respectively. DMF was associated with a 26%, 28%, and 34% reduction in the risk of first relapse relative to IFN (HR 0.74; 95% CI 0.57, 0.97), GA (HR 0.72; 95% CI 0.54, 0.95), and TERI (HR 0.66; 95% CI 0.45, 0.99), respectively. DMF was associated with 1.40 times the risk of discontinuation following 6 mos of continuous therapy vs IFNs (HR 1.40; 95% CI 1.07, 1.83). There was no difference in discontinuation rates between DMF vs GA (HR 1.18; 95% CI 0.89, 1.56) or TERI (HR 0.95; 95% CI 0.66, 1.37). Additional data, including ARR, will be presented.

Interpretation: DMF was similar to a matched cohort of FTY-treated patients in regards to risk of first relapse. Conversely, DMF was associated with a statistically significant reduction in risk of first relapse relative to IFN, GA, or TERI. DMF was associated with an increased risk of discontinuation relative to FTY and IFN, following 6 months of continuous therapy.

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Tomas Kalincik received compensation for conference travel and speaker honoraria from Novartis, Biogen Idec, Genzyme, Sanofi Aventis, Teva, BioCSL and Merck Serono and served on advisory boards for Novartis, Merck Serono and Biogen.

Maria Trojano received honoraria for consultancy and/or speaking from Biogen Idec, Genzyme-Sanofi, Merck Serono, Novartis, and Roche; research grants from Biogen Idec, Merck Serono, Novartis, and Teva.

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Guillermo Izquierdo received consulting fees from Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi, and Teva.

Eva Havrdova received speaker honoraria and consultant fees from Biogen Idec, Merck Serono, Novartis, Genzyme and Teva, as well as support for research activities from Biogen Idec and Merck Serono.

Dana Horakova received speaker honoraria and consultant fees from Biogen Idec, Merck Serono, Novartis, Genzyme and Teva, as well as support for research activities from Biogen Idec and Merck Serono.

Alessandra Lugaresi was a Bayer, Biogen, Genzyme, Merck Serono, Novartis Advisory Board Member. She received travel grants and honoraria from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla, her Institution received research grants from Bayer, Biogen, Merck Serono, Novartis, Sanofi, Teva and Fondazione Italiana Sclerosi Multipla.

Pierre Duquette has received honoraria for organising CME events and has obtained funding to attend meetings from Biogen

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Raymond Hupperts received honoraria as consultant on scientific advisory boards from Merck-Serono, Biogen-Idec, Genzyme-Sanofi and Teva, research funding from Merck-Serono and Biogen-Idec, and speaker honoraria from Sanofi-Genzyme.
Jeannette Lechner-Scott has accepted travel compensation from Novartis, Biogen and Merck Serono. Her institution receives the honoraria for talks and advisory board commitment and also clinic support from Bayer Health Care, Biogen , CSL, Genzyme Sanofi, Merck Serono, Novartis and TEVA.
Franco Granella has served on scientific advisory boards for Biogen Idec, Novartis and Sanofi Aventis and has received funding for travel and speaker honoraria from Biogen Idec, Merck Serono, and Almirall.
Thor Petersen did not declare any competing interests.
Murat Terzi received travel grants from Merck Serono, Novartis, Bayer-Schering, Merck-Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.
Eugenio Pucci served on scientific advisory boards for Genzyme, Novartis and Biogen-Idec; he has received honoraria and travel grants from Sanofi Aventis, Novartis, Biogen Idec, Merck Serono, Genzyme and Teva; he has received travel grants from Associazione Marchigiana Sclerosi Multipla e altre malattie neurologiche.
Patrizia Sola did not declare any competing interests.
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Cavit Boz received conference travel support from Biogen Idec, Novartis, Bayer-Schering, Merck-Serono and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.
Roberto Bergamaschi declared no competing interests
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P1158

Fingolimod real world experience: the French grand-est cohort

A. Tourbah[1], E. Berger[2], L. Chamard[2], M. Debouverie[3], J. De Sèze[4], E. Godet[5], T. Moreau[6], The French Grand-Est Fingolimod study Group

[1]Neurology, CHU de Reims, URCA, Reims, [2]Neurology, CHU de Besançon, Besançon, [3]CHU de Nancy, Hôpital Central, Nancy, [4]Neurology, CHU de Strasbourg, Strasbourg, [5]Neurology, CH de Metz, Metz, [6]Neurology, CHU de Dijon, Dijon, France

Objectives: This study describes efficacy and safety of Fingolimod in patients treated for at least 6 months in the east of France from January 2011 to December 2014.
Background: The Grand-Est is a geographical region in France with a high prevalence of multiple sclerosis (more than 10000 patients registered in the European Database for Multiple Sclerosis EDMUS database). In this region and since January 2011, more than 1014 patients have been treated for at least 6 months with Fingolimod, the first oral therapy for patient with very active relapsing-remitting MS.
Methods: Features of patients followed up in the Grand-Est region and treated with fingolimod in the 6 university hospitals, general hospitals and private neurologists were reviewed in a retrospective study after identification of the clinical files reported in the EDMUS database.
Results: At inclusion: mean age of 29.7±9.4 years; sex ratio F/M 2.59; duration of MS: 10.8 ± 7.45 years; mean EDSS: 3.2±1.7; ARR: 0.8±0.9. Fingolimod was prescribed as a first line treatment in 20.12%, following immunomodulatory treatment in 49.3%, natalizumab in 31.16, and other treatment in 14.16%. Patients were treated for more than 2 years in 92%. Relapses were encountered in 20.8%. Mean time to the first relapse: (8.25 ±7.8 months). Annualized relapse rate was decreased by 83.75% after 1 year of treatment, and mean EDSS was stable after 1 year of treatment and increased by 0.1 after 2 and 3 years. EDSS increased more in patients experiencing relapses. Fingolimod was stopped in 17.42% of patients mainly because of adverse events (9.28%). Results were comparable among centers. Patients treated after 2013 were younger and exhibited lower levels of disability.
Conclusions: This is one of the largest real life series of patients treated with fingolimod in the east of France. The treatment seems well-tolerated and showed high efficacy on clinical activity after one year.

Disclosure

Ayman Tourbah has received consulting and lecturing fees, travel grants and research support from Medday, Biogen Idec, Sanofi-Genzyme, Novartis, Merck Serono, Teva Pharma, and Roche
Eric Berger, Marc Debouverie, Jérôme De Sèze, served as consultant, board and therapeutical trials for Novartis
Thibault Moreau reports receiving consulting fees and speaking fees from Biogen Idec, Sanofi Aventis, Genzyme, Teva Pharma, Bayer Schering, Merck Serono, Roche, Almirall and Novartis, Roche.
Ludivine Chamard and Etienne Godet have nothing to disclose
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P1159

Dimethyl fumarate therapy is associated with increased IL10+ B regulatory cell subsets in patients with multiple sclerosis

E. Staun-Ram[1], E. Najjar[1], A. Miller[1,2]

[1]Neuroimmunology, Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, [2]Neuroimmunology Unit & Multiple Sclerosis Center, Carmel Medical Center, Haifa, Israel

Background: Dimethyl Fumarate (DMF) is a novel oral therapy for patients with relapsing-remitting Multiple Sclerosis (RRMS), with mode of action mainly attributed to anti-oxidative and anti-inflammatory effects. Presented is the interim analysis of our ongoing study aimed to assess the immunological impact of 3 months (m) DMF therapy on immune cells in general and B cell subsets specifically.
Methods: 15 RRMS patients at least 1m free of relapse and steroid treatment were recruited, out of which 6 were offered DMF as 1st line patients and 9 as 2nd line patients, the latter without any prior disease modifying therapy (interferon β, fingolimod or glatiramer acetate) for a minimum of 1m. Blood samples were collected at 0 and 3m after DMF initiation, peripheral blood mononuclear cells (PBMCs) obtained and B cells isolated by negative selection. The levels of $CD4^+$ and $CD8^+$ T cells, $CD14^+$ monocytes and $CD19^+$ B cells, as well as 17 known B cell subsets and functional markers were assessed immediately by flow cytometry.
Results: 3m DMF therapy did not significantly change the absolute cell number of lymphocytes, nor the composition of PBMCs ($CD4^+$, $CD8^+$ T cells, $CD14^+$ monocytes or $CD19^+$ B cells) relative to baseline. While the percentages of $CD27^-IgD^+$ naïve, $CD27^-CD24^{hi}CD38^{hi}$ transitional, $CD27^+IgD^-$ memory, $CD27^+CD38^+$ plasmablast and $CD27^+CD38^+CD138^+$ plasma B cells were unaffected, the percentages of $CD24^+$ and IgD^+ B cells were increased after 3m of DMF therapy. Furthermore, DMF therapy strongly increased the percentage of $IL10^+$ B regulatory cells and the expression level of IL10 per cell. A similar increase was seen in the percentage of other B cell subsets associated with regulatory capacities, including $CD80^+IL10^+$, $CD86^+IL10^+$, $CD1D^+IL10^+$ and $CD5^+IL10^+$ B cells, and the expression level of IL10 was elevated in all these subsets. Finally, while no difference was found in $HLA\text{-}DR^+$, $CD40^+$ and $ICAM^+$ B cells, the expression levels of BAFF-Receptor and activation marker CD69 in B cells were elevated.
Conclusions: DMF therapy modulates B cell markers and increases IL10-producing B regulatory cell subsets, which may explain part of the beneficial effects of the drug in patients with RRMS.

Disclosure

This study was supported by an investigator initiated trial grant from Biogen, Inc.
The authors have nothing to disclose.

P1160

The effect of the short chain fatty acid propionate on immune regulation in MS: a proof-of-concept study

A. Duscha[1], S. Jörg[2], J. Berg[1], R.A. Linker[2], R. Gold[1], A. Haghikia[1]
[1]Department of Neurology, Ruhr University Bochum, Bochum, [2]Department of Neurology, Friedrich-Alexander-University, Erlangen-Nuremberg, Germany

Background: Dietary factors and the gut bacteria are increasingly being suspected to be critically involved in the etiology of autoimmune disorders such as MS. We have recently shown that, in a disease model of MS short chain fatty acids (SCFA) such as propionate (PA) promote regulatory T cell (Treg) differentiation, while long chain fatty acids (LCFA) increase Th17 differentiation in the small intestine. In vivo, PA treatment ameliorated the course of a MOG-induced experimental autoimmune encephalomyelitis (EAE). Conversely, treatment with LCFA worsened disease course by increasing Th17 differentiation.
Objective: Our study investigates the effect of orally-administered PA on Treg levels and function in healthy individuals and MS patients.
Design and methods: In a translational proof-of-concept study to validate our findings in the animal model, and after approval by the ethics committee of the Ruhr-University Bochum either healthy controls (n=30) or MS (n=60; under various DMTs) participants were administered 2x500 mg PA capsules daily for 14-90 days. Sodium-propionate (PA) is approved as a food additive with no safety concerns by European (EFSA) and the American Food Safety Agencies (FDA). We performed both deep immunophenotyping of T cell subsets before and at various time points after PA intake as well as additional functional *ex vivo* analyses.
Results: The PA was well tolerated, with all volunteers reporting no noticeable side effects. We observed a significant increase of Treg of about 30% in MS patients and healthy controls, and a concurrent significant decrease in Th17 (and Th1) levels already after 14d of PA as compared to pre-supplementation, which was more apparent in MS patients. Moreover, our *ex vivo* data show a significant increase in the suppressive capability of the Treg under PA in both groups, suggesting that not only Treg differentiation is increased but also their immune modulatory activity.
Conclusions: These initial results not only translate our previous observation from an animal model to human MS, but more importantly they confirm the impact of dietary fatty acids on human systemic immune response. Thus, our study suggests that PA may serve as a possible immune-supplementary agent to be administered as add-on to current first-line MS drugs.

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P1161

Treating multiple sclerosis with generic cladribine

C. Alvarez-Gonzalez[1,2], K. Allen-Philbey[2], J. Mathews[3], M. Espasandin[2], B.P. Turner[1,2], S. Gnanapavan[1,2], M. Marta[1,2], G. Giovannoni[1,2], D. Baker[1], K. Schmierer[1,2]
[1]Blizard Institute (Neuroscience), Queen Mary University London, Barts and the London School of Medicine and Dentistry, [2]Emergency Care & Acute Medicine Neuroscience Clinical Academic Group, [3]Neurology and Medicines Safety, Barts Health NHS Trust, London, United Kingdom

Background: Trial evidence suggests Cladribine, a purine analogue licensed for treatment of people with hairy cell leukaemia, is also an effective, safe and convenient disease modifying therapy (DMT) for people with multiple sclerosis (pwMS)[1-4]. Cladribine appears to exert its effect through selective long-term suppression of lymphocytes and reduction of pro-inflammatory cytokines and chemokines whilst leaving other cell types relatively unaffected.
Objective: To report our clinical experience with Cladribine in pwMS using a dosing scheme that adapts to individual lymphocyte level.
Methods: Cladribine was offered to pwMS with clinical and/or MRI disease activity, but restricted choice of DMT. Treatment consisted of 1-2 annual cycles of subcutaneous Cladribine (Litak). During each cycle 10mg Cladribine was given for up to 7 days in 5 weeks. The number of injections was adjusted to individual lymphocyte count to avoid levels below 0.5x10*9/L. One way ANOVA was used to analyse differences in white cell counts. We report results after a mean follow-up of 4 months.
Results: Eighteen pwMS (10 women and 8 men) had a first treatment cycle of Cladribine. Mean age was 44 (34-60) years, median EDSS was 5 (2-8). No acute side effects or serious treatment-related adverse event were observed, and neither any clinical disease activity within the follow-up period. Lymphocyte counts dropped from a mean of 1.81 (range: 0.9-3.4 x10*9) at baseline to 1.41 (0.7-3) at 4 weeks, and to 1.02 (0.6-1.6) at 8 weeks, p=0.02. Other white cells remained within normal range.
Conclusion: Cladribine was well tolerated and led to a controlled decrease in lymphocyte counts leaving other cell lines largely unaffected. So far no new disease activity has been detected. Follow-up continues.

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P1162

Effect of natalizumab on global and regional cortical thickness in RRMS. A four year longitudinal study highlights efficacy and stresses the importance of a well-timed intervention

D. Seppi[1], D. Polo[1], F. Rinaldi[1], D. Poggiali[1], A. Favaretto[1], P. Perini[1], M. Ermani[2], P. Gallo[1]

[1]Multiple Sclerosis Centre, Department of Neuroscience, Univerisity of Padova, [2]Section of Biostatistics, Department of Neuroscience, Univerisity of Padova, Padova, Italy

Background: Cortical atrophy has been associated with physical and cognitive disability in Multiple Sclerosis (MS) and can be observed since the early disease stages. Dedicated software applied to MRI allow the evaluation of cortical grey matter loss in terms of cortical thickness (CTh) reduction, and the analysis of the effect of therapies in delaying its progression.
Objectives: To assess the efficacy of Natalizumab (NTZ) versus IFNβ and Glatiramer Acetate (IFNβ/GA) in slowing down cortical thinning in Relapsing Remitting MS (RRMS) over a four-year period.
Methods: 30 NTZ-treated RRMS and 30 IFNβ/GA-treated RRMS were enrolled in a retro-prospective study. NTZ-treated RRMS were characterized by an aggressive disease course not responsive to first-line therapies. IFNβ/GA group, in contrast, had a stable disease and a significantly lower EDSS score compared to the NTZ-treated patients (1.5 vs 2.9, $p< 0.01$). Clinical and MRI evaluations were performed at baseline and then yearly for four years. Global and regional CTh were measured at baseline and after four years by means of FreeSurfer.
Results: In the four-year therapy period, a global reduction in CTh was observed in both NTZ (2.33%) and IFNβ/GA (1.06%) treated RRMS. Despite the better trend observed in the IFNβ/GA group, the difference was not significant. The regional CTh analysis disclosed a significantly higher CTh reduction of the precentral, postcentral, superior parietal, supramarginal and trasversetemporal regions in NTZ-treated compared to IFNβ/GA -treated patients ($p< 0.05$ for all regions). A cluster analysis divided the NTZ-treated patients in two subgroups according to the extent of cortical thinning, but no correlation was found between cortical thinning and any clinical parameter. EDSS remained almost stable in the two groups during the period, while a higher decrease in the clinical relapse rate was scored in the NTZ group.
Conclusions: Our study shows that NTZ is capable to slow down the progression of cortical atrophy associated to inflammation in aggressive RRMS. The better trend observed in IFNβ/GA can be explained with the less aggressive disease course in these patients. Our data further indicate that patients close to EDSS=3.0 (as those treated with NTZ) are getting closer to the progressive phase of the disease in which grey matter loss may be partly independent from inflammation. These findings further support the importance of treating MS patients since the very early disease phases.

Disclosure

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Diana Polo reports no disclosures

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Mario Ermani reports no disclosures

Paolo Gallo 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; has received research support from Bayer, Biogen Idec/Elan, Merk Serono, 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.

P1163

Reduced adhesion to human endothelium as one mechanism of action of dimethyl fumarate in Multiple Sclerosis through down-regulation of VCAM-1 via HCA_2-mediated upregulation of Nrf2

J. Breuer[1], S. Herich[1], T. Schneider-Hohendorf[1], N. Wettschureck[2], L. Klotz[1], H. Wiendl[1], N. Schwab[1]
[1]Department of Neurology, University of Münster, Münster, [2]Centre for Molecular Medicine, University of Frankfurt, Frankfurt, Germany

Dimethyl fumarate (DMF) (BG-12, Tecfidera) is a fumaric acid ester that has been proven to be effective in the oral treatment of multiple sclerosis (MS). However the mechanism of action has not been fully elucidated yet. Here, we investigated the effects of monomethyl fumarate (MMF), the biologically active metabolite of DMF, at the (inflamed) blood-brain barrier (BBB) by utilizing primary human brain-derived microvascular endothelial cells (HBMEC). Physiological shear-flow assays revealed a significantly reduced adhesion of primary human CD4+ T cells to tumor necrosis factor (TNF)a-inflamed HBMEC upon MMF treatment as compared to vehicle control. The MMF-mediated decrease in adhesion was directly correlated to a lower endothelial expression of vascular cell adhesion molecule (VCAM)-1 as quantified by histological as well as by flow cytometry analysis. Moreover, a down-regulation of VCAM-1 on TNFa-inflamed HBMEC could also be observed upon a therapeutic treatment, when MMF was applied after the inflammation of the endothelial cells.
Western Blot analysis revealed that nuclear Factor (erythroid-derived 2)-related factor 2 (Nrf2), a known inhibitor of VCAM-1 expression, translocated to the nucleus upon MMF treatment, suggesting that MMF down regulates VCAM-1 expression via the activation of Nrf2. Expression of the G protein-coupled membrane receptor hydroxycarboxylic acid receptor 2 (HCA_2), a known molecular target of MMF, could further be demonstrated on HBMEC by qPCR, suggesting that the activation of Nrf2 by MMF might be either mediated via HCA_2 or directly in an HCA_2-independent pathway. Corresponding to the reduced VCAM-1 expression on endothelial cells, DMF treatment *in vivo* lead to a strongly reduced expression of very late antigen (VLA)-4 on CD4+ T cells in MS patients responding to therapy.
Taken together, our results demonstrate that DMF exerts its beneficial therapeutic effects on the inflamed BBB by down-regulation of endothelial VCAM-1 expression. The reduction of VLA-4 *in vivo* might be useful to monitor response to treatment.

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Heinz Wiendl: serves on the scientific advisory board for Bayer, Biogen, Sanofi-Genzyme, Merck Serono, Novartis, Roche, and Teva; is on the editorial board for *Journal of Clinical Practice*, *Journal of Neuroinflammation*, and *PLOS ONE*; has consulted for Biogen, Merck Serono, Novartis, Omnamed, Roche, Sanofi-Genzyme; and received research support from Bayer Healthcare, Bayer Vital, Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Sanofi US, Teva, German Ministry for Education and Research, Deutsche Forschungsgesellschaft, European Union, Else Kroner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies Muenster, RE Children´s Foundation, Sanofi Aventis, and NovoNordisk
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P1164

Real-life safety, tolerability and efficacy of Dimethyl fumarate: a multicentre study

G. Mallucci[1], P. Annovazzi[2], M. Matta[3], V. D'Ambrosio[1], M. Zaffaroni[2], A. Ghezzi[2], A. Bertolotto[3], C. Montomoli[4], R. Bergamaschi[1]
[1]Inter-Department Multiple Sclerosis Research Centre, Neurological Institute IRCCS Mondino, Pavia, [2]Multiple Sclerosis Study Centre, ASST Valle Olona, Gallarate (VA), [3]Regional Multiple Sclerosis Centre, San Luigi Gonzaga Hospital, Orbassano (TO), [4]Unit of Biostatistics and Clinical Epidemiology, Department of Public Health, University of Pavia, Pavia, Italy

Objectives: Aim of this study is to evaluate post-marketing Dimethyl fumarate (DMF) safety, tolerability and efficacy profile in a real world setting.
Materials and methods: We enrolled all patients receiving DMF in three northern Italy MS centres. Patients were prospectively followed, collecting demographic and clinical data as well as laboratory assessment.
Results: We included 240 patients (70.8% F; mean age: 38.6±10.5 years; mean disease duration: 10.5±0.7 years). Mean annual relapse rate (ARR) in the two years before DMF was 0.56±0.6, median baseline EDSS was 2 (range 0-6.5).

Seventy-two patients (30%) were treatment naïve or quitted disease modifying drugs (DMDs) more than 12 months before DMF

start. One hundred and thirty-three patients (55%) switched to DMF from first line DMDs (84% of whom from injectables and 16% from orals) due to loss of tolerability (74%) or inefficacy (26%). Thirty-five patients (15%) switched to DMF from second line DMDs due to loss of tolerability (83%) or safety reasons (17%).

The overall mean DMF treatment follow-up was 11±5 months, 102 patients (42%) had at least 12 months of follow-up. Most frequent adverse events (AEs) were flushing/pruritus (37.1%), gastrointestinal side effects (20.8%), rush (2.9%) and fatigue (2%). Only one severe AE was reported (breast cancer). Most frequent laboratory testing abnormality was lymphopenia (6.3%, none severe).

Forty-eight patients (20%) stopped DMF after a mean of 4.1±3 months; causes of stop were AEs (70.8%), disease activity (25%) and pregnancy planning (4.2%). AEs were more frequent in patients that stopped DMF treatment compared to those patients that continue DMF treatment (p=0.045).

Among patients completing one year of follow-up, 70.6% were relapse free. Median interval between DMF start and first relapse was 109 days (range 11-623). The overall mean ARR during treatment was reduced compared to baseline (0.59±0.6 *vs* 0.30±0.5, p=0.0004). But, mean ARR of patients switching to DMF from a second line therapy remained stable.

Discussion and conclusion: Despite the incidence of some AEs (such as flushing and gastrointestinal side effects) and the frequency of treatment discontinuation were mildly increased than that reported in previous studies, our observational data confirm the good tolerability and safety of DMF. Moreover, a positive clinical effect (ARR decrease) was achieved, although in a short treatment period.

Disclosure

- G. Mallucci received support to travel to scientific meetings from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis, Teva.
- P. Annovazzi served on the scientific advisory board for Merck Serono, Novartis, Biogen, and Genzyme, and received speaker honoraria from Biogen, Genzyme, Novartis, and Teva.
- M. Matta has nothing to disclose.
- V. D'Ambrosio has nothing to disclose.
- M. Zaffaroni received honoraria for consultancy, participation in advisory boards or travel grants from Genzyme, Biogen Idec, Merck Serono, Sanofi Aventis, Teva, Novartis.
- A. Ghezzi has served on scientific advisory boards for Merck Serono, Biogen Idec Teva Pharmaceutical Industries Ltd, has received speaker honoraria from Merck Serono, Biogen Idec, Bayer Schering Pharma and Novartis, Serono Symposia International, served as a consultant for Novartis, and receives research support from Sanofi-Aventis, Biogen Idec and Merck Serono.
- A. Bertolotto served on the scientific advisory boards of Almirall, Bayer, BiogenIdec, and Genzyme; received speaker honoraria from BiogenIdec, Genzyme, Novartis, and Teva; his institution has received grant support from Bayer, BiogenIdec, Merck, Novartis, Teva, the Italian Multiple Sclerosis Society, Fondazione Ricerca Biomedica ONLUS, and San Luigi ONLUS; received speaker honoraria from BiogenIdec, Genzyme, Novartis, Sanofi-Aventis, and Teva; is on the editorial board of *Multiple Sclerosis International*, *Progress in Neuroscience*, *Dataset Papers in Neuroscience*, *Journal of Multiple Sclerosis*, *Neurology and Therapy*, and *Multiple Sclerosis and Demyelinating Disorders*; and received research support from Regione Piemonte, Italian Multiple Sclerosis Society, Associazione Ricerca Biomedica ONLUS, and San Luigi ONLUS.
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P1165
Natalizumab treatment modifies peripheral cytokine profile in multiple sclerosis patients

R. Balasa, Z. Bajko, A. Hutanu, S. Voidazan, S.M. Maier
University of Medicine and Pharmacy Targu Mures, Targu Mures, Romania

Natalizumab (NAT) is a very powerful monoclonal antibody used for the treatment of relapsing-remitting subtype of MS (RRMS). Initially was thought that NAT have a clear mechanism of action: blocks the VLA-4 and prevents the leukocyte migration into the brain. Our study attempted to reveal new peripheral immunological effects of NAT with a focus on a T helper (Th) 17 panel of cytokines.

Material and Methods: We performed an observational study in which 19 RRMS patients treated with NAT and 20 healthy subjects were tested, using a Multiplex method, for serum levels of 15 individual pro-inflammatory and anti-inflammatory cytokines representing Th17 cytokine panel (interleukin[IL]-1β, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, interferon [IFN]-γ, sCD40L, tumor-necrosis factor [TNF]-α). This prospective study explored the serum changes of the cytokines by testing initially and after a mean period of 8.2 months (at least 7 months) of NAT treatment. In the study were included NAT-naïve patients and patients who were on NAT treatment for 1, 2, 3 or more than 4 years.

Results: The highest serum levels of pro-inflammatory cytokines have been found in NAT-naïve patients and we observed a decrease in serum titer with increasing duration of treatment. The lowest serum titers were obtained 2 years after initiation of treatment with NAT. Healthy subjects had lower serum levels of IL-1β, IL-10, IL-17F, IL-21, IL-23, IL-31, IL-33, sCD40L, TNF-α compared to RRMS patients**.** There was a marked decline in the serum levels of sCD40L, IL-23, IL-17F, TNF-α and IL-31 after a period of 8 month of NAT treatment.

In conclusion, NAT, a VLA-4 blocker has other independent immunological effects like decreasing the serum levels of some pro-inflammatory cytokines.

Disclosure

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P1166

PREFER*MS* study: *post hoc* analyses of patient retention, key clinical outcomes and patient satisfaction in an African-American patient subgroup

M. Cascione[1], J. Wendt[2], B.A.C. Cree[3], X. Meng[4], L. Schofield[4], N. Tenenbaum[4], on behalf of the PREFERMS investigators
[1]Tampa Neurology Associates, Tampa, FL, [2]Territory Neurology and Research Institute, Tucson, AZ, [3]University of California San Francisco, San Francisco, CA, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Background: Rates of multiple sclerosis (MS) are generally low among African Americans, but the disease course can be aggressive in these patients. PREFER*MS* was the first large, randomized, prospective study of treatment retention comparing fingolimod 0.5 mg with injectable disease-modifying therapies (iDMTs) in patients with relapsing-remitting MS, and included 136 African-American patients.
Objective: To report treatment retention, key clinical, magnetic resonance imaging and patient satisfaction outcomes in the PREFER*MS* African-American patient subgroup.
Methods: PREFER*MS* was a 12-month, phase 4 open-label, active-controlled, randomized, multicentre study. At enrolment, patients were either treatment-naïve or treated with one class of iDMT (interferon or glatiramer acetate). Patients were randomized (1:1) to fingolimod 0.5 mg or to a pre-selected iDMT. One on-study treatment switch was allowed after ⩾3 months of treatment, or before if related to efficacy or safety. At the end of randomized treatment (EoRT), treatment retention, annualized relapse rate (ARR), new gadolinium-enhancing (Gd+) lesion counts, new/enlarging T2 lesion counts, and treatment satisfaction (Medication Satisfaction Questionnaire data, pooled to include somewhat, very and extremely satisfied) were evaluated *post hoc* in the African-American subgroup.
Results: In total, 875 patients were randomized (fingolimod, n=436; iDMT, n=439). In the African-American subgroup (fingolimod, n=67; iDMT, n=69), patient retention was 80.6% on fingolimod and 30.4% on iDMTs (difference: 50.2%, 95% confidence interval [CI]: 35.8-64.6%). Respectively, in the fingolimod and iDMT groups at EoRT: ARRs were 0.13 and 0.23 (ratio, 0.57; 95% CI: 0.21-1.53); median new Gd+ lesion counts were 0 and 0; and median new/enlarging T2 lesion counts were 0 and 0. Proportionally more patients were satisfied with fingolimod (80.6%) than with iDMT (49.3%) at EoRT (difference: 31.3%, 95% CI: 16.2-46.5%).
Conclusions: African-American patients randomized to fingolimod in PREFER*MS* had greater treatment retention and satisfaction, and lower relapse rates at EoRT, than those randomized to iDMTs; new Gd+ and new/enlarging T2 lesion counts were similar in the two treatment groups.

Disclosure

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Bruce A C Cree has received personal compensation for consulting from Abbvie, Biogen, EMD Serono, Sanofi Genzyme, MedImmune, Novartis, Shire and Teva.
Xiangyi Meng, **Lesley Schofield** and **Nadia Tenenbaum** are employees of Novartis Pharmaceuticals Corporation.

P1167

Involvement of HCAR2-triggered pathways in dimethyl fumarate effect on immune and other cells

A. Uccelli[1,2], B. Parodi[1], N. Kerlero de Rosbo[1]
[1]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, Univesity of Genoa, [2]Centre of Excellence for Biomedical Research (CEBR), University of Genoa, Genoa, Italy

Dimethyl fumarate (DMF), a fumaric acid ester with immunomodulatory properties, was recently approved as treatment for relapsing-remitting multiple sclerosis (MS). DMF ameliorates the clinical course of experimental autoimmune encephalomyelitis (EAE), the murine model of MS, where it exerts a neuroprotective action. Recently, we demonstrated that monomethyl fumarate (MMF), the bioactive metabolite of DMF, modulates the activation of microglia towards an alternatively activated phenotype, thereby favoring neuroprotection, through the activation of the hydroxycarboxylic acid receptor 2 (HCAR2). In particular, we observed that such modulation occurs mainly through a novel signaling pathway triggered by MMF binding to HCAR2, which leads to an increase in intracellular Ca^{2+} concentration, with downstream signaling via the AMPK/Sirt1 axis, to inhibit the NF-kB pathway and the consequent expression of inflammatory cytokines.

Since increasing evidence associates signaling through HCAR2 in macrophages and dendritic cells with an anti-inflammatory phenotype, we hypothesized that DMF can exert its effect also in these cells through the activation of the AMPK/Sirt1 axis.

Our preliminary data demonstrate that MMF inhibits lipopolysaccharide-induced macrophage activation by significantly reducing the expression of Tnf, Nos2 and Il1b, typical markers of M1 phenotype. Our ongoing Western blot experiments focus on understanding if MMF signals through this novel HCAR2-mediated pathway in these cells, or through the inhibition of the other HCAR2-dependent pathway where the activation of ERK1/2 MAP kinase is associated with the prostaglandin D2/flushing pathway.

Since HCAR2 is also the receptor for butyrate, a short-chain fatty acid produced by the gut flora that possesses anti-inflammatory properties, we speculate that the intestinal side effects associated with DMF treatment might be associated with competition of MMF with butyrate for HCAR2 signaling. Accordingly, as HCAR2 signaling is tissue-dependent and ligand-biased, we seek to demonstrate that MMF would signal in these cells through the prostaglandin D2/flushing pathway leading to inflammation, whereas butyrate, which blocks LPS-induced NF-kB activation in colonic cells, would signal through the novel signalling pathway via the AMPK/Sirt1 axis. Experiments are ongoing to investigate this possibility.

Disclosure

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P1169

The effects of natalizumab and fingolimod on clinical and MRI measures in relapsing remitting multiple sclerosis: a two-year comparative study

P. Preziosa[1], M.A. Rocca[2], G.C. Riccitelli[2], M. Rodegher[3], L. Moiola[3], A. Falini[4], G. Comi[3], M. Filippi[2]
[1]Ospedale San Raffaele - Vita-Salute San Raffaele University, [2]Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience,, [3]Department of Neurology, [4]Department of Neuroradiology, S. Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Objectives: To compare the effects of natalizumab (NAT) and fingolimod (FTY) on clinical and MRI measures in relapsing-remitting (RR) MS after two years of treatment.
Background: NAT and FTY reduce clinical and MRI disease activity in RRMS, but comparative studies are limited.
Methods: Fifty-four RRMS patients starting natalizumab (NAT) (n=28) or fingolimod (FTY) (n=26) underwent 3T brain scans, and clinical evaluation (including EDSS and evaluation of clinical relapses) at baseline (T0), year 1 (Y1) and year 2 (Y2). T2, T1 and cortical lesion volumes (LV), brain, white matter (WM), gray matter (GM) and deep GM volumes were measured. Between- and within-group analyses were performed using two- and paired-sample t-tests.
Results: At T0, the two groups were matched for demographic, clinical and MRI variables. Both drugs significantly reduced clinical relapses at Y1 and Y2, with a greater reduction at Y1 in NAT *vs* FTY patients (0.23 *vs* 0.04, p=0.04). NAT *vs* FTY patients formed also a lower number of new T2 lesions at Y1 (1.81 *vs* 0.79, p=0.04). In NAT patients, EDSS, T2 and cortical LV remained stable at Y1 and Y2, T1 LV decreased at Y1 (p=0.03) and remained stable at Y2. In FTY patients, EDSS and cortical LV decreased significantly at Y1 (p=0.008 and p=0.0001, respectively), while T2 and T1 LV significantly increased at Y1 (p< 0.0001 and p=0.0001, respectively), and remained stable at Y2. At Y1, thalamic atrophy significantly occurred in both groups (p=0.03 for NAT patients and p=0.002 for FTY patients, respectively); NAT patients had also volume loss of the pallidus (p=0.02), while FTY patients showed significant atrophy of caudate nuclei (p=0.03). At Y2 *vs* Y1, a significant brain atrophy occurred in both groups (p=0.03 for NAT group and p=0.02 for FTY group). NAT patients also had significant GM atrophy (p=0.01). In the direct comparisons of longitudinal differences between patients' subgroups, a significant increased T2 and T1 LV (p< 0.0001 for both comparisons) and a decreased cortical LV (p=0.01) was found in FTY *vs* NAT patients.
Conclusions: NAT and FTY reduce disease activity in RRMS. NAT could have a more significant effect on WM inflammatory lesion accumulation, while both drugs seems to prevent significant regional atrophy.

Disclosure

Drs Preziosa, Riccitelli, Rodegher, Moiola, and Falini have nothing to disclose.
Dr Rocca received speakers honoraria from Biogen Idec, Novartis and ExceMed and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla.
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Prof. Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory boards for Teva Pharmaceutical Industries; has received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer´s Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

P1170

Spanish registry of patients with multiple sclerosis treated with fingolimod (GILENYA registry): safety and effectiveness after four years of registry

J. Meca-Lallana[1], C. Oreja-Guevara[2], D. Muñoz[3], J. Olascoaga[4], A. Pato[5], L. Ramió[6], V. Meca-Lallana[7], M.A. Hernández[8], M.E. Marzo[9], J.C. Álvarez- Cermeño[10], A. Rodríguez-Antigüedad[11], X. Montalbán[12], Ó. Fernández[13], Academia Española de Esclerosis Múltiple y Otras Enfermedades Autoinmunes (ACADEM)
[1]Unidad de Esclerosis Múltiple. Servicio de Neurología, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, [2]Neurology Department, Hospital Clinico San Carlos, Madrid, [3]Neurology Department, Hospital Xeral de Vigo, Vigo, [4]Neurology Department, Hospital Universitario Donostia, San Sebastián, [5]Neurology Department, Hospital Povisa, Vigo, [6]Neurology Department, Hospital Universitari de Girona Dr. Josep Trueta, Girona, [7]Neurology Department, Hospital Universitario de La Princesa, Madrid, [8]Neurology Department, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, [9]Hospital San Pedro, Logroño, [10]Neurology Department, Hospital Universitario Ramón y Cajal, Madrid, [11]Neurology Department, Hospital de Basurto, Bilbao, [12]Neurology Department, Hospital Universitari Vall d'Hebron, Barcelona, [13]Neurology Department, Hospital Regional Universitario de Málaga, Málaga, Spain

Background: The aim of the Spanish Gilenya Registry is to study the evolution of patients being treated with fingolimod in Spain.
Objectives: The aim of this preliminary analysis is to assess the safety and effectiveness of fingolimod after 4 years of registry.
Methods: Observational, retrospective/prospective and multicenter registry of cases, including all patients with relapsing remitting MS starting treatment with fingolimod in Spain.
Results: Data of 613 evaluable patients included in the registry until February 2016 was analyzed out of the 654 patients included on the registry, data were available for 428 patients after 1 year of treatment, 206 after 2 years and 65 after 3 years. Mean age at baseline was 39.0 years (± 8.7), 70.5% women. Mean time since onset of symptoms of MS was 11.0 years (± 6.8) and mean time since diagnosis of MS was 8.9 years (± 6.1). The test for JC virus antibodies was performed in 400 patients (65.6%), being 339

seropositive (84.8%). Patients switched from natalizumab (28.7%), glatiramer acetate (22.8%), interferon beta-1a (Rebif®) (16.3%), interferon beta-1b (10.0%), interferon beta-1a (Avonex®) (10.0%), mitoxantrone (0.5%), and other (2.4%), respectively, to fingolimod. Main reason for switching to fingolimod was efficacy (57.0%), followed by safety (35.1%) and other (15.3%). Mean time under treatment with fingolimod was 26.1 months (± 12.6). 9.8% of patients were monitored more than 6 hours after the first dose of fingolimod and mean monitoring time was 7.2 hours (± 6.7). 36 patients (5.9%) withdraw from the study. 13.5% of patients had adverse reactions, a total of 102 events were observed, being 7 of them serious. After 3 years in treatment with fingolimod and compared to the previous year, 88.3% of patients reported no relapses, 75.0% was free of disability progression [improvement or non-change of Expanded Disability Status Scale (EDSS) scores] and 66.7% was free of clinical activity (no relapses and free of disability progression).

Conclusions: The results obtained in this preliminary analysis support the safety and effectiveness of fingolimod after 4 years of registry.

Disclosure

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C. Oreja-Guevara has received honoraria as moderator and speaker at meetings and participated in clinical trials sponsored by Biogen-Idec, Novartis, Merck-Serono, Almirall, Teva and Genzyme.
D. Muñoz has worked in consulting work, clinical trials and speaker at congresses held by Merck, Biogen, Teva, Novartis and Genzyme.
Javier Olascoaga serves on scientific advisory boards for Biogen Idec, Genzyme and Novartis; has received speaker honoraria from Biogen Idec, Bayer-Schering, Genzyme, Merck-Serono, Novartis and Teva and receives research grants from Biogen Idec, Merck Serono, Novartis and Teva
A. Pato has participated as a speaker and consultant for Novartis , Biogen and Genzyme Almirall .
Ll. Ramió serves on scientific advisory boards for Biogen Idec and Merck-Serono and has received speaker honoraria from Biogen Idec, Novartis, Bayer, Merck-Serono, Genzyme, Teva Pharmaceutical Industries Ltd.
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P1171

Peginterferon beta-1a every 2 weeks increased achievement of NEDA over 4 years in the ADVANCE and ATTAIN studies in patients with RRMS

D. Arnold[1,2], S. Shang[3], C. Castrillo-Viguera[3], D. Fiore[3]
[1]Montreal Neurological Institute, McGill University, [2]NeuroRx Research, Montreal, QC, Canada, [3]Biogen, Cambridge, MA, United States

Background: No Evidence of Disease Activity (NEDA) is an evolving concept that was first proposed as a composite measure of whether patients with relapsing-remitting multiple sclerosis (RRMS) were meeting goals of treatment in the clinical trial setting. In the first year of the Phase 3 ADVANCE study, significantly more patients dosed with subcutaneous peginterferon beta-1a 125 mcg every 2 weeks achieved NEDA versus placebo and every-4-weeks dosing. Similar results were found for the second year of ADVANCE (after placebo-treated patients were re-randomized to peginterferon beta-1a every 2 or 4 weeks) and the first year of the ATTAIN extension study for clinical-, MRI- and overall NEDA.

Objectives: To assess NEDA status during both ADVANCE and ATTAIN by year and explore clinical outcomes in ATTAIN in patients stratified by their overall NEDA (clinical and MRI) status at the end of ADVANCE.

Methods: The proportion of patients in the ATTAIN intent-to-treat (ITT) population experiencing overall (clinical and MRI) NEDA was evaluated for patients treated with peginterferon beta-1a every 2 weeks or every 4 weeks over 4 years. Patients in all dosing groups combined were then stratified based on achievement of overall NEDA during ADVANCE (NEDA+/NEDA-). Annualised relapse rate (ARR) during ATTAIN (Years 3 and 4 since ADVANCE baseline) was analysed based on NEDA status during ADVANCE.

Results: Both peginterferon beta-1a every 2 weeks (n=376) and every 4 weeks (n=354) maintained efficacy on NEDA outcomes over 4 years of treatment, and more patients treated with peginterferon beta-1a every 2 weeks achieved overall NEDA in Years 1-4 (35-54% vs 22-35%, all $p < 0.0001$). Similar results were found for clinical (significantly higher % in Years 2, 3) and MRI (significantly higher % in all years) NEDA. Overall NEDA status in ADVANCE was predictive of positive clinical outcomes in ATTAIN: patients in the NEDA+ group (n=196), compared with those in the NEDA- group (n=877) had lower ARR (0.066 vs. 0.227, $p < 0.0001$) during ATTAIN.

Conclusions: Patients with RRMS administered peginterferon beta-1a every 2 weeks displayed maintained efficacy and increased NEDA over 4 years compared with treatment every 4 weeks. Patients who were free from disease activity at the end of ADVANCE had significantly reduced ARR during ATTAIN than patients who were

not, suggesting that overall NEDA within the first 2 years of treatment is prognostic of long-term clinical outcomes.

Disclosure

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Author disclosures

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P1172

Minocycline reduces immune cell infiltration, but not preclinical microglial activation, during autoimmune optic neuritis

R. Fairless, S.K. Williams, C. Mayer, R. Diem
Neurology, University Clinic Heidelberg, Heidelberg, Germany

Early activation of microglia is a common event during neuroinflammatory diseases, for example it is seen in both preactive multiple sclerosis (MS) lesions, and also during the onset of its animal model, experimental autoimmune encephalomyelitis (EAE). We have previously shown that during the pre-clinical phase of autoimmune optic neuritis, one of the symptoms of myelin oligodendrocyte glycoprotein (MOG)-induced EAE in Brown Norway rats, retinal ganglion cell (RGC) degeneration already begins concomitantly with activation of resident microglia of both the retina and optic nerves. However, the relationship between these events is at present unclear.

Since minocycline, an antibiotic with multiple anti-inflammatory effects, has been reported to reduce activation of microglia, we have treated rats from the time of disease induction to determine its effect on microglial activation and neurodegeneration. Rats were treated either with saline placebo or with 50 mg/kg minocycline daily, and spinal cord, optic nerve and retina were assessed histopathologically at different time intervals following immunisation, with particular focus on the preclinical disease stage.

Minocycline delayed the onset of EAE and reduced immune cell infiltration into the spinal cord and optic nerves during the clinical disease stages, but did not reduce the number of activated microglia in the retina and optic nerves during the preclinical disease. Similarly, minocycline treatment was neuroprotective during the clinical stage, where it reduced RGC loss, but was not protective against earlier RGC degeneration occurring during the pre-clinical disease.

In conclusion, minocycline effectively suppressed the onset of EAE and optic neuritis, primarily by reducing immune cell infiltration. Minocycline-induced RGC protection probably resulted from decreased axonal damage caused by immune cell infiltration of the optic nerves.

Disclosure

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P1173

Expanded mode of action: unphosphorylated fingolimod exerts anti-inflammatory effects by inhibiting the IL-33 induced IFNγ formation in CD8$^+$ Cells

C.A. Mayer[1], F. Ottenlinger[2], C.S. Schuhmann[3], A. Schwiebs[3], N. Ferreiros[4], J.M. Pfeilschifter[5], H.H. Radeke[5]
[1]Neurology, Uniklinik Frankfurt, Bad Homburg, [2]pharmazentrum, [3]Neurology, [4]Pharmacology, [5]Pharmazentrum, Goethe University, Frankfurt, Germany

Background: A significant proportion of multiple sclerosis (MS) patients respond to treatment with the S1P receptor modulator Fingolimod (FTY720). Following phosphorylation by sphingosinekinase 2 (SphK2) FTY720P acts as a partial sphingosine-1-phosphate receptor agonist and internalizes sphingosine-1-phosphate receptors, thereby preventing central memory T-cell sequestration.
Objective: The cytokine IL-33 was recently ascribed a central role in MS as it has been shown to worsen the course of EAE in the mouse model and was detectable in elevated levels peripherally in human plasma and centrally in human normal appearing white matter and MS plaques, whereas IL-33 levels decreased under Interferone-ß-medication. Therefore we aimed at assessing, whether FTY720 might also affect the IL-33 induced T-cell activation. Additionally, we analyzed if FTY720, IFN-b or Natalizumab treatment affects S1P or other bioactive sphingolipids
Methods: Primary murine CD8$^+$Tcells were analyzed for FTY720/-P effects on IL-33-induced cytokines. Additionally, serum- and plasma samples from FTY720 treated MS-patients at steady states were assessed for IL-33 levels and concentrations of 14 bioactive sphingolipids as determined by LC-MS-MS. Fingolimod-treated patients were then compared to other treatment groups (n=8-16/group) and healthy controls (HC).
Results: IL-33 co-activated CD8$^+$ T-cells, especially by increasing IFN-γ formation in vitro. Interestingly, FTY720, but not FTY720P, was able to inhibit this IL-33-induced process. Thus, contrainflammatory effects through IL-33-inhibition work independently from intracellular FTY720-phosphorylation by SphK2. Instead, we found FTY720 interacting with the SET/PP2A-pathway.

However, unlike Fingolimod, IFNb specifically increased plasma sphinganines and ceramides.
Conclusions: We show for the first time an alternative, FTY720-phosphorylation-independent immunomodulatory effect of Fingolimod exerted through IL33-induced IFN-γ-inhibition. Additionally, IFN-b treatment revealed a specific "IFNb signature" on plasma sphinganines and ceramides, the latter being involved in cellular apoptosis and depression. Our data significantly adds to the immunological understanding of therapeutic Fingolimod effects in MS and eventually to decision making in risk/benefit evaluation when intending to treat a patient with this effective substance.

Additionally, the specific "IFNb signature" may be useful in long term therapy control in RRMS patients.

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P1174

PREFER*MS* study: *post hoc* analyses of cross-sectional correlations between oral Symbol Digit Modalities Test scores and clinical, cognitive and radiological outcomes

D.L. Arnold[1,2], R.H.B. Benedict[3], B.A.C. Cree[4], X. Meng[5], L. Schofield[5], N. Tenenbaum[5], on behalf of the PREFERMS investigators
[1]NeuroRx Research, [2]McGill University, Montreal, QC, Canada, [3]University at Buffalo, State University of New York, Buffalo, NY, [4]University of California San Francisco, San Francisco, CA, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States

Background: Cognitive impairment is common in multiple sclerosis (MS). The Symbol Digit Modalities Test (SDMT, oral or written) was used to assess cognitive impairment in PREFER*MS*, a prospective study of treatment retention with fingolimod 0.5 mg compared with injectable disease-modifying therapies (iDMTs) in patients with relapsing-remitting MS. Oral SDMT results showed a clinically meaningful improvement.
Objective: To better understand the relationship between oral SDMT results and clinical, cognitive and radiological outcomes in the study.
Methods: PREFER*MS* was a 12-month, phase 4, open-label, active-controlled, randomized, multicentre study. At enrolment, patients were either treatment-naïve or treated with one class of iDMT (interferon or glatiramer acetate). Patients were randomized (1:1) to fingolimod 0.5 mg or pre-selected iDMT. One on-study treatment switch was allowed after ⩾3 months of treatment, or before if related to efficacy or safety. Cross-sectional, pairwise Pearson correlations of oral SDMT scores with clinical, physical disability measures, radiological and cognitive variables were calculated in the total study population. Correlations with oral SDMT score were examined at baseline, at the end of randomized treatment (EoRT) and at end of study (EoS).
Results: In PREFER*MS*, 875 patients were randomized (fingolimod, n=436; iDMT, n=439). Correlation coefficients (r) ranged from −0.52 to 0.55. Variables correlating most strongly with oral SDMT score at baseline were thalamic volume (r=0.43), Paced Auditory Serial Addition Test 3 (PASAT 3; r=0.47) and timed 25-foot walk (T25FW; r=−0.49), and at EoRT and at EoS, respectively, were PASAT 3 (r=0.55 and 0.50) and 9-hole peg test (9HPT; r=−0.52 and −0.48). Weaker correlations with oral SDMT score were seen at baseline with 9HPT (r=−0.38), T1 lesion volume (r=−0.37), T2 lesion volume (r=−0.36) and total brain volume (r=0.33), and at EoRT and EoS, respectively, with thalamic volume change (r=0.15 and 0.09) and T25FW (r=−0.38 and −0.35). Annualized relapse rate correlated weakly with oral SDMT scores at EoRT (r=−0.10) and EoS (r=−0.04), as did cortical grey-matter volume at each time point (baseline: r=0.16; EoRT, r=0.15; EoS, r=0.19).
Conclusions: In PREFER*MS,* cognitive function, measured by oral SDMT score, correlated strongly with thalamic volume at baseline and with other cognitive function measures (PASAT) and physical disability (T25FW, 9HPT) at various timepoints.

Disclosure

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Bruce A C Cree has received personal compensation for consulting from Abbvie, Biogen, EMD Serono, Sanofi Genzyme, MedImmune, Novartis, Shire and Teva.
Xiangyi Meng, **Lesley Schofield** and **Nadia Tenenbaum** are employees of Novartis Pharmaceuticals Corporation.

P1175

Prevalence of liver injury and hepatitis after pulsed methylprednisolone therapy in multiple sclerosis patients

V. Nociti[1,2], M. Biolato[3], C. De Fino[1], A. Bianco[1], F.A. Losavio[1], M. Lucchini[1], A. Grieco[3], M. Mirabella[1]
[1]Neurosciences, Catholic University, Rome, [2]Don C. Gnocchi Foundation, Milan, [3]Internal Medicine, Catholic University, Rome, Italy

Background and aims: Few isolated cases of methylprednisolone (MP)-induced hepatitis in patients with multiple sclerosis (MS) are reported in literature but a systematic investigation had never been performed. The aim of the study is to evaluate the prevalence of liver injury and hepatitis in patients affected by MS and treated with intravenous (i.v.) MP because of clinical relapses.
Patients and methods: During 12 month observation period, we collected 249 cycles of i.v. high dose steroid treatment from 175 patients (65% females, mean age of 40.8 ± 12.2 years; mean Expanded disability status scale (EDSS) pre-relapse of 2.74 ± 2.11, mean EDSS post-relapse 3.22 ± 1.91). All patients, in relapsing phase of the disease, were treated with i.v. MP (1000 mg/day for 5 days). We tested liver enzymes (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, γ-glutamyl transpeptidase) before treatment and after two weeks. In case of increased enzymes levels, a new laboratory test was made after two weeks, until the normalization of liver function. In case of persistent increasing in liver enzymes a

systemic search of principal causes of acute hepatitis was performed (microbiological and immunological screening, a liver ultrasounds and in some selected cases a liver biopsy) and specific therapy was started.
Results: Twenty-six patients (15%) developed a liver damage, documented by an increase in liver enzyme (particularly ALT) tested two weeks after steroid therapy. Six of them presented a severe hepatocellular injury according to Hy's law: three subsequently were diagnosed as probable methylprednisolone-induced liver injury, while in the other three an autoimmune hepatitis was diagnosed and a treatment with budesonide and azathioprine was started.
Conclusions: This study highlights the importance of close follow-up of liver function following the i.v. administration of MP. Although in most cases the increase in liver enzymes was mild and the recovery was spontaneous and occurred about in a month, some patients developed a major liver disease which need hepatologic work-up. According to our experience, it is advisable to test liver function two weeks after steroid's pulse. While increased, liver tests have to be repeated every two weeks until normalization, otherwise a liver biopsy is recommended to evaluate severity of liver injury and possible alternative diagnosis.
Nociti and De Fino equally contributed to this work

Disclosure

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P1176

Retrospective analysis of a MS cohort patients treated by fingolimod in South France (Marseille- PACA and Corsica)

J. Pelletier, R. Gualtieri, B. Di Lelio, M.E. Fontaine, S. Yaker, M.P. Ranjeva, L. Crespy, B. Audoin, A. Rico
APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France

Objectives: to describe efficacy and safety of Fingolimod in a cohort of patients treated for at least one year in the department of neurology of the Timone university hospital of Marseille.The primary objective was to evaluate the proportion of patients presented with disease free activity (relapse, disability and MRI) at year1 and year2. The secondary objectives were to describe clinical and MRI data before before starting Fingolimod, efficacy and safety profiles of the patients included in this retrospective observational study.
Methods: Patients were identified in the EDMUS database. Patients included had to start Fingolimod between January 1st 2012 and December 31 2013. Clinical, biological and MRI data had to be effective. 204 patients were included in the study with a treatment duration more than one year (130 were treated more than 2 years). 73.5% were female and 26.5% male. Mean age was 40y and mean disease duration was 10ys.
Results: RRMS represents 92% of patients, progressive MS (SP or PP) 8%. 23.5% of patients were treatment naïve (first line treatment) and 66.5% were treated in second line therapy (50.5% after a first line treatment, 26% after a second line). Mean EDSS before treatment was 2.9 and 66% presented one or more relapse one year before treatment (36% 2ys before). 78% of patients presented with new T2MRI lesion(s) and 54% with T1GadMRI lesion(s) at baseline. Mean treatment duration was 22.2months. Mean EDSS at Y1 was 2.7 and at Y2 5.6. Respectively, 86.5% and 92% had no new T2MRI and T1Gad MRI lesion at Y1 (91.5% and 95% at Y2). 80% of patients had no relapse at Y1 and 92% at Y2. At Y1 and Y2 73.7% and 85.8% respectively were NEDA3 (no clinical and MRI activity). 22% of patients stopped definitively Fingolimod (6% in the absence of efficacy: relapse and/or EDSS increase; 1.5% related with serious adverse events; (6% related with no serious AE; 8% related with personal reasons; 0.5% related with pregnancy). Safety profile was good: one death (pancreas cancer), one patient presented with pancreas cancer, 8 patients with liver abnormalities, 2 patients with lymphopenia (below 200), 2 patients with high blood pressure and 2 patients with infection.
Conclusions: This monocentric retrospective study confirm consistent efficacy benefit at Y1 and Y2 of Fingolimod both on clinical and MRI activity. This study also supports the positive safety profile of Fingolimod in real life.

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P1177

Alemtuzumab reduces the rate of brain volume Loss in RRMS patients who switched from SC IFNB-1a to alemtuzumab (4-Year Follow-Up of the CARE-MS I and II studies)

A. Traboulsee[1], D. Pelletier[2], G. Comi[3], A. Rovira[4], S. Schippling[5], D.H. Margolin[6], K. Thangavelu[6], K. Nakamura[7], D.L. Arnold[8,9], on behalf of the CARE-MS I and CARE-MS II Investigators

[1]The University of British Columbia, Vancouver, BC, Canada, [2]University of Southern California, Los Angeles, CA, United States, [3]University Vita-Salute San Raffaele, Milan, Italy, [4]Vall d'Hebron University Hospital, Barcelona, Spain, [5]Neuroimmunology and Multiple Sclerosis Research, University Hospital Zurich and University of Zurich, Zurich, Switzerland, [6]Sanofi Genzyme, Cambridge, MA, [7]Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH, United States, [8]NeuroRx Research, [9]Montréal Neurological Institute, McGill University, Montréal, QC, Canada

Background: Brain volume loss (BVL) derived from relative change in brain parenchymal fraction (BPF) is a measure of evolving brain atrophy in patients with multiple sclerosis (MS). Patients with active relapsing-remitting MS (RRMS) who were treatment-naive (CARE-MS I; NCT00530348) or who had an inadequate response (⩾1 relapse) to prior therapy at baseline (BL) (CARE-MS II; NCT00548405) demonstrated significantly greater reductions in the rate of BVL with alemtuzumab versus subcutaneous interferon beta-1a (SC IFNB-1a) over 2 years. Patients who completed CARE-MS I and II could enter an extension study (NCT00930553); patients treated with SC IFNB-1a in the core studies were crossed-over to alemtuzumab treatment in the extension and experienced marked improvements in clinical and MRI outcomes.
Goal: To evaluate the effect of alemtuzumab on BVL over 4 years in patients switched from SC IFNB-1a.
Methods: Following SC IFNB-1a discontinuation, patients were infused with 2 courses of alemtuzumab 12 mg (Month 0 of extension: 5 days; Month 12 of extension: 3 days), followed by as-needed retreatment for relapse or MRI activity at any time 12 months following the last infusion. Another disease-modifying therapy could be provided at the investigator's discretion. MRI scans were assessed at BL and annually thereafter. BVL was derived from relative change in BPF.
Results: The extension study enrolled 144 (83%) and 146 (83%) SC IFNB-1a-treated patients from CARE-MS I and II, respectively; of these, 125 (87%) and 125 (86%) patients remained on study 4 years later. In CARE-MS I, median yearly BPF change was reduced in Years 1, 2, 3, and 4 after switching to alemtuzumab (Year 1: -0.07%; Year 2: -0.15%; Year 3: -0.05%; Year 4: 0.01%) compared with the 2 years before alemtuzumab, during SC IFNB-1a treatment (-0.94% and -0.50%). Similar results were observed in CARE-MS II (median yearly BPF change was 0.02%, -0.04%, -0.15%, and -0.08% in Years 1, 2, 3, and 4 after switching to alemtuzumab) compared with the 2 years before alemtuzumab during SC IFNB-1a treatment (-0.54% and -0.33%). These results were achieved with most patients (CARE-MS I: 75%; CARE-MS II: 71%) receiving no additional treatment after their initial 2 courses of alemtuzumab following their switch from SC IFNB-1a.
Conclusion: Discontinuing SC IFNB-1a and switching to alemtuzumab markedly slowed BVL over 4 years, despite most patients receiving no additional treatment since the initial 2 courses of alemtuzumab.

Disclosure

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P1178

Real world experience with dimethyl fumarate in relapsing-remitting multiple sclerosis

S.R. Cox[1], S. Jordan[1], D. Sharma[1], G. O'Boyle[1], N. Tubridy[2], M. Hutchinson[2], C. Mcguigan[2]
[1]Neurology, University College Dublin, [2]Neurology, Saint Vincent's University Hospital, Dublin, Ireland

Key words: Multiple Sclerosis, Dimethyl Fumarate, annual relapse rates, lesion load, lymphopenia.
Background: Dimethyl Fumarate (DMF), is licensed as a first line oral therapy for relapsing-remitting Multiple Sclerosis (RRMS). Real life studies confirming the favourable safety and tolerability profiles from the phase three trials are required.
Objectives: To determine the efficacy and tolerability of DMF as a therapy for RRMS in a university MS clinic population.
Methods: A retrospective audit of people with RRMS receiving at least one dose of DMF, either as initial disease modifying therapy (DMT) or after a previous first line DMT, over an 18 month period was performed. Medical records were reviewed and data on annual relapse rates (ARR), change in MRI lesion load, side effects, with particular reference to lymphocyte counts, and discontinuation rates were collected in addition to demographics, treatment history etc.
Results: Ninety-two patients were identified who met the criteria for inclusion, 75 female; mean age (SD) 39 (±10); mean EDSS (SD) 1.5 (±1.0); average time since diagnosis: 6 years (±6 years). 39 patients were treatment naïve prior to DMF, 53 had at least one prior DMT. 20 of 92 (22%) patients discontinued DMF after a mean duration of 5±6 months due to GI symptoms (n=8), sustained lymphopenia (n=4), unspecified tolerability issues (n=4), flushing (n=3), allergic reaction (n=1). Two additional patients stopped for planned pregnancy. Of 78 patients who completed one year of therapy, ARR decreased by 95% 12 months post commencing DMF. Total number of relapses 12 months (12M) pre-DMF: 21 (ARR= 0.27); Total number of relapses 12M

post-DMF: 1 (ARR = 0.01, ** P< 0.01). The most commonly reported side effects were: flushing (n=42), GI symptoms (n=37), grade 2 lymphopenia (n=13), grade 3 lymphopenia (n=4) and headaches (n=5). At month 6 (M6) n=57, Total White Cell Count decreased by 20% (6.0±0.2 10^9/L) compared to baseline n=83 (7.5±0.8 10^9/L n=83). At M6 n=57, Lymphocyte decreased by 30% (1.43±0.1 10^9/L) compared to baseline n=83 (2.03±0.1 10^9/L).

Conclusions: This real world audit of DMF showed it significantly reduced relapse rates in treatment naïve and previously treated people with RRMS. The discontinuation rate was 22% which is consistent with the previously reported phrase 3 trial. No unexpected side effects were seen.

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P1179

One-year MRI and relapse outcomes after initiation of dimethyl fumerate

Y.M. Al Malik[1,2], J. Greenfield[3], L. Metz[1]
[1]Clinical Neuroscinces, University of Calgary, Calgary, AB, Canada, [2]Neurology, King Abdulaziz Medical City/ King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia, [3]University of Calgary, Calgary, AB, Canada

Background: Dimethyl fumerate (DF) is a first line oral therapy for relapsing remitting multiple sclerosis (RRMS). This retrospective study aims to determine the MRI and relapse outcomes within one year after initiation of DF in a real world clinical setting.

Methods: The Calgary MS Clinic manages over 1,800 disease modifying therapy (DMT) patients. Data from all patients with RRMS who initiated DF between July 1, 2013 and December 31, 2014 were included. DMT use is carefully tracked and clinic processes ensure that patients starting a new DMT are offered a brain MRI 6-12 months after DMT initiation and that an annual follow-up is arranged. Patients may phone MS clinic nurses to discuss DMT tolerance and clinical symptoms. Suspected relapses are confirmed at an expedited or routine clinic visit with an MS Clinic neurologist. Demographic, clinical, MRI and relapse information are collected prospectively in a clinic database. We reviewed patient electronic medical records to assure reported relapses were not missed.

Results: This analysis included 170 patients. At treatment initiation mean age was 42.5 years, 75% were women, median disease duration was 11.3 years, median EDSS was 2, and 24% were treatment naïve. Most patients (147, 86%) had a clinic visit at one year (>46 weeks after initiating DF); 23 (14%) patients were assessed earlier (22 at 34-46 weeks and one at 29 weeks). One patient discontinued treatment at 5 days and had no follow-up. Within one year, DF was discontinued by 32 (19%) patients; median time to discontinuation was 4.8 months (range: 0.2-11.9).Among 150/170 (88%) patients on DF for at least 6 months, 133/150 (89%) had a follow-up MRI scan with gadolinium 6-12 months after starting DF. Median time to MRI was 8.7 months (range: 5.5-11.9). Gadolinium-enhancing lesions were detected on 16/133 (12%) MRI scans. At one year, 12 confirmed relapses occurred in 10 (6%) patients; median time to first relapse was 4.4 months (range: 0.2-10.9); 3 relapses occurred at 0-3 months, 6 relapses at 3-6 months, 1 relapse at 6-9 months, and 2 relapses at 9-12 months after starting DF. The annualized on-treatment relapse rate was 0.08 (95% CI: 0.04-0.14).

Conclusions: One year treatment with DF in a real world clinical setting is associated with low risk of relapses and gadolinium enhancing MRI lesions. The one-year discontinuation rate of 19%, however, is higher than we have previously reported for glatiramer acetate (12%) or interferon beta (16%).

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P1180

Design of two phase III open-label trials evaluating ocrelizumab in patients with relapsing-remitting multiple sclerosis and suboptimal response to disease-modifying treatment

R. Bermel[1], G. Comi[2], J.-P. Erälinna[3], T.P. Leist[4], R. Nicholas[5], C. Oreja-Guevara[6], A. Siva[7], B. Van Wijmeersch[8], H. Wiendl[9], C. Bernasconi[10], R. Buffels[10], C. Csoboth[11], J. Han[11], B. Musch[11], P. Vermersch[12]
[1]Mellen Center for MS; Cleveland Clinic, Cleveland, OH, United States, [2]University Vita-Salute San Raffaele, Milan, Italy, [3]NEO Research, Turku, Finland, [4]Thomas Jefferson University, Philadelphia, PA, United States, [5]Imperial College Healthcare NHS Trust and Imperial College, London, United Kingdom, [6]Hospital Clinico San Carlos, Madrid, Spain, [7]Cerrahpasa School of Medicine, Istanbul University, Cerrahpasa, Turkey, [8]University Hasselt and Rehabilitation & MS-Centre Overpelt, Hasselt, Belgium, [9]University of Münster, Münster, Germany, [10]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [11]Genentech, Inc., South San Francisco, CA, United States, [12]Centre Hospitalier Régional Universitaire de Lille, Lille, France

Background: Suboptimal treatment response is not uncommon in relapsing-remitting multiple sclerosis (RRMS), despite an increase in available disease-modifying treatments (DMTs). Disease activity early during DMT is associated with rapid progression of disability and poorer long-term outcomes. Breakthrough disease and treatment side effects are reasons to consider medication switch. Ocrelizumab (OCR), a recombinant humanised monoclonal antibody that selectively targets $CD20^+$ B cells, has demonstrated superior efficacy compared with interferon beta-1a in 2 identical, randomized, double-blind, Phase III trials (OPERA I; OPERA II) in patients with relapsing MS.

Objective: To report the study design and status of CHORDS (US and Canada; NCT02637856) and MA30005 (Europe), 2 prospective, multicentre, open-label efficacy and safety studies in patients with RRMS who have had suboptimal response to an adequate course of a DMT.
Methods: Patients will receive OCR as an initial dose of two 300mg intravenous (IV) infusions (600mg total) separated by 14 days, followed by one 600mg IV infusion every 24 weeks for at least 4 doses (up to a min of 96 weeks). Entry criteria include: diagnosis of RRMS (McDonald, 2010), disease duration ⩽10 years, treated with ⩽2 prior DMT regimens ⩾6 months with discontinuation of the last due to suboptimal disease control, defined as 1 of the following despite being on a stable dose of the same DMT for ⩾6 months: ⩾1 clinically reported relapse; or ⩾1 T1 gadolinium-enhanced (Gd^+) lesion; or ⩾2 new/enlarging T2 lesions on MRI. For those on stable doses of the same DMT for >1 year, events must have occurred within the prior 12 months of treatment with this DMT. The primary outcome measure in both studies is the proportion of patients free of any protocol-defined events during a 96-wk period, i.e. no protocol-defined relapses, no 24-week confirmed disability progression (based on Expanded Disability Status Scale score), no T1 Gd^+ lesions, and no new/enlarging T2 lesions (defined as no evidence of disease activity [NEDA] in MA30005).
Results: Enrolment began in 2016 with a planned total of 600 patients in each study. Studies are ongoing; updated status will be reported.
Conclusions: These studies will provide information on the efficacy and safety of OCR in patients who have had a suboptimal response to a DMT.
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P1181

Alemtuzumab durably slows brain volume loss over 6 years in the absence of continuous treatment in patients with active RRMS who were treatment-naive (CARE-MS I) or had an inadequate response to prior therapy (CARE-MS II)

A. Traboulsee[1], M. Barnett[2], G. Comi[3], C. LaGanke[4], D. Pelletier[5], A. Rovira[6], S. Schippling[7], D.H. Margolin[8], K. Thangavelu[8], K. Nakamura[9], D.L. Arnold[10,11], on behalf of the CARE-MS I and CARE-MS II Investigators
[1]The University of British Columbia, Vancouver, BC, Canada, [2]University of Sydney, Sydney, NSW, Australia, [3]Universita Vita-Salute San Raffaele, Milan, Italy, [4]North Central Neurology Associates, Cullman, AL, [5]University of Southern California, Los Angeles, CA, United States, [6]Vall d'Hebron University Hospital, Barcelona, Spain, [7]Neuroimmunology and Multiple Sclerosis Research, University Hospital Zurich and University of Zurich, Zurich, Switzerland, [8]Sanofi Genzyme, Cambridge, MA, [9]Cleveland Clinic, Cleveland, OH, United States, [10]NeuroRx Research, [11]Montréal Neurological Institute, McGill University, Montréal, QC, Canada

Background: Brain volume loss (BVL, which is a measure of brain atrophy) occurs more rapidly in patients with relapsing-remitting multiple sclerosis (RRMS) (0.5%-1.35% per year) than in healthy individuals (0.1%-0.3% per year). Patients with active

RRMS who were treatment-naive (CARE-MS I; NCT00530348) or had an inadequate response (⩾1 relapse) to prior therapy at baseline (BL) (CARE-MS II; NCT00548405) demonstrated improved clinical and MRI efficacy outcomes following treatment with alemtuzumab versus subcutaneous interferon beta-1a over 2 years. MRI efficacy outcomes included significant slowing of BVL. An extension study (NCT00930553) has shown durable efficacy through 5 years in the absence of continuous treatment.

Goal: To evaluate the effect of alemtuzumab on BVL over 6 years.

Methods: In the CARE-MS studies, patients received 2 courses of alemtuzumab 12 mg (Month 0: 5 days; Month 12: 3 days). Patients who completed the studies could enter the extension study, with as-needed alemtuzumab for relapse or MRI activity. Alternate disease-modifying therapy could be provided per investigator discretion. MRI scans were performed at BL and annually thereafter. BVL was derived by relative change in brain parenchymal fraction.

Results: 349 (95%) CARE-MS I and 393 (93%) CARE-MS II alemtuzumab-treated patients entered the extension study. Through 6 years, 325/349 (93%) CARE-MS I and 344/393 (88%) CARE-MS II remained on study. In patients who were treatment-naïve (CARE-MS I), alemtuzumab consistently slowed median yearly BVL over 4 years, with BVL remaining low in Years 5 and 6 (Year 1: -0.59%, Year 2: -0.25%, Year 3: -0.19%, Year 4: -0.14%, Year 5: -0.20%, Year 6: -0.17%). In patients who had an inadequate response to therapy prior to BL (CARE-MS II), median yearly BVL progressively decreased over 3 years and remained low in Years 4, 5, and 6 (Year 1: -0.48%, Year 2: -0.22%, Year 3: -0.10%, Year 4: -0.19%, Year 5: -0.07%, Year 6: -0.10%). These effects were achieved with 63% (CARE-MS I) and 50% (CARE-MS II) of patients receiving no additional treatment after their initial 2 courses of alemtuzumab.

Conclusion: Slowing of BVL with alemtuzumab was maintained over 6 years. Median annual BVL was ⩽0.2% in Years 3-6, despite ⩾50% of patients receiving no additional treatment since the initial 2 courses of alemtuzumab. Based on these findings, alemtuzumab may provide uniquely durable efficacy in the absence of continuous treatment for RRMS patients.

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P1182

Serious adverse events (SAE), autoimmunity (AI), and infections following alemtuzumab (ALE) therapy in a large, high disability, treatment-refractory MS clinic cohort

R.S. Ghodasara[1], S.R.S. Smith[1], M. Mosley[1], R. Morgan[1], M. Bower[1], L. Kagan[1], D. Kantor[2], J. Derwenskus[1], S.F. Hunter[1]

[1]Advanced Neurosciences Institute, Franklin, TN, [2]Kantor Neurology, Coconut Creek, FL, United States

Background: Anti-CD52 IgG ALE provides powerful, long-term (LT), disease-modifying effects with a liability for infusion-related, infectious, and autoimmune side effects; we present a large clinic cohort of highly treatment-refractory, older, higher disability subjects with LT data.

Objectives: Report complications of hospitalization, infection, AI, and malignancy following ALE in highly treatment refractory LT and short-term (ST) cohorts.

Methods: NCT01624714 Retrospective and prospective data collection of subjects in open label phase I clinical trial for treatment refractory MS. 61 subjects were followed for a mean 54 months (254 patient-years (PY)) post-ALE. Baseline median age was 49 (32-68) years. The LT cohort had a mean of 83 months follow up (FU), and ST had mean of 25 months FU.

Results: 41 SAE, nearly entirely hospitalization, occurred at a rate of 0.16 events per PY; only 1 for MS relapse. Serious events differed for LT 0.10/PY and ST 0.35/PY. Serious infections caused 16 hospitalizations (0.063/PY). Major infections included 4 opportunistic infections (fungal osteomyelitis 1, disseminated histoplasmosis 2, granulomatous fish handlers´ disease 1). Other infections included Urinary tract infection 3, 1 with paraparesis pseudorelapse; Pulmonary: pneumonia 2, pneumonia-sepsis 1; Gastroenteritis: C.difficile 1, Rotavirus gastroenteritis 1, fecal impaction with enteritis 1 and Other: post-operative MRSA osteomyelitis 1, and pseudofolliculitis 1. Serious infections also differed in rate between LT 0.04/PY and ST 0.1/PY. AI occurred, not usually requiring hospitalization: 5 Grave´s disease, 5 hypothyroidism, 2 goiter/nodule, 2 hemolytic anemias (HA), 1 ITP, 1 recurrent alopecia totalis. The total thyroid AI rate of 12/61 (20%) subjects or 0.047 events/PY. AI caused 4 hospitalizations (7% of subjects): thyrotoxicosis (2), ITP with mild pancytopenia and HA, and HA. AI rate was similar between the LT 0.061/PY and ST 0.08/PY. One HA resolved but recurrent infections after rituximab led to study withdrawal and death in hospice care. Malignancies

other than basal cell carcinoma (BCC) did not occur, 3 BCC were excised (0.01 per PY).
Conclusions: Safety of ALE in this challenging and refractory cohort is similar to prior reports; AI, infections and hospitalizations occur. Histoplasmosis occurred multiple times in our cohort and is an endemic pathogen in our region. Serious infections may be higher than previously reported.

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P1183

A real life monocentric study on efficacy and tolerability of dimetilfumarate

L. Moiola, M. Pisa, G. Dalla Costa, F. Sangalli, M. Radaelli, P. Preziosa, F. Esposito, M. Romeo, F. Martinelli Boneschi, B. Colombo, V. Martinelli, G. Comi
San Raffaele Hospital, milan, Italy

Background: Registrative studies showed the efficacy of Dimethyl Fumarate (DMF) in reducing annualized relapse rate (ARR), the number of gadolinium enhancing lesions and brain volume loss compared to placebo. However real life studies are needed to confirm these results.
Methods: Of 385 MS patients (pts) treated with DMF at San Raffaele Hospital 152 pts have at least 12 months (mo) follow up (fu). 24 of them discontinued DMF within 9 months: 6 for disease activity and 18 (not included in the analysis) for intolerance. Therefore 134 pts were included: 75% female, mean age 36.6; mean disease duration 10.4 years; mean EDSS 1.88. Mean ARR in the 2 years before DMF was 0.399.
12.7% were naïve, 49.3% switched to DMF from injective disease modifying therapies (DMT) for intolerance, 27.6% for inefficacy, 10.4% after an induction therapy. All pts had a brain MRI at DMF initiation and neurological examinations every 3 mo.
Results: At last FU: 83% of patients were relapse free. Mean ARR was reduced to 0.093 (Wilcoxon; $p < 0.001$). The ARR reduction was statistically significant in all subgroups: naïve pts (p=0,01), switchers from DMT for intolerance (p=0.018) for inefficacy ($p < 0.001$) and switchers after induction therapy (p=0.027).
The analysis of ARR reduction in switchers from DMT for inefficacy could be biased by higher ARR before DMF; in fact, in these pts, ARR during DMF treatment was 0.108 whereas it was 0,053 in switchers for intolerance (Wilcoxon; ns). A binary logistic regression was performed to find possible predictors of relapse free status: previous ARR, active baseline MRI, disease duration, previous DMT, EDSS, age, sex. The model (X2=14,2 p=0,014) correctly classified 82,1% of pts with significant contribution only from ARR: high ARR is a predictor of DMT failure.

79 pts had also a brain MRI at 12 mo: 51 of them (64%) reached NEDA3 criteria.

The only predictor of NEDA3 was the presence of MRI activity at baseline (X2=4.45; p=0,035). Mild flushing and gastrointestinal symptoms were reported during the first 6 mo in 64,1% and 36,9% of pts, while at 12 mo the frequency was 33% and 3,8%, respectively.
Conclusions: Our data confirm the efficacy of DMF as first line treatment for naïve pts or switchers from DMT for intolerance or mild inefficacy. A longer FU and a comparison with a well matched population treated with injectable DMT is needed to better understand the actual efficacy of DMFto define the actual level of efficacy of DMF.

Disclosure

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P1184

Patient real-world clinical, neurological, tolerability, and safety outcomes for dimethyl fumarate and interferon beta-1a 44 µg subcutaneously three times weekly: A retrospective study using propensity score stratification and matching (PROTRACT)

R. Zivadinov[1], C. Cha[2], G. Buckle[3], J. Aldridge[4], G. Haas[5], J. Reed[2], B. Hughes[6]
[1]State University of New York at Buffalo, Buffalo, NY, [2]EMD Serono, Inc., Rockland, MA, [3]Shepherd Center, Atlanta, GA, [4]EMD Serono Research & Development Institute, Billerica, MA, United States, [5]IMS Health, Frankfurt, Germany, [6]Mercy Ruan Neurology Clinic, Des Moines, IA, United States

Background: To date there is no comparative study on the real-world effectiveness and tolerability of interferon beta-1a (IFN β-1a) subcutaneously (SC) three times weekly (tiw) and dimethyl fumarate (DMF) in relapsing-remitting multiple sclerosis (RRMS). Real-world studies can explore medical needs of patients (pts) in a more naturalistic setting and broader population than randomised controlled trials.
Objective: To evaluate the proportion of pts who demonstrate no medical need to discontinue therapy (Tx) among disease-modifying drug (DMD)-naïve pts with RRMS after 1 year of Tx with IFN β-1a 44 µg SC tiw or DMF 240 mg twice daily. No medical need to discontinue Tx will be measured by the primary endpoint, which is a composite of (1) no evidence of disease

activity (NEDA-2), defined as no relapses, no new or enlarging T2 lesions, and no T1 gadolinium-enhancing lesions, and (2) no discontinuation due to disease activity, tolerability, or adverse events.

Methods: This ongoing, Phase IV, retrospective, magnetic resonance imaging (MRI)-reader-blinded, longitudinal, cohort study will examine data from medical records and high-quality MRI scans of around 5400 pts from about 50 US MS treatment centres. Included pts will have a diagnosis of RRMS or clinically isolated syndrome; be aged 18-55 years; have initiated Tx with IFN β-1a SC tiw or DMF (index date); and have no prior DMD use. All eligible pts will be enrolled consecutively, regardless of their outcome, in reverse chronological order starting with those whose index date is 15 months before study launch. Enrolment will continue until each Tx group includes 400 pts who have MRI scans available at baseline and 1 year post-index and remained on initial Tx at the 1-year scan. To mitigate potential selection bias, groups will be stratified by propensity scores derived from pts' baseline characteristics. Propensity score matching will also be explored. Each component of the composite primary endpoint will also be evaluated individually as secondary endpoints. This study is designed for estimation rather than hypothesis confirmation. 90% confidence intervals will be reported.

Results: Enrolment began on 1 March 2016. Interim analysis results will be available in Q3 2016, with final results expected by end of 2016.

Conclusions: By examining clinical and MRI data in pts stratified by propensity scores, this trial design allows for rapid analysis of large cohorts for real-world effectiveness and tolerability outcomes.

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Guy Buckle received research support from Biogen and personal fees for consulting and/or speaking from Bayer, Biogen, EMD Serono, Inc. (a business of Merck KGaA, Darmstadt, Germany), Genentech Pharmaceuticals, Genzyme, Mallinckrodt, Novartis, , and Teva.

Julie Aldridge is an employee of EMD Serono Research & Development Institute, Billerica, MA, USA (a business of Merck KGaA, Darmstadt, Germany).

Gabriele Haas is employed by IMS Health, which is executing the study on behalf of the sponsor. Neither GH nor IMS Health have any conflict of interest regarding the outcome of the study.

Josh Reed is an employee of EMD Serono, Inc., Rockland, MA, USA (a business of Merck KGaA, Darmstadt, Germany).

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P1185

Peginterferon beta-1a is effective in RRMS regardless of pretreatment expression of interferon signature genes: Results from a sub-study of ADVANCE

S. Eraly, D. Fiore, N. Allaire, H. Li, W. Tang, Y. Cui, D. Cadavid, J. Carulli

Biogen, Inc., Cambridge, MA, United States

Background: A gene expression signature associated with endogenous activation of the type I interferon (IFN) system has been observed in a number of autoimmune diseases including relapsing remitting multiple sclerosis (RRMS). It has been hypothesized that high pretreatment expression of IFN signature genes in RRMS patients may be associated with poor response to IFN-beta treatment on the basis that patients with activation of endogenous IFN pathways are less likely to respond to exogenous IFNs.

Objectives: To assess the relationship between pretreatment IFN signature and treatment outcomes in a 384 subject sub-study of ADVANCE, the pivotal trial of Peginterferon beta-1a efficacy in RRMS.

Methods: RNA was isolated from whole blood obtained from subjects at baseline (pretreatment), the relative expression of 20 IFN-induced genes was determined by quantitative PCR and normalized to a panel of 4 house-keeping genes, and a pretreatment IFN signature score was calculated for each subject as the geometric mean of the relative expression values of the 20 genes (which were all highly correlated with one another). The relationship between pretreatment IFN signature score and treatment outcomes at 48 weeks, including annualized relapse rate (ARR) and counts of Gd+ and/or new or newly enlarging T2 hyper-intense lesions, was assessed using negative binomial regression, adjusting for baseline age, disability, and relapse rate among other covariates.

Results: The beneficial effects of Peginterferon beta-1a on relapses and MRI lesions in this sub-study population were similar to those observed in ADVANCE as a whole. There was no association between pretreatment IFN score and on-treatment ARR among placebo-treated subjects ($p=0.897$). There was also no interaction between peginterferon beta-1a treatment and pretreatment IFN score with regard to the outcome of ARR regardless of dose ($p=0.851$ for placebo vs. every 2 weeks peginterferon treatment; $p=0.497$ for placebo vs. every 4 weeks peginterferon treatment). Similar lack of interaction was observed when testing against inflammatory MRI outcomes: Gd+ and new/newly enlarging T2 hyper-intense lesions.

Conclusions: In this large sub-study of a pivotal trial of Peginterferon beta-1a, pretreatment IFN score did not influence efficacy outcomes or treatment response. Peginterferon beta-1a is effective in RRMS regardless of pretreatment IFN score.

Disclosure

Satish Eraly: I am an employee of Biogen and hold equity in the company

Damian Fiore: I am an employee of Biogen and hold equity in the company

Norm Allaire: I am an employee of Biogen and hold equity in the company

Huo Li: I am an employee of Biogen and hold equity in the company
Weihua Tang: I am an employee of Biogen and hold equity in the company
Yue Cui: I am an employee of Biogen and hold equity in the company
Diego Cadavid: I am an employee of Biogen and hold equity in the company
John Carulli: I am an employee of Biogen and hold equity in the company

P1186

Effect of the human recombinant sIFNAR2 protein on the patterns of expression of cytokines in Multiple Sclerosis patients

I. Hurtado-Guerrero[1], M.J. Pinto-Medel[2], M. Suardíaz[2], J.L. Rodriguez Bada[2], P. Urbaneja[2], V. Fernández[2], Ó. Fernández[2], L. Leyva[2], B. Oliver-Martos[2]
[1]Hospital Regional Universitario de Málaga, IBIMA, [2]UGC de Neurociencias, Hospital Regional Universitario de Málaga, IBIMA, Málaga, Spain

Background: The soluble isoform of the IFNß receptor (sIFNAR2), generated by alternative splicing, has been identified in human biological fluids and is able to modulate the activity of both the endogenous and the systemically administered IFNß. We have previously cloned a recombinant protein analogous to human sIFNAR2 that was identified by Western Blot and also by MALDI-TOF. This recombinant protein has shown to exert antiviral activity against viruses relevant to human health, such as HIV, respiratory syncytial virus, or encephalomyocarditis virus. We have also tested the effect of the sIFNAR2 administered as a monotherapy in a chronic mice model of MS (CPEAE) and we demonstrate for the first time that sIFNAR2 shows intrinsic properties by modulating the CP-EAE progression and the neuroinflammation processes related to this disease. On the whole, recombinant sIFNAR2 has shown to exert per sé similar activities to IFNß, but independently of it.
Aim: According to our previous results, we evaluate the ability of recombinant sIFNAR2 to modify in vitro the patterns of expression of cytokines and chemokines in peripheral blood mononuclear cells (PBMC) and in the supernatants from multiple sclerosis patients and healthy controls.
Methods: PBMC from 10 MS patients and 10 healthy controls were cultured in the presence of recombinant sIFNAR2, including the appropiate controls. After 4 hours, cells were stained with a panel of specific monoclonal antibodies to detect intracellular cytokines by flow cytometry. The production of cytokines in supernatants was assessed using Procartaplex Multiplex Inmunoassay with Luminex technology.
Results: Of all the results, a significant decrease in the intracellular production of IFN gamma and TNF alpha in the presence of recombinant sIFNAR2, both in MS patients and controls, should be emphasized. The result was confirmed in the analisys of supernatants, where a significant decrease in the production of IFN gamma and TNF alpha in presence of recombinant sIFNAR2 was also observed.
Conclusion: Our human recombinant sIFNAR2 protein has an important immunomodulatory activity in all the subjects by decreasing the production of proinflammatory cytokines (IFN gamma and TNF alpha), assessed by two different technologies. We describe, for the first time, an immunomodulatory activity of the soluble isoform of IFNß receptor, and the results point to this molecule as a potential drug.

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P1187

Comparing rituximab induction therapy followed by glatiramer acetate therapy to glatiramer acetate monotherapy in MS patients on clinical and imaging

J.H. Honce[1], K.V. Nair[2], S. Stefan[3], V. Brooke[3], T. Ildiko[3], A. Miravalle[3], E. Alvarez[3], S. Teri[3], J.L. Bennett[3], J.R. Corboy[3], T.L. Vollmer[3]
[1]Radiology, [2]Pharmacy, [3]Neurology, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

Background: Induction therapy with rituximab may decrease immunological regulatory circuits in MS by removing key antigen presenting B cells. Subsequent initiation of glatiramer acetate (GA) may induce new B cell dependent regulatory circuits as the B cell population recovers from induction. This may result in a larger treatment effect versus GA monotherapy. We prospectively examined the efficacy of rituximab versus placebo induction, followed by GA.
Methods: This was a single center, double-blind, placebo-controlled study. 64 relapsing MS patients were screened. 53 were randomly assigned to either rituximab (R-GA) or placebo induction (P-GA) arms and had at least one MRI follow-up. Patients received infusion of 1000 mg of rituximab or placebo (normal saline) on days 1 and 15. On day 28, all patients initiated GA therapy. Patients were followed quarterly up to 3 years. Primary endpoint was the number of disease-free patients, defined as those without protocol relapse, new combined unique lesions (CUL) on MRI and without sustained change in EDSS over 3-months. Secondary endpoints included annualized relapse rate (ARR), new T2 and gadolinium enhancing lesions (GEL). Patients with at least two visits including baseline were part of the analysis. Proportions were tested with chi-square or Fisher's exact tests. Rates were estimated and tested with Poisson and negative binomial models. All models were adjusted for followup time.

Results: 27 patient received rituximab and 26 received placebo. Mean age was 37 years, and 70% were female. Baseline EDSS score was $2.80_{R\text{-}GA}$ vs $2.63_{P\text{-}GA}$. (p=0.7270). Mean follow-up was 1.63 years (0.370-3.26). 44.44% of R-GA patients experienced no protocol defined disease event, vs 19.23% of P-GA patients (p = 0.0493). There was no difference in protocol defined ARR ($0.1550_{R\text{-}GA}$ vs $0.3706_{P\text{-}GA}$, p=0.1219) or annualized sustained disability ($0.0919_{R\text{-}GA}$ vs $0.0797_{P\text{-}GA}$, p=0.8484), but clinically defined ARR was lower for R-GA ($0.2203_{R\text{-}GA}$ vs $0.5412_{P\text{-}GA}$, p=0.0420). MRI lesion activity was different between groups with lower annual rate of new CUL for R-GA ($0.3290_{R\text{-}GA}$ vs $2.5887_{P\text{-}GA}$, p=0.0115. Differences in rate of CUL were driven by new T2 lesions ($0.2754_{R\text{-}GA}$ vs $2.0142_{P\text{-}GA}$, p=0.0188) rather than GEL ($0.0583_{R\text{-}GA}$ vs $0.4795_{P\text{-}GA}$, p=0.0699).

Conclusions: Preliminary evidence suggests that induction therapy with rituximab vs GA monotherapy may provide superior efficacy in MS treatment. Larger studies are needed to assess sustainability of results.

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P1188

Rebound of disease activity after discontinuation of natalizumab or fingolimod can be successfully treated with autologous haematopoietic stem cell transplantation

D. Curro'[1], F. Gualandi[2], P. Cavalla[3], E. Capello[1], A. Uccelli[1], A. Mattioda[3], G. Boffa[1], G. Mancardi[1]
[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova and IRCCS AOU San Martino-IST, [2]Bone Marrow Transplantation Unit, IRCCS AOU San Martino IST, Genova, [3]MS Center, & I Division of Neurology, Department of Neuroscience, University of Turin & City of Health and Science of Turin University Hospital, Torino, Italy

Discontinuation of natalizumab (NTZ) and, more rarely, fingolimod (FTY) therapy can be followed by a recurrence of disease activity increasing to a level beyond the pre-treatment level, often resulting in significant irreversible disability. Several strategies to control the rebound of inflammatory activity have been tested with unsatisfactory results and yet the best therapeutic approach needs to be found. Here we report two cases of dramatic recurrence of disease activity after interruption of NTZ and FTY, successfully treated with autologous haematopoietic stem cell transplantation (AHSCT). Patient #1 was treated for 7 years with NTZ and he was almost free from disease activity, but in January 2014 the therapy was suspended considering the high risk of developing a progressive multifocal leukoencephalophaty (PML). In April 2014 he experienced a severe relapse reaching a high disability level (EDSS 8), he was treated with plasmapheresis and i.v. cyclophosphamide (CY) with only partial recovery, followed by a new clinical relapse and persistent disease activity at MRI. It was decided to treat the patient with intense immunosuppression with BEAM (carmustine, cytarabine, etoposide and melphalan) followed by AHSCT. Transplantation was followed by a marked clinical improvement (EDSS 3) and disappearance of clinical and MRI activity. Patient #2 was treated with FTY for 3 years, suspended for a planned pregnancy. Four months after the discontinuation of FTY, a severe relapse occurred (EDSS 6.5). She was treated with steroids and i.v. CY, with only partial improvement and MRI signs of activity were still persistent. The patient was therefore treated with intense immunosuppression followed by AHSCT. After 9 months no relapses occurred (EDSS 3) and MRI does not show any evidence of disease activity. Several studies have demonstrated that AHSCT has a profound effect on relapses and has the capacity to completely suppress MRI activity with an effect that is maintained with time. The present cases indicate that AHSCT can be a possible strategy in MS cases with a severe rebound of disease activity after discontinuation of NTZ or FTY treatment, unresponsive to the usual conventional therapies.

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P1189

Changes of cerebrospinal fluid cytokine profile as a result of switching from first line MS-therapies to rituximab

P. de Flon[1], L. Söderström[2], K. Laurell[1], M. Gunnarsson[3], A. Svenningsson[4]
[1]Department of Pharmacology and Clinical Neuroscience, Umeå University, [2]Unit of Research, Education and Development, Region Jämtland Härjedalen,Sweden, Östersund, [3]Department of Neurology and Neurophysiology, Faculty of Medicine and Health, Örebro University, Örebro, [4]Department of Clinical Sciences, Karolinska Institute, Stockholm, Sweden

Background: New treatment strategies in multiple sclerosis provide insights not only in the clinical effects but also, by their differences in mechanisms of action, in the immunopathological mechanisms behind disease activity.
Objective: This study describes the change in cyto- and chemokine profile over a two-year period in a cohort of patients with clinically stable RRMS after treatment shift from ongoing first-line injectable disease modifying therapy (iDMT), e.g. interferon beta or glatirameracetat, to the anti-CD20 depleting agent rituximab and the differences compared with a cohort of healthy controls.
Method: CSF from 73 patients with clinically stable RRMS was analysed by an elektrochemiluminiscens-based ELISA for a panel of 22 cytokines before and one and two year after treatment shift to rituximab and compared with 55 healthy controls.
Results: During the first year of treatment it was a significant reduction ($p < 0.005$) in levels of IL-6, IL-8, IL-10, IL-12, IL-15, IP-10, MCP-1, MDC, TARC, sICAM, sVCAM and a significant elevation ($p < 0,005$) in levels of IL-7 and MIP-1b.
Compared to healthy controls it was a significantly higher ($p < 0,005$) level of IFN-gamma, IL-6, IL-8, IL-10, IL-12, IL-15, TNF, IP-10, MDC, MIP-1a, MIP-1b, TARC, SAA, sICAM and sVCAM in patients with RRMS before treatment shift. Levels of IL-5 and IL-7 were significantly lower. One year after treatment shift the levels of IFN-gamma, IL-6, IL-7, IL-15, MIP-1a and SAA did not differ significantly between patients with RRMS and healthy controls.
Conclusion: This study demonstrates significant changes in cyto- and chemokine profile in patients with RRMS after treatment shift from iDMT to rituximab and compared with healthy controls.

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P1190

Efficacy and safety of alemtuzumab in 104 patients with active relapsing-remitting MS: one-year follow-up in France

X. Ayrignac[1], N. Collongues[2], J. De Sèze[2], P. Vermersch[3], D. Biotti[4], D. Brassat[4], C. Carra-Dallière[1], S. Vukusic[5], F. Durand-Dubief[5], G. Edan[6], E. Lepage[6], V. Deburghgraeve[6], E. Maillart[7], C. Papeix[7], P. Alla[8], E. Berger[9], B. Bourre[10], O. Casez[11], S. Pittion[12], M. Debouverie[12], M. Theaudin[13], N. Derache[14], G. Defer[14], O. Gout[15], R. Deschamps[15], A. Tourbah[16], F. Zagnoli[17], A. Ruet[18], J.C. Ouallet[18], B. Brochet[18], E. Manchon[19], T. Moreau[20], A. Fromont[20], P. Clavelou[21], F. Taithe[21], A.M. Guennoc[22], J.P. Camdessanche[23], A. Carpentier[24], I. Coman[24], B. Audoin[25], J. Pelletier[25], A. Rico[25], L. Magy[26], J. Ciron[27], S. Wiertlewski[28], D. Laplaud[28], T. De Broucker[29], C. Lebrun[30], M. Cohen[30], P. Labauge[1], Club Francophone de la Sclérose en Plaques; Société ´francophone de la Sclérose en Plaques
[1]Neurology, University Hospital of Montpellier, Montpellier, [2]Neurology, University Hospital of Strasbourg, Strasbourg, [3]Neurology, University Hospital of Lille, Lille, [4]Neurology, University Hospital of Toulouse, Toulouse, [5]Neurology, University Hospital of Lyon, Lyon, [6]Neurology, University Hospital of Rennes, Rennes, [7]Neurology, pitié Salpêtrière Hospital, APHP, Paris, [8]Neurology, Hospital of Toulon, Toulon, [9]Neurology, University Hospital of Besançon, Besançon, [10]Neurology, University Hospital of Rouen, Rouen, [11]Neurology, Univerisity Hospital of Grenoble, Grenoble, [12]Neurology, University Hospital of Nancy, Nancy, [13]Neurology, Kremlin Bicetre Hospital APHP, Paris, [14]Neurology, University Hospital Center of Caen, Caen, [15]Neurology, Rotschild Foundation Hospital, Paris, [16]Neurology, University Hospital of Reims, Reims, [17]Neurology, University Hospital of Brest, Brest, [18]Neurology, University Hospital of Bordeaux, Bordeaux, [19]Neurology, Hospital of Gonesse, Gonesse, [20]Neurology, University Hospital of

Dijon, Dijon, [21]Neurology, University Hospital of Clermont-Ferrand, Clermont-Ferrand, [22]Neurology, University Hospital of Tours, Tours, [23]Neurology, University Hospital of Saint Etienne, Saint Etienne, [24]Neurology, Avicenne Hospital APHP, Paris, [25]Neurology, University Hospital of Marseille APHM, Marseille, [26]Neurology, University Hospital of Limoges, Limoges, [27]Neurology, University Hospital of Poitiers, Poitiers, [28]Neurology, University Hospital of Nantes, Nantes, [29]Neurology, Hospital of Saint Denis, Saint Denis, [30]Neurology, University Hospital of Nice, Nice, France

Introduction: Alemtuzumab had superior effect over interferon beta-1a in 3 phase 3 studies. It has been approved by the European Medicines Agency for relapsing-remitting multiple sclerosis (RRMS). Considering its safety profile the French National authority for health (HAS) has restricted its use to very active RRMS characterized by at least 2 relapses under treatment and currently, its use relies on special authorization.
Objectives: To characterize the efficacy and safety profile of alemtuzumab in patients with active RRMS treated in France.
Methods: We retrospectively recorded clinical and radiological data of 104 patients who underwent Alemtuzumab treatment since January 2015.
Results: One hundred and four patients (79 women/25 men) have been treated (mean age at treatment: 36.4 years). All but one had RRMS (probable progressive form in 1). Mean age at onset of the disease was 25.4 years (range: 13-54). Indications of alemtuzumab (explicit for 101 patients) were either treatment failure (first line: n=3; second line: n=47) or high risk of PML (n=51). 84 patients were JCV positive. Mean time from MS onset to treatment was 10.6 years (range: 1-30). Mean EDSS was 4.9 (range 0-9.5) at treatment onset. During the year preceding the treatment, EDSS increased by 0.65 point and mean number of relapses was 1.7. Gadolinium-enhancing lesions were found in 83 / 104 patients. During a mean follow-up 11.8 months, 48 patients were relapse-free whereas 13 patients had at least one relapse (missing data for 42 patients). Mean EDSS decreased by 0.15 after one year. Infusion associated reactions were found in 70% of the cases (mainly rash and headache/pyrexia). Six patients suffered from infections whereas one developed immune thrombocytopenia at 11 months and another a thyroid disorder. Thirteen patients had other adverse events.
Conclusion: In France, Alemtuzumab is given to patients with very active disease characterized by mean EDSS of 4.9 and mean annualized relapse rate of 1.7. Alemtuzumab seems to be effective and relatively safe after 1 year of follow-up.

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P1191

Analysis of B cell trafficking in multiple sclerosis patients receiving natalizumab and fingolimod immunomodulatory therapy

M.C. Kowarik[1,2], D. Astling[3], C. Gasperi[1], A. Ritchie[4], G.P. Owens[4], J.L. Bennett[5]
[1]Neurology, TU-München, [2]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, [3]Department of Biochemistry and Molecular Genetics, [4]Neurology, University of Colorado, [5]Neurology and Ophthalmology, Program in Neuroscience University of Colorado, Aurora, CO, United States

Background: B cells play an important role in multiple sclerosis (MS), and the understanding of B cell trafficking is highly relevant for defining the role of B cells in MS pathogenesis. Natalizumab and fingolimod are effective MS therapies that interfere with the migration of lymphocytes but exert differential effects on B cells. In order to investigate B cell migration patterns between the periphery and CNS, we compared longitudinal heavy chain (VH) transcriptomes from cerebrospinal fluid (CSF) and peripheral blood (PB) B cells obtained from MS patients receiving either therapy.
Methods: Four MS patients were treated with fingolimod or natalizumab, and their CSF and PB VH transcriptome repertoires were assessed at baseline and after 6 months of treatment. VH repertoires were generated from FACS sorted CSF and PB B cell populations by next generation deep sequencing (Illumina MiSeq) using barcoded primers with unique molecular identifiers.
Results: We established clonal relationships between CSF and PB B cells at baseline and after 6 months treatment in 3 out of 4 fingolimod- and 4 out of 4 natalizumab-treated patients. The average number of CSF and PB B cell VH transcriptome clusters correlated with the number of sorted B cells. As expected, VH clusters recovered from natalizumab-treated patients were increased in PB, but decreased in the CSF. In contrast, the number of B cell VH clusters decreased in the PB but varied in the CSF with fingolimod therapy. Comparative analyses of clonal overlap between CSF and PB B cell clusters revealed reduced overlap under natalizumab treatment (9% at baseline, 4% under treatment) and increased overlap under fingolimod therapy (7% at baseline, 25% under therapy). PB VH clusters showed significantly greater overlap following natalizumab therapy (17%) than following fingolimod therapy (1%). CSF VH clusters overlapped with similar frequency (3.8% following natalizumab therapy and 5.8% following fingolimod therapy).
Conclusions: Our findings suggest that natalizumab treatment might diminish but not completely block the migration of B cells into the CSF. Fingolimod appears to significantly reduce peripheral blood B cell numbers and clonal populations. Surprisingly, these B cells seem to continue to exchange across the blood brain barrier. Additional effects of fingolimod on CNS germinal center activity and B cell exit from the CNS are under investigation.

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P1192

Autologous haematopoietic stem cell transplantation and it`s impact on patient`s quality of life

M. Smilowski, L. Szczechowski, G. Helbig, M. Krawczyk-Kulis, S. Kyrcz-Krzemien
Department of Hematology and Bone Marrow Transplantation, Silesian Medical University, Katowice, Poland

Background: Quality of life (QoL) in multiple sclerosis (MS) patients is a very important issue depending on disability status, fatigue and mental health. Autologous haematopoietic stem cell transplantation (AHSCT) which is a therapeutic approach for patients with active relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) who failed the I- and II- line therapy is considered improving the patient`s QoL.
Objectives: The aim of this study was to evaluate the QoL and fatigue for RRMS/SPMS patients treated with AHSCT in a two-year follow-up as well as to assess the relationship with neurological disability status.
Methods: 57 patients with refractory RRMS (53 patients) and SPMS (4 patients) met the eligibility criteria for AHSCT and completed a 2 year follow-up. All patients were involved to the study according to the guidelines of the European Group for Blood and Marrow Transplantation (EBMT) 2012. The patient`s QoL was evaluated using MSIS-29 and MusiQol questionnaire. The fatigue was evaluated using MFIS. All above mentioned scales are validated for polish population. The disability status was assessed using Expanded Disability Status Scale (EDSS). The examination was performed before AHSCT, and 6, 12 and 24 months thereafter.
Results: The mean MSIS-29 score before AHSCT was 86. In the 6, 12 and 24 months follow-up of AHSCT - the mean score was 78, 66 and 62 respectively. The mean MFIS score before AHSCT was 36 and after treatment it decreased to 28, 24 and 21 after 6, 12 and 24 months respectively. The MusiQoL score before AHSCT was 45, and decreased to 36, 31 and 29after AHSCT. We noticed improvement in EDSS score (from 6.0 before AHSCT to 5.25 after 24 months observation). A positive correlation between EDSS and MSIS-29, MusiQoL and MFIS was observed.
Conclusions: Treatment with AHSCT is a promising option for active RRMS and active SPMS for patients who failed the I- and II- line therapy and and has a significant impact on QoL.

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P1193

Using cells to cure disease: Tolerogenic dendritic cells for the treatment of MS

W.-P. Lee[1], M. De Laere[1], B. Willekens[2], G. Nijs[3], P. Cras[2], E. Martinez-Caceres[4], Z.N. Berneman[1,3,5], N. Cools[1,3]
[1]Laboratory of Experimental Hematology, University of Antwerp, Wilrijk, [2]Department of Neurology, [3]Center for Cell Therapy and Regenerative Medicine, Antwerp University Hospital, Edegem, Belgium, [4]Germans Trias i Pujol University Hospital and Research Institute, Badalona, Spain, [5]Department of Hematology, Antwerp University Hospital, Edegem, Belgium

While emerging evidence indicates that dendritic cells play a central role in the pathogenesis of multiple sclerosis (MS), their modulation with immunoregulatory agents provides prospect of using dendritic cells as disease-modifying therapy. Indeed, since the introduction in the clinic in 1996, the clinical benefit of dendritic cell-based therapy has been well documented in numerous clinical trials in patients with cancer and infectious diseases. More recently, tolerance-inducing or tolerogenic dendritic cells (tolDC) also became a promising immunotherapeutic tool for restoring immune tolerance in several autoimmune diseases including MS. To guarantee utmost patient safety, clinical trials using cell-based medicinal products such as tolDC need to be conducted under stringent good manufacturing practice (GMP) guidelines and regulations defined by the European Union and the US Food and Drug Administration. In line with these rules and regulations, we report here a standardized method for the generation of tolDC according to GMP guidelines. Critical parameters including identity, viability, cell yield and potency were assessed. In doing so, specification limits for the final drug substance were determined using statistical process controls. For this, the results from the qualification batches following the ex vivo tolDC generation protocol were determined. In brief, our results reveal that tolDC display a maturation-resistant phenotype, indicated by a reduction of 35% or more in the upregulation of the expression of costimulatory markers as compared to control DC following cytokine-induced acivation. For functional release, tolDC should induce a reduction of at least 65% in IFN-gamma production by co-cultured T cells as compared to control DC.

In conclusion, a reproducible method for the generation of human tolDC according to GMP guidelines is described with minimal risk of contamination and reduced process time. Our specifications regarding tolDC identity and potency allign with the consensus view of the international community of investigators active in the field of tolDC research for negative vaccination. Recently, we received approval from the national competent authorities to test the safety of administering tolDC in patients with MS in a first-in-human clinical trial.

Disclosure

The authors have nothing to disclose.

P1194

The efficacy of intravenous immuneglobulin for preventing relapses in neuromyelitis optica and its spectrum disorders

H. Kim, Y.-M. Lim, J.-Y. Jin, K.-K. Kim
Departments of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

The efficacy of intravenous immune globulin (IVIG) for preventing relapses in neuromyelitis optica (NMO) and its spectrum disorders (NMOSD) has been investigated in a limited number of studies. The purpose of this study was to determine the effectiveness of IVIG in the prevention of NMO/NMOSD relapses. We identified 40 NMO-IgG-positive NMO/NMOSD patients who were treated with regular IVIG infusions. Five patients were excluded due to short follow-up periods (< 6 months), and the remaining 35 patients (34 women and 1 man; median age 44 years) were included. The outcome was evaluated based on decrement in the number of relapses, annualized relapse rates (ARR),

and expanded disability status scale (EDSS) scores before and after treatment. IVIG (0.4g/kg/day) were infused every 2 to 3 months. The median duration of treatment was 3.0 years (range, 0.5 to 9.3 years). The median number of infusions was 18 (range, 3 to 53). Before beginning of IVIG, 17 patients (49%) received plasma exchanges for the treatment of acute relapse. 15 patients discontinued IVIG infusions after a median period of 1.5 years (range, 0.5-5.4 years). The median disease duration at the start of IVIG treatment was 4 years (range, 0.3 to 13 years). Median number of relapses prior to IVIG initiation was 4 (range, 1 to 14 relapses) with median ARR of 1 (range, 0.3 to 4.0). Median number of relapses and median ARR significantly decreased from 4.0 to 1.0 (p=0.000) and 1 to 0.3 (p=0.000) respectively. 12 patients (34%) remained free of relapses. After discontinuation of IVIG, recurrence was observed in 5 patients (33%). The median EDSS score was 3.5 at the IVIG initiation (range, 0-8.5) and 3.5 at last follow-up (range, 0-8.5). Median EDSS on IVIG remained unchanged (p=0.805). The EDSS scores stabilized in 16 patients (46%) and improved in 11 patients (31%). Relapse rates decreased and disability stabilized or improved in 27 patients (77%). In our study, regular maintenance therapy with IVIG reduced the relapse frequency and stabilized or improved disability. Our results suggest that IVIG may be an effective therapy for the prevention of relapse in NMO/NMOSD. Further randomized controlled trials are necessary to prove the effectiveness of IVIG in the treatment of NMO/NMOSD.

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P1195

Phase 1b, open label study of ublituximab in acute relapses of neuromyelitis optica spectrum disorder

M.A. Mealy[1], M. Levy[2]
[1]Neurology, [2]Johns Hopkins University, Baltimore, MD, United States

Background: Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disease targeting the spinal cord and optic nerve leading to paralysis and blindness. The pathology of acute NMOSD lesions demonstrates a robust humoral response with significant perivascular antibody (IgG and IgM) deposition. The standard of care for acute NMOSD lesions is geared towards suppressing the immune response with steroids and/or plasmapheresis as quickly as possible. In order to minimize inflammatory-mediated damage, we tested a CD20 B-cell depleting monoclonal drug, ublituximab, added to current standard of care.
Methods: We conducted an open-label phase 1b safety and proof-of-concept trial in 5 subjects with NMO-IgG seropositive NMOSD who presented with acute transverse myelitis and/or optic neuritis. In addition to treating acutely for 5 days with 1 gram of daily intravenous methylprednisolone, we infused 450 mg intravenous ublituximab. The primary outcome measure was safety, and the secondary efficacy measures are change in Expanded Disability Scale Scores (EDSS) and timed 25-foot walk.
Results: Three NMOSD subjects have been enrolled thus far, all of whom presented with acute transverse myelitis. Ublituximab proved safe in all 3 subjects with no serious adverse events. Two subjects had an infusion-related body pain amenable to acetaminophen. One subject had an acute lymphopenia following the infusion that resolved over the next few days. EDSS scores dropped from a mean of 7.1 on admission to 6.8 on day +5. Two of the three subjects required escalated therapy with plasma exchange due to persistent significant deficits on day +5.
Conclusions: Ublituximab is a safe add-on therapy for NMOSD patients presenting with acute relapses. Preliminary evidence suggests a promising benefit with ublituximab in reducing damage and improving outcomes. A placebo-controlled trial is necessary to confirm these findings.

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P1196

Intense immunosuppression followed by co-transplantation of hematopoietic and mesenchymal cells for multiple sclerosis

A. Uccelli[1], G. Ferrara[1], F. Ivaldi[1], D. Currò[1], N. Kerlero de Rosbo[1], A. Laroni[1], F. Gualandi[2], G.L. Mancardi[1]
[1]University of Genoa, [2]Bone Marrow Transplantation Unit, IRCCS AOU San Martino IST, Genoa, Italy

Stem cells are considered a possible source of tissue repair in multiple sclerosis (MS) and both hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) are being considered promising therapeutic approaches in MS. As single treatments, both HCS and MSC ameliorate experimental autoimmune encephalomyelitis (EAE), the model for MS. Besides its certain immunosuppressive properties, intense immunosuppression followed by HSC transplantation could result in a resetting of the immune system enabling recovery of tolerance to self-antigens. Treatment with MSC ameliorates EAE through modulation of the peripheral immune response to myelin antigens and CNS repair promotion. We propose that in EAE double transplantation with HSC and MSC could promote hematopoietic engraftment and accelerate lymphocyte recovery thereby ameliorating disease course and survival from intense immunosuppression associated with the HSC transplantation protocol. We have used relapsing-remitting (RR) EAE in mice to investigate this possibility. While the effect of HSC in this model has not been investigated, we have previously shown the beneficial effect of MSC in RR-EAE. HSC treatment resulted in a drastic reduction of clinical disease expression during the early phase of disease, but the treated mice relapsed to the same extent as the untreated mice. There was no apparent difference in EAE clinical course between mice treated with HSC alone and HSC-treated mice co-transplanted with MSC. To analyze the hematopoietic engraftment and immunoreconstitution, we quantified the circulating immune cells in naïve and EAE-affected mice treated or not with

HSC or HSC/MSC. Lymphocyte recovery did not differ in cotrasplanted mice in comparison with HSC-treated mice. Analysis of pro- and anti-inflammatory cytokines in serum during the early recovery phase revealed that IL4 was significantly elevated in cotransplanted mice, as compared to mice treated with HSC alone. Based on these data, we cotranspanted with autologous HSC and bone-marrow derived MSC two patients with an aggressive form of MS not responding to conventional therapies. One patients died following sepsis during the aplastic phase occurring at day 10 post-transplant. The other patient fully recovered improving by 4 EDSS points 16 months after transplantation. Clinical implications of these results will be discussed.

Disclosure

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P1197

Lower relapse rates with natalizumab as compared with fingolimod as second-line treatment in relapsing-remitting multiple sclerosis

C. Lienert[1], P. Benkert[2], S. Beer[3], P. Hänni[4], M. Pardini[5], M. D'Souza[2], T. Derfuss[2], J. Kuhle[2], L. Kappos[2], Ö. Yaldizli[2]
[1]Rheinburg Klinik, Walzenhausen, [2]University Hospital Basel, Basel, [3]Kliniken Valens, Valens, [4]Schweizerische Versicherungskasse, Solothurn, Switzerland, [5]Universita di Genova, Genova, Italy

Background: Placebo controlled phase III trials have shown superiority of fingolimod and natalizumab on clinical and MRI two year outcomes. No randomized controlled trial compared fingolimod and natalizumab in relapsing-remitting(RRMS) directly.
Objective: To compare clinical outcomes in patients with RRMS receiving fingolimod or natalizumab as second line disease modifying treatment(DMT) in a large observational study in Switzerland.
Methods: Data were derived from the Swiss Federation for Common Tasks of Health Insurances that controls reimbursement of DMT prescription in Switzerland. Inclusion criteria were: RRMS, switch to fingolimod or natalizumab after DMT with Interferon Beta or Glatiramer aceteate for at least one year and one or more relapses in the year prior to switch. Patients treated with fingolimod or natalizumab were 1:1 propensity score matched using age, gender, disease duration, Expanded Disability Status Scale(EDSS), relapses in the previous year, time to last relapse, previous DMT, number of and time on previous DMTs as baseline matching characteristics. Quality matching was assessed using the analysis of standardized differences. Time to relapse and time to one-year confirmed EDSS progression data were calculated using Kaplan-Meier curves. Patients who discontinued or switched DMT were censored.
Results: In total, 438 patients were included: 219 fingolimod vs. 219 natalizumab treated; 74.4% were female, mean age 38.2±10.2 and disease duration 7.7±6.6 years, median EDSS 3.0(IQR 2.0-3.5), number of relapses in the previous year 2.0±2.3. Proportions of relapse-free patients on fingolimod and natalizumab were 76% vs. 88% after 1 year, 64% vs. 83% after 2 years and 60% vs. 78% after 3 years, respectively. Time to relapse was shorter with fingolimod vs. with natalizumab(HR: 0.50; 95% CI: 0.34-0.73; p< 0.001). EDSS data were complete in 132 patients with natalizumab and 132 patients with fingolimod. The cumulative proportions of patients with EDSS progression on fingolimod vs. natalizumab were 2.3% vs. 4.2% after 1 year, 6.4% vs. 10.8% after 2 years, 9.6% vs. 17.6% after 3 years, respectively. Time to one-year confirmed EDSS progression was similar in both treatment groups(HR: 1.67; 95% 0.74-3.77; p=0.215).
Conclusions: In clinically active RRMS switch from Interferon Beta or Glatiramer acetate to natalizumab was associated with lower relapse-rates vs fingolimod over three years. No difference with regard to disability progression was observed.

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P1198

Mitoxatrone treatment in MS patients with Secondary Multiple Sclerosis. A six-year follow-up. Evaluation of adverse effects and impact on disability

M.E. Evangelopoulos, P. Katsika, P. Koutsoudaki, G. Koutsis, E. Andreadou, M. Anagnostouli, N. Nianiakas, C. Kilidireas
Neurology, Eginition University Hospital, Athens, Greece

Mitoxantrone (MTX) represents a treatment option for the stabilization of patients with secondary progressive multiple sclerosis (SPMS). Cardiac toxicity and malignancies are the more serious adverse effects

Methods: One hundred patients with Secondary Progressive Multiple Sclerosis (mean EDSS 5.5±1.2) were treated with MTX. Demographic and MRI data, clinical course and adverse effects were evaluated. All patients were treated with 12mg/m^2 MTX every three months. MTX dose was adjusted in case of leucopenia after the first dose.

All patients were submitted to M-mode and color Doppler echocardiography, prior to inclusion and every three months before MTX administration. Measurements of the left and right ventricular diastolic and systolic dimensions were obtained and the LV ejection fraction was calculated. Blood cells counts were monitored 10 and 20 days after MTX treatment

Results: One hundred patients, EDSS 5±2 were treated with MTX and received 7±2 infusions All patients received pretreatment with ondansetron. A stabilization of disability progression and a slight improvement in disability was found in patients with EDSS < 6. White blood cells decreased significantly 10 days after MTX treatment (3599 ± 830) but increased again 20 days after treatment (5400 ± 1200). One female patient 45 years old presented with severe leucopenia after 10 MTX infusions without any signs of infection. The bone-marrow biopsy revealed promyelocytic leukemia.

Two patients demonstrated a significant reversible decrease in ejection fraction following second infusion and MTX was discontinued. Diastolic dysfunction was found in 8 patients after the 5th infusion. All other patients had cardiac ejection fraction values within normal values (63,67±5.4). All pre-menopause female patients developed menstrual disorder. Ten patients developed recurrent urinary tract infections during MTX treatment.

Conclusion: A stabilization of disability was noted during MTX treatment. One patient (1%) presented with leukemia. During MTX treatment a careful follow up is mandatory.

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P1199

Treatment of refractory tumefactive multiple sclerosis with high-dose iv methotrexate with leucovorin rescue

R.N. Narayan[1], S.C. Beh[1], E. Kildebeck[1], A. Desena[1], D. Schell[2], E.S. Rowe[2], V. Rowe[2], D. Burns[3], L. Whitworth[4], T.C. Frohman[1], B. Greenberg[1], E.M. Frohman[1]
[1]Neurology, UT Southwestern Medical Center, Dallas, TX, [2]Neurology, Rowe Neurology Institute, Lenexa, KS, [3]Pathology, [4]Neurosurgery, UT Southwestern Medical Center, Dallas, TX, United States

Background: Refractory tumefactive MS is a rare and severely disabling disease variant that warrants aggressive immunotherapy. The use of high dose intravenous methotrexate in this setting has not been adequately described in medical literature.

Objective: To report the response to high-dose intravenous methotrexate with leucovorin rescue (HDMTX-LR) in tumefactive multiple sclerosis refractory to conventional immunotherapy.

Methods: A retrospective descriptive analysis of 2 patients with severely disabling tumefactive multiple sclerosis who received HDMTX-LR after they failed conventional immunotherapy. Clinical assessments were done at 1 month, 3 months and 6 months using the EDSS scores and MR images with gadolinium were compared prior to and after treatment.

Results: There were no major adverse effects reported by either of our patients. The EDSS improved from 7.5 to 4.5 for patient 1 and from 9.5 to 7.5 for patient 2 at 1, 3 and 6 months respectively. Patient 1 improved from being wheelchair-bound to ambulation without aids and Patient 2 improved from being bed-bound to being able to use a rolling walker. Of note, patient 2 had developed left sided hemiplegia and global aphasia while being on steroids, plasma exchange and mitoxantrone and was noted to have completely normal language function 1 month post-treatment with HDMTX-LR. Resolution of vasogenic edema, improvement of abnormal FLAIR/T2 signal and resolution of gadolinium-enhancement was observed on follow up MRIs of both these patients after treatment. Brain biopsy (right frontoparietal lesion) of Patient 2 was performed before HDMTX-LR treatment, in order to rule out presence of an underlying neoplastic process.

Conclusion: In treatment-recalcitrant fulminant tumefactive MS, HDMTX-LR was observed to be a safe and highly effective treatment, producing the rapid and near complete cessation of disease activity. A brain biopsy early in the course of such syndromes, may reveal 'relative axonal sparing' which may be an important prognostic signature suggesting the need for intensive therapy to mitigate permanent tissue damage and compromise of neurologic capabilities.

Disclosure

Ram Narayan,Shin Beh, Eric Kildebeck, Allen Desena, Doug Schell and Elizabeth Rowe have nothing to declare.
Vernon Rowe -The application of the HDMTX-LR protocol described in our study was patented by one of the authors (VR); specifically, US 6,903,100 B2, title, Use of regularly scheduled high dose intravenous methotrexate therapy, with interim administration of immunomodulatory agents, to treat multiple sclerosis and other diseases of the central nervous system, issued in 2005, and owned by the MidAmerica Neuroscience Research Foundation, a 501c(3).
Dennis Burns has nothing to declare.
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Neuroprotection

P1200

Interleukin-4 enhances the survival rate of multiple sclerosis-patient derived neurons under oxidative stress

S. Hirschberg, B. Gisevius, M.G. Massa, N. Schneiders, R. Gold, A. Haghikia
Department of Neurology, Ruhr University Bochum, Bochum, Germany

Background: It was recently observed that T-cell mediated neuroprotection after CNS injury can be assigned to the direct action of Interleukin-4 (IL-4) on neurons. In order to study this phenomenon in detail and on a more human- and Multiple Sclerosis (MS)-specific context, we used human primary neurons (hPNs) generated from MS patients' renal cells via an induced pluripotent stem cell (iPSC) method. These hPNs, carrying all the genetic characteristics of MS patients, were analysed for cell survival and their regenerative behaviour after injury in the presence of IL-4.
Obejctive: This study focuses on the direct effect of IL-4 on human MS patient-specific neurons under oxidative stress and axonal transection conditions, characteristic cellular stressors in the context of MS.
Methods: MS patient-derived hPNs were used for an apoptosis assay with H_2O_2 acting as the cellular stressor, mimicking inflammatory conditions. Cells were also used for analysing axonal regrowth and calculating a general growth potential after axotomy. Experiments were done in the presence of IL-4 in comparison to control. Additionally, the potential effect of IL-4 on axonal mitochondrial transport was assessed.
Results: hPNs treated with 25 µm H_2O_2 for 24 hours resulted in a high apoptosis rate, which was significantly reduced by the addition of 250 pg/ml IL-4. However, while IL-4 treatment did not significantly alter the axonal regrowth and growth potential of hPNs after mechanical axonal transection, 24-hours IL-4 pretreatment slightly enhanced growth response following injury. Finally, one hour of IL-4 exposure to unstressed hPNs resulted in a significant decrease in average retrograde mitochondrial speed as compared to cells not exposed to IL-4.
Conclusion: These results demonstrate a highly relevant neuroprotective effect of IL-4 in the context of oxidative stress in a human MS disease-in-a-dish model, though its effect on axonal transection remains to be elucidated. Furthermore, the observed retrograde mitochondrial velocity alteration demonstrates the potential of IL-4 in modulating important metabolic functions in MS derived neurons.

Disclosure

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P1201

Mesenchymal stem cells induce the acquisition of neuroprotective and reparative traits by cortical astrocytes

A. Voulgari-Kokota[1], T. Vigo[1], A. Buffo[2], N. Kerlero de Rosbo[1], A. Uccelli[1]
[1]Dep. Neurosciences, Ophtalmology, Genetics and Maternal and Child Health, University of Genoa, Genoa, [2]Dep. of Neurosciences, University of Torino, Torino, Italy

Mesenchymal stem cells (MSC) display immunomodulatory properties exerted on cells of both adaptive and innate immunity and these features, together with their reported ability to protect neural cells from death and foster neural repair, account for their therapeutic effect on experimental autoimmune encephalomyelitis (EAE), a mouse model for multiple sclerosis (MS). In EAE, neuroprotective and neurotrophic activities of transplanted MSC appear provided indirectly through instructive interactions with host cells, including CNS cells. However, as yet investigations on the interactions between MSC and CNS have mainly focused on microglia and neural progenitor cells, largely neglecting other cellular players such as astrocytes, despite their crucial role in the CNS reaction to damage and in the regulation of neuronal functioning and plasticity. Upon damage, astrocytes orchestrate nervous tissue healing and remodelling, including axonal sprouting and modulation of re-myelination. Further, in defined injury conditions, astrocyte subsets also acquire neural stem cell properties and display spontaneous neurogenic activity, becoming fully capable of exerting 'bystander' effects and actions supportive of neural plasticity that are typical of undifferentiated progenitors.
Here, we co-cultured cortical astrocytes with MSC in the presence of interferon gamma (IFN-gamma) to assess changes in pro-inflammatory, neuroprotective and stemness functions of astrocytes. Our data show that MSC significantly reduced the expression of Ccl2, which sustains immune cell infiltration in EAE, and impaired the expression of endothelin-1, which negatively regulates remyelination. Moreover, MSC attenuated IFN-gamma-dependent astrogliosis and induced the release of factors that protect neurons from N-methyl-D-aspartate (NMDA) induced death. Finally, we showed that IFN-gamma induced astrocyte de-differentiation, resulting in formation of multipotent astrospheres *in vitro*, and that MSC enhanced the proliferation of astrosphere-forming cells in which the activity of Notch pathway was reduced, possibly leading to the promotion of a latent pro-neural program.
These results suggest that in an inflammatory milieu, MSC may drive the astrocytic phenotype toward the acquisition of an anti-inflammatory, protective and pro-reparative phenotype, possibly able to mitigate the pathological outcome of EAE.

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P1202

Revealing neuroprotective properties of axon-myelin interactions: Its impact on glutamate-mediated axonal damage in MS

A.L. Viinetto[1], A. Palandri[1], V. Rozes Salvador[1], J.I. Rojas[2], L. Patrucco[2], E. Cristiano[2], P.H. Lopez[3,4]
[1]Neurobiologia, INIMEC-CONICET-UNC, Córdoba, [2]Centro de Esclerosis Múltiple de Buenos Aires (CEMBA), Hospital Italiano de Buenos Aires, Buenos Aires, [3]Neurobiología, INIMEC-CONICET-UNC, [4]Facultad de Psicología, Universidad Nacional de Córdoba, Córdoba, Argentina

Recent studies propose to Myelin-associated glycoprotein (MAG) as a functional receptor in oligodendrocytes (OLs), acting as a docking platform for different signal transduction pathways. However the impact of MAG activation in OLS remains elusive. We studied the effect of antibody-mediated MAG activation in OLS using a well characterized anti-MAG mAb that induces MAG crosslinking/activation of intracellular signaling.
Methods: A MOG-induced animal model of chronic inflammatory demyelination characterized by the presence of extensive axonal degeneration and OLs cultures (primary or derived from CG4 cell line) were used to study the role of extracellular glutamate (Glu) uptake induced by antibody-mediated activation of MAG at the cell membrane of OLs. Monitoring of Glu concentrations in OL cultures was studied by using Föster resonance energy transfer (FRET)-based Glu biosensors.
Results: We found that in primary OLs cultures mAb-mediated MAG activation induce: i) increase resistance to oxidative stress caused by Glu overload, ii) increase Glu uptake by OLs measured by Glu biosensors with differential cellular expression, iii) activates antioxidant defenses associated with a PKC-dependent activation/translocation of *nuclear* factor *erythroid-related factor 2* to the nucleus analyzed by immunofluorescence and confocal microscopy, iv) increase the levels of reduced glutathione (GSH), the main cellular antioxidant element in a Xc^- cysteine/Glu antiporter and Glu transporters-dependent manner and v) dramatically increase neuronal and glial survival exposed to Glu overload in cerebellar organotypic cultures. The impact of mAb-mediated MAG activation was then analyzed in the animal model of EAE induced by MOG. Compared to IgG isotype-matched control groups, intraperitoneal treatment with anti-MAG mAb prior to disease onset significantly delays the onset of clinical symptoms, ameliorates clinical expression of the disease, reduce axonal damaged of myelinated sensory axons from spinal cord (analyzed by electron microscopy) and reduce the amount of IL-17 secreted by peripheral mononuclear cells.
Conclusion: these results allow us to propose OLs as critical modulators of high extracellular Glu concentration in white matter. This event results critical toward understanding demyelination-associated axonal damaged induced by Glu toxicity, opening a new opportunity for therapeutic intervention in MS.

Disclosure

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P1203

MS-SMART trial design and recruitment status: a multi-arm phase IIB randomised double blind placebo-controlled clinical trial comparing the efficacy of three repositioned neuroprotective drugs in secondary progressive multiple sclerosis

P. Connick[1], D. Miller[2], S. Pavitt[3], G. Giovannoni[4], C. Wheeler-Kingshott[2], C. Weir[5], N. Stallard[6], C. Hawkins[7], B. Sharrack[8], G. Cranswick[9], S. Chandran[1], J. Chataway[2], The MS-SMART Trialists
[1]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, [2]Queen Square Multiple Sclerosis Centre, NMR Research Unit, Department of Neuroinflammation, UCL Institute of Neurology, University College London, London, [3]Leeds Institute of Health Sciences, University of Leeds, Leeds, [4]Department of Neurology, Barts and The London NHS Trust, The Royal London Hospital, London, [5]Edinburgh Clinical Trials Unit, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, [6]Statistics and Epidemiology, Division of Health Sciences, Warwick Medical School, University of Warwick, Warwick, [7]Keele University Medical School, Royal Stoke University Hospital, Keele, [8]Department of Neurology, Royal Hallamshire Hospital, Sheffield, [9]Edinburgh Clinical Trials Unit, University of Edinburgh, Edinburgh, United Kingdom

Background: Drug repurposing (repositioning) provides an attractive paradigm to accelerate academic-led development of neuroprotective therapies for secondary progressive multiple sclerosis (SPMS), where there is no treatment. Having systematically reviewed all published animal and human literature to identify the leading candidates, we designed a multi-arm phase IIB trial as an efficient way to evaluate neuroprotective efficacy in SPMS.
Objectives: We will test if three candidate drugs chosen from an extensive search of published animal and human literature, will ultimately be effective in slowing the rate of brain volume loss in SPMS measured by MRI-derived atrophy rate against placebo.
Methods: The MS-SMART trial (ClinicalTrials.gov NCT01912059) is a multi-centre, multi-arm, double-blind, placebo-controlled phase IIB randomised controlled trial. 440 patients with worsening SPMS are being recruited across 13 UK sites. Patients with an EDSS score of 4.0-6.5, not on DMT, are randomised 1:1:1:1 between placebo, amiloride 5mg bd, riluzole 50mg bd and fluoxetine 20mg bd. Patients will be followed for 96 weeks with outcome data collected after 0, 24, 48 and 96 weeks. The primary endpoint is brain atrophy (percent brain volume change) on structural MR imaging at 96 weeks. Secondary endpoints are clinician and patient reported outcome measures, including Multiple Sclerosis Impact Scale v2 and Multiple Sclerosis Walking Scale v2. Exploratory endpoints include: grey and white matter, cervical cord atrophy, Magnetic Transfer Ratio and

MR spectroscopy cerebrospinal fluid biomarkers and Optical Coherence Tomography (OCT).
Results: Recruitment has commenced since December 2014. Currently 321 patients have been randomised. The mean (sd) baseline features are: age 54yrs (7), duration of MS 22yrs (10), duration of SPMS 7yrs (5), and EDSS 5.9 (median 6). Significant co-morbidity (⩾10%) includes: hypertension, hyperlipidaemia and hypothyroidism.
Conclusion: The cohort recruited is representative of the SPMS population. MS-SMART trial opens up a new platform for more efficient trial design and implementation in progressive MS and will report in 2018.

Disclosure

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P1204

Mixed-lineage kinase 3 inhibitor URMC-099 protects hippocampal synapses in experimental autoimmune encephalomyelitis

M.J. Bellizzi[1], H.A. Gelbard[2]
[1]Dept. of Neurology and Center for Neural Development and Disease, University of Rochester, [2]Center for Neural Development and Disease, University of Rochester Medical Center, Rochester, NY, United States

Background: Gray matter neuroprotection is a crucial component of treatment to prevent cognitive impairment and progressive disability in multiple sclerosis (MS). Neuronal injury in MS gray matter is associated with microglial activation, and studies using *in vitro* and animal models suggest that microglia-derived inflammatory molecules promote synaptic injury independent of demyelination or the severity of white matter inflammation. URMC-099, a brain-penetrant inhibitor of mixed-lineage kinase 3 (MLK3), has been shown to attenuate microglial activation and pro-inflammatory cytokine production and protect neurons in models of HIV-1-associated neuroinflammatory disease. We hypothesized that URMC-099 would protect neurons in an experimental autoimmune encephalomyelitis (EAE) hippocampal model of MS gray matter injury.
Methods: C57BL/6 mice with EAE induced by direct immunization with MOG35-55 peptide were randomized to 12 days of treatment with URMC-099 (10 mg/kg i.p. twice daily) or vehicle after the onset of motor deficits. Using fluorescent immunostaining of fixed brain sections and grid confocal microscopy, we measured effects of URMC-099 vs. vehicle on integrity of synapses, markers of microglial activation, and microglia-synapse interactions in hippocampal area CA1 of mice with EAE and sham-immunized controls.
Results: URMC-099 treatment beginning after disease onset had little impact on severity of motor deficits but prevented hippocampal synapse loss in EAE, maintaining PSD95-positive synaptic puncta at levels similar to controls versus a 24% decrease in vehicle-treated EAE mice. URMC-099 attenuated microglial activation in EAE, reducing microglial CD68 expression to control levels, and reduced the engulfment of PSD95-positive structures by microglia in EAE hippocampi.
Conclusions: URMC-099 attenuates microglial activation and protects against excitatory synapse injury in the hippocampus of EAE mice, a model that recapitulates the hallmarks of MS gray matter degeneration. With ability to restore microglial homeostasis and preserve neuronal integrity after disease onset, URMC-099 may provide a strategy for adjunctive neuroprotective treatment in MS.

Disclosure

Matthew Bellizzi has nothing to disclose.
Harris Gelbard holds patents for URMC-099 and related kinase inhibitors and their methods of use, and serves as the chair of the Scientific Advisory Board for Wavodyne Therapeutics, which holds licensing rights for therapeutic development of URMC-099.
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P1205

Regenerative potential of fumarate treatment and its impact on Nrf2-downstream signaling: crosstalk of immune and degenerative mechanism

A. Blusch[1,2], C.F. Vogelaar[3], R. Nitsch[3], R. Gold[2], G. Ellrichmann[2]
[1]International Graduate School of Neuroscience, Ruhr-University Bochum, [2]Neurology, St Josef Hospital, Ruhr University Bochum, Bochum, [3]Institute of Microanatomy and Neurobiology, Johannes Gutenberg-University, Mainz, Germany

Background: The fumaric acid ester dimethyl fumarate (DMF) is an established disease modifying therapy in multiple sclerosis (MS). DMF exerts neuroprotective effects via induction of the

transcription factor "nuclear factor E2-related factor 2" (Nrf2) and detoxification pathways.
Goals: We investigate the role of fumarates on axon growth and regeneration in wild type and Nrf2 knock-out mouse dorsal root ganglia (DRG) model to verify the neuroprotective potential.
Methods: Utilizing DRG explants of wild type and Nrf2 knock-out mice, we examine axon regeneration after in vitro transection under the influence of fumarates. We repeat experiments under conditions of oxidative stress. Transferring the techniques into a central nervous system we focus the cortex layer V tissue. Getting an idea of downstream mechanisms of fumarates, we analyse effects on mRNA level using qPCR.
Results: Fumarate treatment, dimethyl fumarate (DMF) and monomethyl fumarate (MMF), promotes axon growth and regeneration. 10µM DMF improved growth cone regeneration of transected DRG axons significantly ($p \leq 0.05$) after 4 hours (h) incubation (DMF 52.78 % vs control 24.42%) and 24 h of incubation (DMF 53.37% vs control 26.82%). 5µM MMF treatment resulted in significant higher numbers of growth cones in relation to the number of transected growth cones after all different incubation timepoints (4h: MMF 62.3% vs control 36.07%; 24h: MMF 71.14% vs control 39.6%; 48h: MMF 50.66% vs control 33.08%; $p \leq 0.05$;).

First analysis under conditions of oxidative stress (500µM H_2O_2) underlines the neuroprotective potential of fumarates. Regarding current number of n=1 experiment, significances are not obvious by now.
We detected a significant higher expression of NQO-1 (NAD(P)H dehydrogenase quinone 1) as a target gene in downstream pathways in 4h DMF treated DRGs compared to control ($p \leq 0.05$). However, mRNA level of the other target genes, named HO-1 (heme oxygenase 1), Nrf2, TXNRD (thioredoxin reductase), Pik3ca (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) and Pi3r4 (phosphoinositide-3- kinase, regulatory subunit 4), was not significantly influenced normed to GAPDH (Glycerinaldehyd-3-phosphat-dehydrogenase).
Conclusion: Fumarate-induced neuroprotection and the knowledge of downstream mechanisms may lead to new treatment options for both inflammatory diseases such as MS and neurodegenerative diseases (e.g. Parkinson's and Huntington's disease).

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P1206

Impact of dimehtylfumarate on cognitive dysfunction and its correlates in the EAE mouse model

S. Neves, D.R. Pereira, C. Mota, S. Monteiro, R. Ferreira, A.L. Sousa, F. Marques, J.J. Cerqueira
Neurosciences, Life and Health Sciences Research Institute, University of Minho, Braga, Portugal

Cognitive deficits are common in patients with multiple sclerosis. Interestingly, they correlate poorly with white matter inflammatory activity, but seem to be better explained by pathological processes in the grey matter, such as demyelination and axonal damage. Dymethyl fumarate (DMF) is a recently approved MS disease modifying drug which targets both neuroinflammation and neurodegeneration and has the potential to impact cognition in MS. The present study aimed at characterizing the impact of dymethylfumarate in cognition in a mouse model of multiple sclerosis.

Sixteen C57Bl6 11 week-old female mice were administered MOG35-55 to induce single relapse-chronic experimental autoimmune encephalomyelitis (EAE). Between days 18-40, half were treated po bid with DMF, the remainder with vehicle. A group of 18 non-EAE female mice, half treated with vehicle and half with DMF, served as controls. At day 40, all mice were evaluated in a cognitive hippocampal-dependent task (the Morris Water Maze). After cognitive testing, animals were sacrificed and their brains analysed for dendritic tree morphology in the hippocampus using the Golgi method.

DMF treatment had no effect in non-EAE animals. As expected, compared with non-treated EAE mice, treated EAE animals had significantly milder disease course and a significantly better cognitive performance (faster learning), similar to that of non-EAE animals. Importantly, motor performance in the maze was similar between treated and non-treated EAE animals, and significantly different from non-EAE controls, suggesting that the observed cognitive improvement was independent of the impact of treatment on motor abilities. To our surprise, dendritic tree morphology did not differ between groups.

Our results show that dymethylfumarate has an impact in hippocampal-dependent learning that appears to be independent of the effect on dendritic trees.

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P1207

Long term preservation of neurological function in relapsing MS. Natalizumab „walks the walk, hand over hand"

A. Pace, W. Lusher, T. Mihalova, N. Sharaf, P. Talbot, D. Rog
Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, United Kingdom

Background: Post-hoc analyses of data from pivotal clinical trials have suggested that natalizumab may stabilise neurological functioning and slow disability progression in people with multiple sclerosis, as measured by the Expanded Disability Status Scale.
Aim: To determine real-world effectiveness of natalizumab on physical functioning, using:

1. Long-term serial observations from a large cohort of patients monitored at the Greater Manchester Neurosciences Centre, UK.

2. Nine hole peg test (9HPT) and timed 25 metre walk (T25MW) data as meaningful markers of upper and lower limb functioning.

Methods: All patients in Greater Manchester receiving treatment with natalizumab for ⩾2years were included for analysis (N=160). Patients undergo 9HPT and T25MW every 4 weeks before their elective natalizumab infusion. Data was analysed up to the end of October 2015.

Results: Mean T25MW dropped notably from 31.1 at baseline to 24.1 seconds (-22.5%) after 4 weeks, an improvement sustained for 24 months (23.9s). 9HPT measures initially fluctuated but similarly improved in both right (26.9 to 22.2s; -17.5%) and left (29.0 to 24.4s; -15.9%) hands. Considering attrition in numbers, there was no significant deterioration in function in patients who continued on treatment for 48 months (N=74; T25MW 22.0s; (R)9HPT 20.4s; (L)9HPT 21.7s), 60 months (N=52; T25MW 20.2s; (R)9HPT 23.3s; (L)9HPT 25.4s) and 72 months (N=29; T25MW 20.1s; (R)9HPT 22.6s; (L)9HPT 24.5s).

Conclusion: Serial data from clinical practice provide valuable additional evidence that natalizumab protects neurological performance, as quantified by two clinically meaningful measures of limb function, for up to 6 years of treatment.

Disclosure

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Neurorepair

P1208

Randomized controlled pilot trial of domperidone in relapsing remitting multiple sclerosis

W.-Q. Liu[1,2], S. Zhornitsky[1], J. Greenfield[1], R. Pasha[1], G. Cerchiaro Farah[1], Y. Zhang[3], G.B. Pike[3], V.W. Yong[1], L. Metz[1]
[1]Clinical Neurosciences, University of Calgary, Calgary, AB, [2]University of British Columbia, Vancouver, BC, [3]Radiology and Clinical Neurosciences, University of Calgary, Calgary, AB, Canada

Objectives: We are conducting a phase 2, single-centre, randomized, controlled trial comparing domperidone add-on therapy versus no add-on therapy in relapsing remitting multiple sclerosis (RRMS) patients taking disease modifying therapy (DMT) and who have breakthrough lesions identified on MRI monitoring. Our primary objectives are:
(1) to demonstrate that we can recruit to this trial; and
(2) to obtain estimates of the magnitude and variability of lesion repair over 32 weeks.

Background: Prolactin enhances remyelination in animal models but moving to clinical trials is challenged by the lack of a marketed prolactin and lack of a clinical model to evaluate lesion repair, other than possibly optic neuritis. While prolactin can be produced we have chosen to use domperidone, a safe, inexpensive drug marketed to enhance gastric motility because it also raises serum prolactin levels sufficiently to be used off-label to improve lactation.

Methods: Consenting RRMS patients aged 18-60, taking an approved DMT, and shown to have breakthrough gadolinium enhancing lesions on DMT monitoring MRI, will be randomized (2:1) to domperidone add-on treatment 10 mg three times daily or no add-on treatment. After screening and baseline visits, follow-up will be at 6, 16, and 32 weeks. MRI scans will be obtained at baseline, 16 and 32 weeks. In addition to routine MRI sequences, we will evaluate and compare three MRI measures [texture analysis, diffusion tensor imaging (DTI), and magnetization transfer imaging (MTI)] for their ability to measure repair within acute enhancing lesions. We aim to enroll 24 patients over 36 months.

Results: Recruitment is ongoing. Between November 2015 and April 2016 we screened 25 patients; 12 more are scheduled for screening. One patient has been randomized to domperidone and has tolerated treatment without any adverse effects. As expected, the majority of screen failures are due to the absence of enhancing lesions on MRI.

Conclusions: We intend to determine if this trial model is appropriate for studying lesion repair in MS and determine if any of these imaging methods are sensitive enough to measure repair within enhancing lesions. We will present the study design and updated recruitment data. Recruitment was slow in the first few months but many more patients are currently being scheduled for screening. We anticipate that the results from this trial will inform the design of future phase 2 trials of therapies to promote lesion repair in MS.

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Metz, L.M.: nothing to disclose.

P1209

ABT-555, a potential neurorestorative treatment in multiple sclerosis: pharmacokinetic, pharmacodynamic and safety results from phase 1 studies in healthy volunteers and multiple sclerosis patients

B.A.C. Cree[1], G. Giovannoni[2], B.K. Mueller[3], R. Rajagovindan[3], J. Beaver[3], C. Locke[3], M. Rosebraugh[3], S. Goss[3], B. Barger[3], J. Genius[3], G. Haig[3], S.J. Greenberg[3]
[1]University of California, San Francisco, CA, United States, [2]The London School of Medicine and Dentistry, London, United Kingdom, [3]AbbVie Inc., North Chicago, IL, United States

Background: ABT-555 is a fully human, high-affinity repulsive guidance molecule a (RGMa) specific monoclonal antibody. In rodent models of demyelination and nerve injury, ABT-555 demonstrated axon regeneration, neuroprotection, remyelination, and immune modulation. (Mueller. *Mult Scler* 2015;21(11suppl):P582.)

Method: In the single ascending dose (SAD) study, healthy adults were randomized 3:1 to ABT-555 or placebo (5 intravenous [IV] 50 - 1600mg, n=8/group; 1 subcutaneous [SC] dose, n=7). Safety and pharmacokinetic (PK) assessments were performed ⩽140

days post-dose. In the ongoing multiple ascending dose (MAD) study, subjects with relapsing MS (RMS) receive 1 of 5 ABT-555 doses or placebo IV once monthly plus maintenance glatiramer acetate (n=8/group, 3:1 ratio) for 4 months. The effect of ABT-555 on axon and myelin pathophysiology measured by magnetization transfer ratio, fractional anisotropy and radial diffusivity are being assessed. In a PET study, ABT-555's effect on translocator protein (TSPO) expression and thus CNS inflammation is being assessed with [^{11}C]-PBR28 volume of distribution (VT) in brain regions of interest (ROIs) in RMS subjects; Part 1 (n=4, completed), assesses the test-retest variability of VT, and Part 2 (n=14, ongoing) examines the effect of a single dose of ABT-555 on VT in brain ROIs.

Results: In the completed SAD study, a total of 65 adverse events (AE) were reported in 28/47 subjects with no trend in frequency of adverse events with each ascending dose group. The most frequently reported AEs were headache, nausea and local back pain. All treatment-related AEs assessed by the investigator were minor in severity and spontaneously resolved without treatment. There was no discontinuation due to treatment related AEs, nor major dose-related biochemical or hematological alterations. Two subjects had SAEs resulting in death; one due to coronary artery disease and toxicity of multiple illicit drugs and one due to toxicity of cocaine and oxycodone, both determined to be unrelated to ABT-555. The mean plasma half-life ranged from approximately 20 to 40 days with an estimated CSF to serum ratio of approximately 0.2%. In Part 1 of the ongoing TSPO PET study, the intra-subject coefficient of variation of lesion and perilesion VT was estimated to be 15%.

Conclusion: In the SAD study, ABT-555 was well tolerated in healthy subjects up to 1600 mg. PK data were consistent with monoclonal antibody administration and CSF to serum distribution.

Disclosure

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P1210

Voluntary physical activity enhances remyelination in mice after spinal cord demyelination: mechanisms of benefit of exercise for repair

S. Jensen, V.W. Yong
University of Calgary, Calgary, AB, Canada

Objective: To determine whether physical activity leads to the promotion of remyelination in mice after experimental demyelination, and to investigate mechanisms underpinning the benefits of physical activity.

Background: A large body of literature has now established that physical activity promotes wellbeing in multiple sclerosis (MS). However, whether physical activity induces reparative processes including remyelination of a demyelinated plaque is unknown. We evaluated whether mice with spinal cord demyelination have improved remyelinating capacity if these animals were allowed voluntary physical activity after injury. If so, we sought to uncover biological mechanisms underlying exercise-induced repair.

Methods: We induced a focal demyelinating lesion by injection of lysolecithin into the ventrolateral white matter of the murine spinal cord. Mice were singly housed and given free access to an electronically monitored running wheel, which were locked in control animals, immediately after injury until sacrifice at either 3, 7 or 14 days post lesion (dpl). Spinal cord tissues were processed for various analyses.

Results: Immediate access to a running wheel enhances oligodendrocyte generation following a lysolecithin-induced demyelinating insult; we observed a 39% and 30% increase in oligodendrocytes at 7 and 14 dpl, respectively. At 7 dpl, the % of PDGFRα$^+$ progenitors that label for the proliferation marker Ki67 was elevated in the exercise compared to sedentary demyelinated animals ($p< 0.01$). At 14 dpl, these newly formed progenitors functionally differentiate into CC1$^+$ mature oligodendrocytes in active mice. Moreover, exercise increases the capacity for individual oligodendrocytes to form myelin segments resulting in a 2.7 fold elevation in the number of myelinated axons at 14 dpl. Several mechanisms appear to contribute to exercise-enhanced remyelination, including an altered local inflammation, and elevated expression within oligodendrocyte lineage cells of PPARgamma co-activator 1-alpha (PGC1a), a transcriptional co-activator that regulates genes involved in lipid and energy metabolism.

Conclusions: Physical exercise improves white matter regeneration and may help account for activity-enhanced wellbeing in patients with MS.

Disclosure

Sam Jensen and Wee Yong have nothing to disclose

P1211

Teriflunomide enhances oligodendrocyte maturation *in vitro*

M.-S. Aigrot, B. Zalc, C. Lubetzki, B. Stankoff
Institut du cerveau et de la moelle epiniere, Sorbonne Universités, UPMC Univ Paris 06, UMR S 1127, and CNRS UMR 7225, and ICM,, Paris, France

Background: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing remitting multiple sclerosis. To date no direct effect has been reported on central nervous system cells. We investigated in cell culture models the influence of teriflunomide on oligodendroglial cells at various developmental stages.

Methods: Cell cultures enriched in oligodendrocyte precursor cells (OPCs) were derived from rat new-born brain hemispheres. Cultures were maintained in standard culture medium without or with increasing concentration of teriflunomide ranging from 10 nM to 1mM. The influence of teriflunomide on cell migration and shape was analyzed using the XCELLigence® system. OPCs

proliferation was assayed by quantifying the nucleoside analog 5-bromo-2'-deoxyuridine (BrdU) incorporation. OPCs differentiation and maturation was quantified as the percentage of Olig2 positive cells also expressing the tardive MOG marker. Cell survival was evaluated using the MTT assay. The effect of teriflunomide was further investigated on cultures of highly purified OPCs -sorted by flow cytometry from either new-born or young adult PDGF-R alpha-GFP transgenic mice brains.

Results: There was no effect of teriflunomide on OPCs shape, migration, and survival in the range of concentrations tested. By contrast teriflunomide significantly reduced OPCs proliferation in new-born OPCs enriched cultures, with a 41% and 32% decrease at 10 nM and 1 mM, respectively (experiences performed in triplicate, $p< 10^{-4}$ and $p= 10^{-3}$ respectively, Mann Whitney test). Teriflunomide also increased OPCs differentiation toward mature MOG-positive oligodendrocytes, at both 10 nM (86% increase, $p < 10^{-4}$, Mann Whitney test) and 1 mM (62% increase, $p < 10^{-4}$, Mann Whitney test) concentrations. A significant effect on OPCs differentiation was also detected when teriflunomide was applied in cultures of flow-cytometry -purified OPCs from either new-born or adult brain, as measured by the proportion of cells displaying typical differentiated mature oligodendrocytes morphology.

Conclusion: Beyond the well-described effects on adaptive immune cells, teriflunomide can influence oligodendrocyte precursor cells by decreasing proliferation and enhancing differentiation/maturation in vitro. Experiments are on-going to determine whether this effect could result in enhanced myelin formation, and whether this could translate in increased remyelination in vivo in animal models of MS.

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Long-term treatment monitoring

P1212

Long-term efficacy of fingolimod treatment in relapsing-remitting patients who did not respond to interferon treatment

J. Cohen[1], N. Tenenbaum[2], A. Bhatt[3], Y. Chen[2], L. Kappos[4]
[1]Neurological Institute, Cleveland Clinic, Cleveland, OH, [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States, [3]Novartis Healthcare Pvt. Ltd., Hyderabad, India, [4]Neurological Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital Basel, Basel, Switzerland

Background: Fingolimod (FTY) has been shown to reduce clinical and MRI activity in relapsing-remitting patients who switched from interferon (IFN) due to suboptimal treatment response. Assessment of long-term efficacy in this population is an ongoing effort.

Objective: To evaluate the longer-term efficacy of FTY in MS patients who were non-responders to IFNβ-1a treatment over one year in the TRANSFORMS phase 3 trial.

Methods: Patients who received intramuscular IFNβ-1a in the TRANSFORMS core study over 1 year and switched to either 0.5 or 1.25 mg FTY thereafter were classified into responders (R, n=101) and non-responders (NR, n=240). Responders to IFNβ-1a treatment were defined as those patients with none of the following during the core study: confirmed relapses, new/enlarging T2 (neT2) lesions, gadolinium (Gd)-enhancing T1 lesions, or 3-month confirmed disability progression (CDP). Efficacy of fingolimod was evaluated by the annualized relapse rate (ARR, confirmed relapses [defined as ⩾0.5 rise on the Expanded Disability Status Scale (EDSS)/1 point on two functional systems (FS) of the EDSS/ 2 points on one of the FS [excluding Bowel/Bladder/Cerebral FS] and unconfirmed relapses [without EDSS confirmation]) up to 96 months (M) of FTY treatment ($_{M0\text{-}M96}$), annualized rate of neT2 lesions during first 36 months of FTY treatment ($_{M0\text{-}M36}$), and estimated by negative binomial regression model.

Results: Median (min, max) exposures to IFNβ-1a and FTY were comparable between the groups; IFNβ-1a: NR 364 [229, 427] vs. R 365 [333, 407] days; FTY: NR 2064 [1, 2826] vs. R 2223 [1, 2833] days. Patients in the NR vs. R group, were younger (Age, mean±SD: 35.6±8.4 vs. 37.3±8.2 years); prior to enrolment in core study, 36% of NR vs 24% of R had 2-3 relapses, and 33% of NR vs. 24% of R had >3 relapses in the previous 1 and 2 years, respectively. In the NR group, post switch to FTY, ARR (95% CI) decreased from 0.74 (0.628; 0.868) during IFNβ-1a treatment to 0.24 (0.201; 0.292) during $FTY_{M0\text{-}M96}$; annualized rate of neT2 lesions (95% CI) also decreased from 3.3 (2.763; 3.846) during IFNβ-1a treatment to 0.81 (0.615; 1.073) during

$FTY_{M0\text{-}M36}$. Corresponding estimates in R group were: ARR, 0.15 (0.107; 0.204) during $FTY_{M0\text{-}M96}$ and annualized rate of neT2 lesions, 0.33 (0.195; 0.554) during $FTY_{M0\text{-}M36}$.

Conclusions: Patients with a suboptimal response to IFNβ-1a in the TRANSFORMS core study had improved long-term efficacy outcomes after switching to FTY.

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Nadia Tenenbaum, **Alit Bhatt**, **Yu Chen** are employees of Novartis.

P1213

Impact of continuous fingolimod therapy and switching to fingolimod on relapse severity in patients with relapsing-remitting multiple sclerosis

J. Haas[1], T. Vollmer[2], D. Jeffery[3], D. Piani Meier[4], B. Stadler[4], S. Ritter[5], J. Cohen[6], H.P. Hartung[7]
[1]Jewish Hospital Berlin, Berlin, Germany, [2]University of Colorado Denver, Department of Neurology, Aurora, CO, [3]Piedmont Health Care, Mooresville, NC, United States, [4]Novartis Pharma AG, Basel, Switzerland, [5]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [6]Neurological Institute, Cleveland Clinic, Cleveland, OH, United States, [7]Department of Neurology, Heinrich Heine University, Düsseldorf, Germany

Background: In RRMS patients, relapses vary in severity and may affect daily activities, requiring steroid intervention and hospitalization. Relapse frequency is often associated with MS prognosis. In the fingolimod (FTY) phase 3 core studies (FREEDOMS/FREEDOMS II and TRANSFORMS), frequency of overall and severe relapses were significantly reduced in the FTY vs placebo or interferon (IFN) treated RRMS patients.
Objective: To report the effect of FTY on relapse severity and associated healthcare utilization in RRMS patients who continued with or switched to FTY during the extensions of the phase 3 studies.
Methods: This post hoc descriptive analysis of data from pooled FREEDOMS and FREEDOMS II studies and from TRANSFORMS study analyzed 2 groups: patients randomized to FTY 0.5mg from the start (continuous group) or re-randomized to FTY in the extension (switch group). ARR was calculated for severe relapses (SR; EDSS score increase >1 point or >2-point change in 1 or 2 (or >1-point change in >4) functional systems), relapses requiring steroid use (RSU), or hospitalization (RH) or those affected daily activities (RADA).
Results: In the pooled FREEDOMS/FREEDOMS II extensions, the continuous group had sustained reductions in ARR over 4 years for SR (core: 0.032 vs extension: 0.015), RSU (0.149 vs 0.123), RH (0.049 vs 0.039) or RADA (0.155 vs 0.112) and lower percentage of relapses being SR (15.8 vs 9.3%). Similarly, in the TRANSFORMS extension at year 2, continuous group had sustained reductions in ARR for SR (core: 0.024 vs extension: 0.018), RSU (0.156 vs 0.161), RH (0.027 vs 0.033) or RADA (0.112 vs 0.109) and lower percentage of SR (11.8 vs 9.8%).

During the TRANSFORMS extension, ARR decreased post switch (IFN to FTY) for SR (core: 0.079 to extension: 0.029), RSU (0.366 to 0.232), RH (0.092 to 0.055) or RADA (0.285 to 0.144). Numerically fewer confirmed relapses were severe upon switch from IFN to FTY (18.0 vs 11.1%). Results were consistent in the FREEDOMS/FREEDOMS II extensions post switch from placebo to FTY.

Complete recovery was reported for majority of relapses during core and extension in both the continuous and switch groups (FREEDOMS pooled: 59.7-67.7%; TRANSFORMS: 65.4-80.0%).
Conclusions: In RRMS, frequency of severe relapses and relapse severity remained low in the continuous FTY group over 4 years. Reduction in the frequency of severe relapses post switch from IFN to FTY, underscores the gain in clinical benefit and the relevance of early switch to FTY in RRMS.

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P1214

The potential of individualized patient coaching to optimize treatment with delayed-release dimethyl fumarate: a retrospective analysis of patients with multiple sclerosis treated in a real-world setting

Y. Begus-Nahrmann[1], G. Niemczyk[2], B. Schmid[2], M. Mäurer[3]
[1]Konzept Pharma Service GmbH, Elze, [2]Biogen, Ismaning, [3]Caritas Krankenhaus, Bad Mergentheim, Germany

Background: Benefit of patient programs for injectable therapies is widely accepted. Various studies for oral drugs have shown that efficient therapy handling and adherence is not guaranteed. Though oral therapies lack the barrier of self-injection, medications like delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) have challenges. Objective of this retrospective study is to evaluate the real-world experience for patients on DMF for up to 24 months. Furthermore, the potential benefit of individual patient coaching is analysed.
Methods: Recruitment, still ongoing, was started in Feb 2014. All patients signed an informed consent form and received a code for a smartphone application with reminder function. Coached patients were in contact by phone at least 2 times in the 1st therapy month with the personal coach. After the 1st month contents and coaching frequency were adapted according to patient needs including motivational interviewing and compliance coaching. The control cohort of uncoached patients was contacted 1-2 times per year.
Results: As of February 2016, 9064 patients taking DMF have been recruited. After median follow up of 16 months, data for 8102 DMF patients including 1884 dropouts were analyzed.

While 24% were newly diagnosed, 65.2% switched from standard disease modifying therapies, 10.8% got the prescription for DMF receiving a 2nd line escalation therapy like Natalizumab before. Overall, gastrointestinal (GI) events were reported as the most frequent reason for discontinuation (28.6%), followed by ongoing disease activity (16%), changes in blood counts (13.9%) and flushing/pruritus (9.9%). GI events were most frequently reported in the first three months of therapy, incidence declines in the ongoing months. Reasons and timing to therapy discontinuation differed for coached and control patients. 5.7%, 17.4% and 21.9% of coached patients stopped therapy after 3, 12 and 18 months compared to 10.1%, 24.7% and 33.4% of the controls, respectively. Patients in the control cohort tended to discontinue therapy more often because of partly manageable side effects such as GI events and flushing/pruritus.

Conclusions: Side effects reported in the phase III studies are also the main reasons for discontinuing DMF therapy in the real-world setting. Patient coaching provides essential contribution to overcome preventable or manageable tolerability issues and may drive regular blood count controls.

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P1215

The ACROSS study: long-term efficacy of fingolimod in patients with RRMS (Follow-up at 10 years)

T. Derfuss[1], J. Sastre-Garriga[2], X. Montalban[2], M. Rodegher[3], G. Gannon[4], M. Bezuidenhoudt[4], M. Van Hoef[4], D. Silva[4], L. Kappos[5]

[1]Departments of Neurology and Biomedicine, University Hospital Basel, Basel, Switzerland, [2]Department of Neurology / Neuroimmunology, MS Centre of Catalonia (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona, Spain, [3]Neuroimaging Research Unit, Institute of Experimental Neurology, Scientific Institute and University Ospedale San Raffaele, Milan, Italy, [4]Novartis Pharma AG, [5]Neurological Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital Basel, Basel, Switzerland

Background: Long-term assessment of disability outcomes is important in the evaluation of the effectiveness of multiple sclerosis (MS) treatments.

Objective: In relapsing-remitting MS patients initially enrolled in the phase II proof of concept study we evaluated the effect of fingolimod on disability at 10 years. We also determined time to first use of an ambulatory device or wheelchair, change in MS functional composite (MSFC) score and MRI outcomes.

Methods: ACROSS was a multicentre, single visit, follow-up study at 10 years, of patients originally enrolled in the phase II fingolimod trial. Disability progression is defined as an increase in EDSS score of 1.5 (from baseline score 0), or 1 (from baseline score 1-5), or 0.5 (from baseline score >5). Patients in the continuous fingolimod treatment group (contin-fingo; patients with ⩾8 years of exposure to fingolimod) and non-continuous treatment group (non-contin-fingo; patients with < 8 years of exposure to fingolimod) were compared using ANCOVA (EDSS) and Cox proportional hazards model (use of wheel chair) analysis. MRI outcomes will be presented separately.

Results: ACROSS enrolled 62.3% (175/281) patients of the original phase II study; mean age was 37.4 years and 66.9% were women. A total of 59.4% (104/175) were in contin-fingo, 37% of the full phase II cohort (104/281).

Disability progression at 10 years was reported in 72 (41.1%) patients. Significantly less patients progressed in contin-fingo vs non-contin-fingo groups (33.7% vs 52.7%, p=0.0268). Change from baseline EDSS was significantly lower in the contin-fingo vs non-contin-fingo groups (0.58 vs 1.17; p=0.0155). A four-fold difference in the time to use of wheelchair was found in favour of contin-fingo vs non-contin-fingo groups (HR: 0.24 [95%CI: 0.07 to 0.85]).

Twenty- six (14.9%) patients developed secondary progressive MS, significantly less in the contin-fingo vs non-contin-fingo groups (10 [9.6%] vs 14 [25.5%]; p=0.0107).

Conclusions: Ten year single visit follow up of patients enrolled in the fingolimod phase II study shows high treatment persistence. Disability progression was lower in patients on continuous fingolimod compared to those who interrupted treatment. Although the study was of observational nature, a causal link between reduced disability progression and fingolimod treatment is plausible.

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P1216

Implementing quality recommendations in multiple sclerosis care - a strategic approach to improve brain health

J. Hobart[1], M. Alexander[2,3], A. Bowen[4], H. Butzkueven[5], G. Giovannoni[6], T. Kenny[7], G. Kobelt[8], T. Ziemssen[9]
[1]Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, United Kingdom, [2]Consultant in patient involvement in healthcare decision making, Epidavros, Greece, [3]Former CEO, European Multiple Sclerosis Platform, Brussels, Belgium, [4]Multiple Sclerosis Trust, Letchworth Garden City, United Kingdom, [5]Melbourne Brain Centre, Royal Melbourne Hospital, Melbourne, VIC, Australia, [6]Queen Mary University London, Blizard Institute, Barts and the London School of Medicine and DentistryBarts and the London School of Medicine and Dentistry, London, [7]Faculty of Health & Social Sciences, University of Bournemouth, Bournemouth, United Kingdom, [8]European Health Economics, Mulhouse, France, [9]Klinik und Poliklinik für Neurologie, Zentrum für Klinische Neurowissenschaften, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

Introduction: A 2015 consensus report[1] highlights the need to improve the quality of diagnosis, treatment and monitoring in multiple sclerosis (MS).
Methods: We present a quality improvement (QI) approach in MS informed by action effect (AE) methodology,[2] and data that illustrate the need to improve: A) Time to diagnosis, B) Treatment optimization, C) Quality standards. A) MS patients ⩽5 years from diagnosis in 8 Western European countries retrospectively reported time from first symptoms to diagnosis.[3] B) Data on switching from a 1st line disease-modifying therapy (DMT) in Germany were obtained for: i) hospital outpatients with relapsing-remitting MS in 2010-2013 from a prospective study;[4] ii) non-hospital-based MS patients in 2015 from pharmacist databases. DMTs were defined as 1st/2nd line based on European Medicine Agency indications. C) UK neurologists were surveyed by email in July 2015.
Results: The aim of the QI approach is to maximize lifelong brain health in MS patients and improve outcomes. An AE diagram presents interventions, contributing factors and measure concepts for diagnosis, treatment, and monitoring.

New data that support the need for QI are: A) 49% of 2374 respondents reported being diagnosed ⩽4 years from first symptoms; the mean (standard deviation) time was 8.64 (10.06) years. B) In Germany the proportions who switched from a 1st to a 2nd line DMT were: 37% of 1st- and 50% of 2nd-switch hospital outpatients (2010-13; n=278); 21% of 1st- and 22% of 2nd-switch non-hospital-based patients (2015; n>3500). C) Of the 49/115 UK neurologists who responded, the majority favoured including the following in a quality standard: MRI for diagnosis (38/49); DMT treatment rates (overall [33/49]; 2nd line [31/49]); MRI for monitoring (30/49).
Conclusions: There is room for improvement in time to diagnosis; clinical practice in treatment optimization varies widely; neurologists support a quality standard that incorporates DMT treatment rates and MRI for diagnosis and monitoring. These data support the need for QI in MS.

A QI approach aims to improve diagnosis, treatment and monitoring in order to maximize lifelong brain health in MS patients. It is informed by iterative AE methodology; engaging with the wider MS community, including patients, will be key to its success.

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NEDA as a predictor of conversion to secondary progressive multiple sclerosis in patients with relapsing-remitting multiple sclerosis

L. Kappos[1], N.D. Stefano[2], M.P. Sormani[3], G. Giovannoni[4], D. Häring[5], D. Tomic[5], D. Piani Meier[5], T. Chitnis[6]
[1]Neurological Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital Basel, Basel, Switzerland, [2]University of Siena, Siena, [3]Biostatistics Unit, Department of Health Sciences, University of Genoa, Genoa, Italy, [4]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary

University of London, London, United Kingdom, [5]Novartis Pharma AG, Basel, Switzerland, [6]Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, Boston, MA, United States

Background: The concepts of No Evidence of Disease Activity (NEDA) are being increasingly considered to assess disease evolution. After 6-10 years, approximately 25-40% of patients with relapsing-remitting multiple sclerosis (RRMS) convert to secondary progressive multiple sclerosis (SPMS).
Objective: To investigate proportion of patients with RRMS converting to SPMS over 8 years and the predictive value of NEDA status and baseline parameters of patients converting to SPMS.
Methods: Post-hoc analysis of pooled FREEDOMS and FREEDOMS II studies (both 2 year placebo-controlled) and their extensions in a total of N=2355 RRMS patients. Kaplan-Meier estimates of time to conversion to SPMS are presented at month (M) 96, hazard ratios (HR) and p-values are from a Cox proportional hazard model. Onset of SPMS was defined by a progressive increase in Expanded Disability Status Scale (EDSS) of at least 6 months duration in the absence or independent of relapses, from an initial EDSS $\geqslant$3.0 (increase in EDSS by $\geqslant$1 from an initial EDSS of 3-5 or by $\geqslant$0.5 points for EDSS $\geqslant$5.5, respectively). NEDA-3 is defined as: no MRI lesion activity, no relapses, and no confirmed progression of disability. NEDA-4 also includes annual brain volume loss < 0.4%.
Results: By M 96, the cumulative conversion probability to SPMS was 7.5% for patients who were continuously treated with FTY 0.5mg and 10% for patients who were initially treated with placebo and switched to FTY 0.5mg. Patients who did not convert to SPMS tended to be younger (38.5 vs 40.6yrs), with shorter disease duration (9.2 vs 11.0yrs), lower EDSS (2.3 vs 3.9), lower T2 burden of disease (5.7 vs 9.9 cc) and higher brain volume (1521 vs 1473 cc) at baseline. Differences were also seen for Paced Auditory Serial Addition Test (48.2 vs 43.0), 9-Hole Peg Test (22.1 vs 27.5) and Timed 25-Foot Walk Test (5.8 vs 8.2), while no difference was found for pre-study relapses and T1 Gadolinium-enhancing lesion activity. Comparing FTY-treated patients who did not achieve NEDA-3 in year 1 with those who did, the HR for time to SPMS was 1.59 (p=0.0568) while for NEDA-4 it was 2.01 (p=0.0225).
Conclusions: Less than 10% of patients on continuous FTY treatment converted to SPMS over 8 years. Disease severity at baseline and NEDA-4 status at one year were significantly predictive of time to conversion to SPMS. These findings support long-term benefit of FTY and the use of NEDA-4 as a comprehensive and balanced measure for predicting future disease evolution.

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COPAXONE® active registry - documentation of efficacy, tolerability and quality of life in outpatients with relapsing remitting multiple sclerosis (RRMS) treated with glatiramer acetate

T. Ziemssen[1], U. Faude[2], D. Fendji[2]
[1]Department of Neurology, University Hospital Garl Gustav Carus, Dresden, [2]Teva Pharma GmbH, Berlin, Germany

Background: Real-world treatment settings of multiple sclerosis (MS) patients might be considered being different to the situation in clinical trials due to the number of patients enrolled and selection criteria applied.
Goals: This non-interventional observational protocol measured long term efficacy and safety profile in MS patients using glatiramer acetate (GA) for disease modifying therapy.
Methods: The non-interventional study was performed to measure effectiveness, safety, quality of life in patients treated with GA (20 mg/ml daily) using established instruments including Expanded Disability Severity Score (EDSS), Fatigue Scale Motoric and Cognition (FSMC), MS Functional Composite (MSFC), Functional Assessment MS (FAMS) and MRI.
Results: 1619 patients (74.5% female), mean age 38 ±11 years, were enrolled (248 German centers), and treated for 12 months (median). 30.2% of the patients switched from another treatment. The annualized relapse rate (ARR) decreased significantly from 0.75 ±0.57 at baseline to 0.30 ±1.10 (p< 0.0001). In de-novo patients ARR decreased from 0.70 ±0.47 at baseline to 0.27 ±1.09 after 12 months, in switch patients from 0.84 ±0.64 to 0.31 ±0.87 (all p< 0.001). Proportion of patients without relapses increased from 12.87% to 83.24% (p< 0.001; n=1313) in all patients,

comparable for switch and de-novo patients too. Mean EDSS remained unchanged at 2.1 ±1.5 points. 81% of the patients remained stable or improved in the EDSS. The total score of FSMC remained stable (baseline 53.1 ±21.0; last observation 53.7 ±21.2). Quality of life measured by FAMS improved in 48.7% of all patients, mostly in switchers (53.7%) compared to naïve patients (46.3%). MSFC improved from 0.28 to 0.39, mostly in de novo patients (71.1%). The number of patients with significant depression decreased by 52%, new onset of significant depression was observed in 10%. MRI was more often considered as stable by the treating neurologist (41.05% to 62.11% (p=0.0012)).
The tolerability of GA was rated "very good" or "good" in >87% of the patients. Adverse events were reported by 14% of the patients, predominately as injection site reactions.
Conclusion: The treatment with GA led to a reduction of the relapse rate, improved health state and severe depression. In other aspects of clinical outcome parameters, stabilization was observed. De novo patients might have a greater benefit from a treatment with GA compared to patients switching from another therapy.

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Real-life long-term effectiveness of fingolimod in a Swiss relapsing-remitting multiple sclerosis cohort

C. Zecca[1], S. Roth[2], O. Findling[3], G. Perriard[4], V. Bachmann[4], M.L. Pless[5], A. Baumann[6], C.P. Kamm[7], P.H. Lalive[8], A. Czaplinski[9]
[1]Department of Neurology, Regional Hospital Lugano (EOC), Lugano, [2]Neurology Practice, Carouge, [3]Department of Neurology, Cantonal Hospital Aarau, Aarau, [4]Novartis Pharma Switzerland AG, Rotkreuz, [5]Departments of Neurology and Ophthalmology, Hospital of the Canton of Luzern, Luzern, [6]Neurozentrum, Langenthal, [7]Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, [8]Department of Neurosciences, Division of Neurology, University Hospital of Geneva and Faculty of Medicine, Geneva, [9]Bellevue Neurocenter, Zurich, Switzerland

Background: Fingolimod has been approved in Switzerland since January 2011 as the first oral treatment for relapsing-remitting multiple scleroses (RRMS) to reduce frequency of relapses and delay disability progression. As opposite to the label granted by the European Medicines Agency, fingolimod has a first-line indication in Switzerland. With this study we wanted to assess the effectiveness of fingolimod in a real-world population that has been treated for up to 60 months with fingolimod.
Methods: For this cross-sectional, retrospective study conducted in 19 centers in Switzerland, consecutive RRMS patients receiving fingolimod for a minimum of 7 and up to 58 months were included of whom demographic as well as clinical data were collected. The primary endpoint was number of patients being relapse-free. Key secondary endpoints included freedom of disability progression (EDSS score increase by ⩾1 points) and treatment retention. All analyses have been performed using descriptive statistical methods including Wilcoxon- and paired t-tests as well (SAS® package, version 9.2 or higher).
Results: 275 RRMS patients were included. Seventy-nine (28.7%) patients were treatment-naïve and the remaining 196 (71.3%) patients were switched from another therapy. Fingolimod treatment duration was < 2 years in 75 (27.3%) patients, 2 to < 3 years in 91 (33.1%) patients and ⩾ 3 years in 109 (39.6%) patients. After a mean treatment duration of 32 months (range: 7 - 57.9 months) 214/275 (77.8%) [95% CI: 72.4%, 82.6%] patients were free from relapses. In addition, 244/270 (90.4%) [95% CI: 86.2%, 93.6%] patients were free from disability progression, and 195/270 (72.2%) [95% CI: 66.5%, 77.5%] patients were free from both relapses and disability progression. Treatment retention with fingolimod was 89.5%. Fingolimod was discontinued in 29 (10.5%) patients, of whom ten (3.6%) because of adverse events.
Conclusion: In this Swiss cohort of naïve and pre-treated RRMS subjects fingolimod treatment prevented the occurrence of relapses and disability progression in the majority of patients over 3 years. These findings support that fingolimod used in a real-life setting maintains the effectiveness shown over 2 years in the pivotal phase III trials.

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A low percentage of CD4+ T-cells can predict disease reactivation after natalizumab discontinuation

M. Lo Re[1], M. Capobianco[1], S. Malucchi[1], M. Matta[1], A. di Sapio[1], M. Malentacchi[1], F. Sperli[1], A. Oggero[1], M. Pautasso[2], P. Berchialla[3], A. Bertolotto[1]

[1]AOU San Luigi Gonzaga, Regional Multiple Sclerosis Center, [2]Clinical Pathology Unit, University San luigi Gonzaga Hospital, Orbassano, [3]University of Torino, Torino, Italy

Objective: to evaluate whether lymphocytes sub-population could be related to MS disease reactivation at natalizumab suspension.

Background: Natalizumab is a very effective second-line treatment for active MS but its suspension can cause MS disease reactivation and rebound. At the moment the only risk factor for disease reactivation is the number of relapses before natalizumab introduction. Previously it has been suggested that low blood lymphocytes count during natalizumab treatment could be a risk factor for MS reactivation.

Methods: Data were retrospectively collected from one Italian MS centre. Peripheral lymphocyte subsets were analyzed by FACS in 91 MS patients before natalizumab discontinuation.

Results. At the end of natalizumab treatment, a high percentage of CD4+ (OR 0.61) and a high CD4+/CD8+ ratio (OR 0.56) confer a low risk of disease reactivation. On the contrary, a high percentage of CD8+ cells is a risk factor for disease reactivation (OR 1.22). No correlation has been found for CD19+ and CD16+56+ cells. Roc analysis show a significant threshold for CD4+ cells of 40.45 with an OR of 2.65 (p-value 0.034).

Conclusion: Lymphocytes sub-population analysis could add important information on the risk of disease reactivation after natalizumab; in particular a low percentage of CD4 cells can predict disease reactivation.

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Alemtuzumab suppresses MRI disease activity over 6 years in patients with active relapsing-remitting multiple sclerosis and an inadequate response to prior therapy (CARE-MS II)

A. Traboulsee[1], M. Barnett[2], G. Comi[3], J. De Sèze[4], G. Giovannoni[5], D. Pelletier[6], A. Rovira[7], S. Schippling[8], D.H. Margolin[9], K. Thangavelu[9], D.L. Arnold[10,11], on behalf of the CARE-MS II Investigators

[1]The University of British Columbia, Vancouver, BC, Canada, [2]University of Sydney, Sydney, NSW, Australia, [3]University Vita-Salute San Raffaele, Milan, Italy, [4]Strasbourg University, Hôpital Civil, Strasbourg, France, [5]Queen Mary University of London, Barts and The London School of Medicine, London, United Kingdom, [6]University of Southern California, Los Angeles, CA, United States, [7]Vall d'Hebron University Hospital, Barcelona, Spain, [8]Neuroimmunology and Multiple Sclerosis Research, University Hospital Zurich and University of Zurich, Zurich, Switzerland, [9]Sanofi Genzyme, Cambridge, MA, United States, [10]NeuroRx Research, [11]Montréal Neurological Institute, McGill University, Montréal, QC, Canada

Background: In the 2-year, phase 3 CARE-MS II clinical trial (NCT00548405), alemtuzumab significantly reduced the annualised relapse rate and brain volume loss, improved disability outcomes, and increased the proportion of patients with no evidence of MRI disease activity versus SC IFNB-1a in patients with active relapsing-remitting multiple sclerosis (RRMS) and an inadequate response (⩾1 relapse) to prior therapy at baseline. An extension study (NCT00930553) has shown durable efficacy through 5 years in the absence of continuous treatment.

Goals: To evaluate the effect of alemtuzumab on MRI lesion outcomes over 6 years in patients who had an inadequate response to prior therapy at baseline.

Methods: In CARE-MS II, patients received 2 courses of alemtuzumab 12 mg (Month 0: 5 days; Month 12: 3 days). At the end of Year 2, patients who completed the study could enter the extension, with as-needed alemtuzumab for relapse or MRI activity. Another disease-modifying therapy could be provided per investigator discretion. MRI scans (baseline and annually thereafter) were assessed for gadolinium (Gd)-enhancing T_1, new/enlarging T_2 hyperintense and new T_1 hypointense lesions. Assessments: proportions of patients with no evidence of MRI disease activity (defined as no new Gd-enhancing T_1 and no new/enlarging T_2 lesions) and no evidence of disease activity (NEDA).

Results: Of the 423 alemtuzumab patients who completed CARE-MS II, 393 (93%) entered the extension; of these, 344 (88%) remained on study through 6 years. In each year of the extension, high proportions of patients remained free of new Gd-enhancing T_1, new/enlarging T_2, and new T_1 lesions (Year 6: 91%, 69%, and 89%, respectively). In each year, most patients showed no evidence of MRI disease activity (69% had no evidence of MRI activity in Year 6), and most achieved NEDA annually in the extension (Year 3: 53%; Year 4: 54%; Year 5: 58%; Year 6: 60%). These results were achieved with 50% of patients receiving no additional treatment after their initial 2 courses of alemtuzumab.

Conclusion: Efficacy on MRI outcomes with alemtuzumab was durable over 6 years in patients with an inadequate response to prior therapy at baseline, despite 50% of patients receiving no additional treatment since the initial 2 courses of alemtuzumab. Based on these findings, alemtuzumab may provide a unique treatment approach with durable efficacy in the absence of continuous treatment for RRMS patients.

Disclosure

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Importance of early treatment initiation in the clinical course of multiple sclerosis

A. Kavaliunas[1], A. Manouchehrinia[1], L. Stawiarz[1], R. Ramanujam[1,2], J. Agholme[1], A.K. Hedström[3], O. Beiki[1], A. Glaser[1], J. Hillert[1]
[1]Clinical Neuroscience, Karolinska Institutet, [2]Department of Mathematics, KTH Royal Institute of Technology, [3]Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

Background: Although disease modifying drugs (DMDs) have proven efficacy in randomised controlled trials, it is still not definitively shown that they influence the long term outcome of MS. It is also possible, albeit not proven, that the "natural course" of MS in general is influenced by the wide-spread use of DMDs. Therefore it is less clear to what extent the classical predictors of disability are still relevant in a situation where the majority of patients receive DMD treatment.
Objectives: The aim of this study was to identify factors influencing the long-term clinical progression of multiple sclerosis (MS). A special objective was to investigate whether early treatment decisions influence outcome.
Methods: We included 639 patients diagnosed with MS from 2001 to 2007 at the department of Neurology in the Karolinska University Hospital and former Huddinge University Hospital (Stockholm, Sweden). The median follow-up time was 99 months (8.25 years). Cox regression models were applied to identify factors correlating with the outcome variable defined as time from treatment start to irreversible score 4 of the Expanded Disability Status Scale (EDSS), as well as time to EDSS 6.
Results: Patients initiated on treatment later had a greater risk of reaching EDSS 4 (hazard ratio of 1.067 (95% CI 1.044−1.091)), increased by 6.7% for every year of delay in treatment start after MS onset. Patients that started treatment after 3 years from MS onset reached the outcome sooner with hazard ratio of 2.43 (95% CI 1.60−3.69) compared with the patients that started treatment within 1 year from MS onset. Similar results were obtained by analyzing time to EDSS 6. Baseline EDSS and age at onset were found to be predictive factors of disability progression. Gender (male) was associated with a greater risk to reach EDSS 6 only.
Conclusion: Early treatment initiation was associated with a better clinical outcome. In addition, we confirmed the well-established prognostic factors of late age at onset and early disability.

Disclosure

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P1223

4 years PANGAEA: effectiveness update of a 5 year non-interventional study on the daily use of fingolimod in Germany

T. Ziemssen[1], H. Albrecht[2], J. Haas[3], L. Klotz[4], M. Lang[5], C. Lassek[6], S. Schmidt[7], B. Tackenberg[8], C. Cornelissen[9]
[1]Zentrum für klinische Neurowissenschaften, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, [2]Praxis für Neurologie, München, [3]Zentrum für Multiple Sklerose, Jüdisches Krankenhaus Berlin, Berlin, [4]Klinik für allgemeine Neurologie, Uniklinik Münster, Münster, [5]NTD Study Group, Ulm, [6]Neurologische Gemeinschaftspraxis Kassel und Vellmar, Kassel, [7]NTD Study Group, Bonn, [8]Klinik für Neurologie, Philipps-University and University Clinics Gießen and Marburg, Marburg, [9]Novartis Pharma GmbH, Nuremberg, Germany

Background: Once-daily fingolimod (Gilenya®, Novartis Pharma AG) is a sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing MS. More than 134.000 patients have been treated with fingolimod; total patient exposure now exceeds 289.000 patient-years.
Objective: PANGAEA (Post-Authorization Non-interventional German sAfety of GilEnyA in RRMS patients) is a non-interventional study (NIS), conducted in Germany, to investigate long-term safety, tolerability and effectiveness in daily clinical practice.

Here we present data on effectiveness of fingolimod in daily clinical practice from patients treated for up to 4 years.
Methods: PANGAEA is a prospective, multi-center, non-interventional, long-term study of fingolimod for the treatment of patients with RRMS. The observation period under PANGAEA is up to 60 months with follow-up visits every 3 months. Recruitment finished in December 2013. 4229 patients from 374 centers were enrolled. Data presented are part of an interim analysis conducted in January 2016
Results: The proportion of female patients was 71.9 % and the mean age was 39.1 (±10.0) years. The mean annual relapse rate of PANGAEA patients improved from 1.5 ± 0.04 (95% CI; baseline) to 0.43 ± 0.02 (year 1), 0.34 ± 0.03 (year 2), 0.31 ± 0.03 (year 3) and 0.29 ± 0.04 in year 4 of treatment. In the first year of treatment 68.5% of the patients were relapse free. This number increased to 75.5% in the fourth year. The mean baseline EDSS in PANGAEA was 3.0 (±0.03; 95%CI)) and remained stable over 4 years. In each year of treatment app. 90% of the patients had a stable EDSS or experienced a 6 months confirmed EDSS improvement. In the fourth year of treatment 73.2% of the patients were free of relapses and 6 months confirmed disability progression. 42.3% of the patients neither had a relapse nor a 6 months confirmed disability progression over 4 years of treatment. Patient reported outcomes (EQ-5D, TSQM-9) evaluated in a substudy (n=830) over a period of 24 months confirmed the good effectiveness and convenience profile of Fingolimod from a patient point of view.
Conclusions: The results of the 4 year interim analysis of PANGAEA support the positive efficacy profile in phase III clinical trials with real world evidence data.

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Development of former fingolimod study patients in a real world setting: results from the 4 year interim analysis of the non-interventional trial PANGAEA

T. Ziemssen[1], H. Albrecht[2], J. Haas[3], L. Klotz[4], M. Lang[5], C. Lassek[6], S. Schmidt[7], B. Tackenberg[8], C. Cornelissen[9]
[1]Zentrum für klinische Neurowissenschaften, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, [2]Praxis für Neurologie, München, [3]Zentrum für Multiple Sklerose, Jüdisches Krankenhaus Berlin, Berlin, [4]Klinik für allgemeine Neurologie, Uniklinik Münster, Münster, [5]NTD Study Group, Ulm, [6]Neurologische Gemeinschaftspraxis Kassel und Vellmar, Kassel, [7]NTD Study Group, Bonn, [8]Klinik für Neurologie, Philipps-University and University Clinics Gießen and Marburg, Marburg, [9]Novartis Pharma GmbH, Nuremberg, Germany

Background: Once-daily fingolimod (Gilenya®, Novartis Pharma AG) is a sphingosine 1-phosphate receptor modulator approved for the treatment of relapsing MS. More than 134.000 patients have been treated with fingolimod; total patient exposure now exceeds 289.000 patient-years.
Objective: PANGAEA (Post-Authorization Non-interventional German sAfety of GilEnyA in RRMS patients) is a non-interventional study (NIS), conducted in Germany, to investigate long-term safety, tolerability and effectiveness in daily clinical practice. PANGAEA included a subpopulation of patients treated with fingolimod in clinical trials prior to inclusion into PANGAEA. Here we presenr data on this population from first intake of fingolimod up to 4 years of Fingolimod treatment in PANGAEA.
Methods: PANGAEA is a prospective, multi-center, non-interventional, long-term study of fingolimod for the treatment of patients with RRMS. The observation period in PANGAEA is up to 60 months with follow-up visits every 3 months. Recruitment into the study finished in December 2013. 4229 patients from 374 centers were enrolled. 874 patients switched from clinical trials to PANGAEA. The baseline characteristics of 498 patients in the former study patient cohort (FSC) are presented.
Results: The proportion of female patients in the FSC was 74.1 % and the mean age was 38.8 (±9.1) years. The mean time since diagnosis was 7.0 (±5.8) years. The mean annual relapse rate (ARR) before start of fingolimod was 1.2 (±1.2), and the mean EDSS was 2.4 (±1.5). Prior to PANGAEA study entry these patients were pre-treated with fingolimod for 235.4 (±172.2) days. The baseline characteristics of the FSC slightly differed in comparison to patients that were fingolimod naïve. From fingolimod baseline to year 4 in PANGAEA the ARR of the FSC was reduced by 78% to 0.26 ± 0.05 (95% CI) and the mean EDSS remained stable over this time period. 88% had a stable or improved 6 months confirmed EDDS in year 4. 41.7% of the patients neither had a relapse nor an EDSS progression over a period of 4 years in PANGAEA.
Conclusions: Baseline characteristics were different in treatment-naïve patients and those who switched to Fingolimod from clinical trials. Nevertheless the effectiveness data of the FCO within PANGAEA are comparable to the patients that were treatment-naïve and support the positive efficacy profile presented in phase III clinical trials with real world evidence data.

Disclosure

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P1225

Discontinuation of disease-modifying therapies in relapsing remitting multiple sclerosis - outcome and prognostic factors

G. Bsteh, J. Feige, R. Ehling, H. Hegen, M. Auer, F. Di Pauli, F. Deisenhammer, T. Berger
Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

Background: Multiple sclerosis (MS) is a chronic inflammatory neurological disease requiring long term disease-modifying treatment (DMT). Disease activity declines over time and prolonged periods of disease quiescence may prompt DMT discontinuation. However, there are no recommendations available when to discontinue DMT. The aim of this study was to investigate the clinical outcome after DMT discontinuation in relapsing-remitting MS (RRMS) patients and identify factors predictive of outcome.
Methods: In this retrospective, observational study, we screened the Innsbruck MS database for RRMS patients who had received DMT for a minimum period of 12 months, discontinued DMT and had a follow up of at least 2 years available. Patients who restarted DMT within 6 months or were discontinued due to conversion to secondary progressive MS were excluded. Hazard ratios (HRs) with 95% confidence intervals (CIs) with regard to relapse and disability progression (defined as a confirmed EDSS increase of 0.5) after DMT discontinuation were calculated from Cox regression models including age, disease duration and time of DMT intake.
Results: A total of 230 patients (70.4% female) were included. Mean age at discontinuation was 37.9 years (SD 16.1), mean disease duration 6.2 years (SD 8.1), mean time of DMT intake 3.3 years (SD 3.7) and mean time of follow up 5.0 years (SD 1.2). DMTs included interferon beta preparations (67.0%), glatiramer-acetate (15.2%) or other drugs (17.8%). Reasons for DMT discontinuation were safety/tolerance issues (45.7%), personal reasons (23.4%), stable disease course (26.5%) or pregnancy (4.4%). Median EDSS at discontinuation was 2.0 (range 0.0 - 5.5). During follow up, relapses occurred in 102 (44.3%) and disability progression in 50 patients (21.7%). Patients aged > 45 years taking DMT for > 4 years before discontinuation without a relapse had a cumulative HR of 0.06 (CI 0.01 - 0.46, $p < 0.001$) to suffer a relapse and a cumulative HR of 0.65 (CI 0.18 - 2.34, ns) for disability progression.
Conclusions: The outcome of discontinuation of DMT in RRMS depends on individual factors. While freedom from subsequent disease activity is impossible to predict, there seems to be a subset of patients (age > 45 years, DMT intake > 4 years without evidence of clinical disease activity) having a high likelihood of remaining stable after DMT discontinuation. However, clinical monitoring for recurrent disease activity is mandatory in those discontinuing treatment.

Disclosure

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P1226

Effect of exposure to branded glatiramer acetate during pregnancy on rates of pregnancy loss

O. Neudorfer[1], P. Baruch[1], S. Pery[1], N. Ashtamker[2], S. Kolodny[3], N. Gavrielov[1]
[1]Teva Pharmaceutical Industries, Petach Tikva, [2]Teva Pharmaceutical Industries, Netanya, Israel, [3]Teva Pharmaceutical Industries, Frazer, PA, United States

Background: Multiple sclerosis (MS) is a disabling neurological disease, which largely affects women of childbearing age. The disease is not associated with an increase in spontaneous abortions, stillbirth, cesarean delivery, premature birth, or birth defects. Limited information is available on the association of disease-modifying therapies with adverse pregnancy outcomes. Teva's global safety database includes over 8000 pregnancy cases exposed to branded GA, with more than half of them reported prospectively. Thus this database allows a unique large-scale examination of pregnancies exposed to branded GA during pregnancy. Previous comparison of rates of congenital anomalies from this database to EUROCAT and MACDP reference rates showed no increased anomalies or fetal toxicities in pregnancies exposed to branded GA.
Objective: Assess the possible impact of exposure to branded glatiramer acetate (GA, Copaxone) treatment during pregnancy on pregnancy loss (spontaneous abortions, still births and fetal demise) in patients with MS.
Methods: Data of branded GA exposure during pregnancy was retrieved from Teva's global safety database (since product launch and until 30 June 2015). Data from prospective reports with confirmed exposure to GA 20 mg daily during pregnancy were analyzed per pregnancy outcome. The rates of pregnancy loss (spontaneous abortions, still births and fetal demise) were

calculated and compared to rates from general population, derived from the center for disease control (CDC) data, the leading national public health institute of the United States.

Results: From all prospectively reported pregnancies, a cohort of 2068 cases, with confirmed GA exposure and known outcome, was used in this analysis. Outcomes included 1760 (85%) live births, 227 (11%) pregnancy loss, 63 (3%) elective pregnancy terminations, 3 (0.15%) molar and 15 (0.7%) ectopic pregnancies. The 227 pregnancy loss cases include 208 spontaneous abortions, 11 fetal deaths and 8 still births. In comparison to CDC data, GA-exposed pregnancies show no increase in the percentage of pregnancy loss (17% and 11%, respectively).

Conclusion: Using a large database, this analysis demonstrated that exposure to branded GA during pregnancy does not increase the risk for pregnancy loss compared to the reference pregnancy loss rates observed in the general population. This provides further support to the growing notion that GA is the drug of choice for women of childbearing age who consider pregnancy.

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P1227

Effect of fingolimod on multiple sclerosis severity score (MSSS) in patients with relapsing multiple sclerosis

X. Montalban[1], A.T. Reder[2], J. Cohen[3], S. Ritter[4], D. Tomic[5], D. Piani Meier[5], L. Kappos[6]

[1]Department of Neurology-Neuroimmunology. Cemcat. Vall d'Hebron University Hospital, Barcelona, Barcelona, Spain, [2]University of Chicago Medical Center, Chicago, IL, [3]Neurological Institute, Cleveland Clinic, Cleveland, OH, [4]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States, [5]Novartis Pharma AG, [6]Neurological Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital Basel, Basel, Switzerland

Background: Multiple Sclerosis Severity Score (MSSS) is a method of assessing disease severity over time based on expanded disability status scale (EDSS) scores and accounting for disease duration (Roxburgh et al Neurology 2005; Pachner et al J Neurol Sci. 2009).

Objective: To assess the effect of fingolimod on MSSS in patients with relapsing MS.

Methods: This post hoc analysis used pooled data from FREEDOMS and FREEDOMS II (fingolimod 0.5 mg vs placebo, n=1556) core studies (24 month [M]) and their extensions and from TRANSFORMS (fingolimod 0.5 mg vs intramuscular interferon beta-1a [IFN-β], n=860) core trial (12M) and its extension. MSSS was assessed during core study and up to M48 (TRANSFORMS extension, n=509) and M96 (FREEDOMS/FREEDOMS II extension, n=251). During the core periods, change in MSSS from baseline (BL) to M24 (for the pooled FREEDOMS studies) and from BL to M12 (TRANSFORMS study) was analysed with ANCOVA models adjusted for treatment, age and BL MSSS. We present least squares (LS) means and p values of these models, and summary means of MSSS for core and the extension phases.

Results: In the pooled FREEDOMS and FREEDOMS II core studies, improvement in MSSS from BL to M24 was significantly higher in fingolimod vs placebo group (-0.53 vs -0.37; p=0.0385). Over 96 M, fingolimod had sustained benefit on MSSS in patients continuing the therapy (BL: 3.56, M24: 3.03, M48: 2.74, M96: 2.28). MSSS also improved in patients switching from placebo to fingolimod at 24 M (BL: 3.68, M24: 3.27, M48: 2.93, M96: 2.26). In the TRANSFORMS study, the change in MSSS from BL to M12 was significantly lower in fingolimod vs IFN-β group (-0.433 vs -0.224, p=0.0216). Over 48 M, fingolimod had sustained beneficial effect on MSSS in patients continuing the therapy (BL: 3.71, M12: 3.25, M24: 3.19, M48: 2.76). The MSSS was improved in the group of patients who switched from IFN-β to fingolimod after the core phase at M12 (BL: 3.68, M12: 3.43, M24: 3.15, M48: 2.74).

Conclusions: The MSSS improved significantly in fingolimod-treated patients not only vs placebo- but also vs IFN-β-treated patients. An improvement was also seen in placebo and IFN-β patients, and after switching to fingolimod during the extension. Continuous fingolimod therapy maintained its beneficial effect over 96 months. These findings suggest that fingolimod has a favourable and sustained impact on MS severity over the long-term.

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P1228

Long-term real-world effectiveness of natalizumab: treatment outcomes from the Tysabri® observational program (TOP) stratified by baseline disability

L. Kappos[1], H. Butzkueven[2,3], Y. Chen[4], P.-R. Ho[4], H. Köndgen[4], N. Campbell[4]

[1]University Hospital and University of Basel, Basel, Switzerland, [2]University of Melbourne, Melbourne, [3]Monash University, Box Hill, VIC, Australia, [4]Biogen, Cambridge, MA, United States

Background: Clinical trial data have shown that relapsing-remitting multiple sclerosis (RRMS) patients initiating natalizumab treatment at low levels of disability have better treatment outcomes. Real-world data over longer treatment durations are needed to confirm the importance of starting natalizumab early in the disease course. TOP is an ongoing multinational observational study following natalizumab-treated RRMS patients in clinical practice settings for ⩾10 years.
Objective: To compare long-term outcomes in TOP patients initiating natalizumab at various disability levels.
Methods: Patients were grouped by baseline Expanded Disability Status Scale (EDSS) score using clinically relevant milestones: EDSS ⩽1.5 (n=814), EDSS 2.0-3.5 (n=2511), EDSS 4.0-5.5 (n=1778), and EDSS ⩾6.0 (n=705). Annualized relapse rates (ARRs) in the year pre- and 7 years post-natalizumab initiation, EDSS score changes, and the likelihood of 24-week confirmed EDSS worsening (score increase of ⩾1.5 from 0, ⩾1.0 from 1.0-5.5, or ⩾0.5 from ⩾6.0) or improvement (score decrease of ⩾1.0 from ⩾2.0) were analyzed using data through November 1, 2015.
Results: At baseline, patients with more disability tended to have longer disease duration than those with less disability (median 4.9, 6.1, 8.8, and 11.1 years for patients with EDSS scores ⩽1.5, 2.0-3.5, 4.0-5.5, and ⩾6.0, respectively). After starting treatment, ARRs were significantly reduced regardless of baseline disability (85.3-91.7%, each $P< 0.0001$), with the largest reduction observed in the group with EDSS scores ⩽1.5 ($P< 0.001$ vs each other group). Over 7 years of treatment, mean EDSS score changes from baseline were < 1.0, and the risk of EDSS worsening was similar among patients with scores ⩽1.5 (28.1%), 2.0-3.5 (23.7%), and 4.0-5.5 (25.6%) and higher in those with scores ⩾6.0 (36.8%, HR 1.34 [95% CI 1.03-1.73], P=0.029 vs ⩽1.5 group). A pattern was observed in which patients with EDSS scores ⩽5.5 were more likely to improve than worsen, whereas those with scores ⩾6.0 were more likely to worsen than improve.
Conclusions: Over 7 years of natalizumab treatment, ARRs were reduced, mean EDSS scores were stable, and EDSS worsening rates were low regardless of baseline EDSS score. RRMS patients initiating treatment with less disability had better outcomes, suggesting that, though patients benefit from natalizumab regardless of baseline disability, natalizumab use earlier in the disease course is associated with better long-term outcomes.

Disclosure

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Chen Y: employees of and hold stock and/or stock options in Biogen.
Ho PR: employees of and hold stock and/or stock options in Biogen.
Köndgen H: employees of and hold stock and/or stock options in Biogen.
Campbell N: employees of and hold stock and/or stock options in Biogen.

P1229

Long-term safety of natalizumab treatment in multiple sclerosis (MS) in clinical practice: results from the tysabri global observational program in safety (TYGRIS)

J. Foley[1], C. Carrillo-Infante[2], M. Wenten[2], N. Lavallee[3], J. Smith[2], K. Evans[2], B. Haddock[2], D. Steiner[2], P.-R. Ho[2], L. Lee[2], P. Vermersch[4], M. Hutchinson[5], C. Pozzilli[6], G. Bloomgren[2]
[1]Rocky Mountain Multiple Sclerosis Clinic, Salt Lake City, UT, [2]Biogen, [3]PROMETRIKA, LLC, Cambridge, MA, United States, [4]University of Lille, Lille, France, [5]Department of Neurology, St. Vincent's University Hospital, Dublin, Ireland, [6]Department of Neurology and Psychiatry, Sapienza University, Rome, Italy

Background: TYGRIS was a 5-year observational cohort study designed to obtain long-term safety data in natalizumab-treated MS patients in clinical practice.
Objectives: To examine the incidence and pattern of serious adverse events (SAEs) in a large postmarketing sample of natalizumab-treated MS patients.
Methods: Investigators monitored natalizumab-treated patients and reported SAEs occurring during the study. Malignancy incidence rates were compared with rates in the Surveillance, Epidemiology and End Results and Globocan databases.
Results: Of 6508 enrolled patients (US, 2207; rest of world, 4301), 4938 (76%) completed the 5-year study. At enrollment, mean (SD) age was 40.1 (10.44) years, and 91% of patients had prior immunomodulatory/immunosuppressant use. Patients received a median (range) of 44 (0-77) natalizumab doses before/during the study, accruing ≈21,795 patient-years of natalizumab exposure. Of 6434 dosed patients, 987 (15%) experienced ⩾1 treatment-emergent (TE) SAE, 222 (3%) reported ⩾1 TE SAE leading to natalizumab discontinuation, and no individual SAE occurred in ⩾1% of patients. SAEs occurring in >0.5% of patients included urinary tract infection (0.8%), pneumonia (0.7%), progressive multifocal leukoencephalopathy (PML; 0.7%), and immune reconstitution inflammatory syndrome (0.6%). Fifty-five patients (< 1%) experienced ⩾1 TE serious opportunistic infection, 44 of which were PML. Most PML cases (42/44) occurred after >24 infusions; 23 cases were anti-JCV antibody positive ⩾6 months pre-diagnosis; serostatus ⩾6 months prior to PML development was unknown or not reported in 21 cases. Two patients with PML had fatal outcomes. The malignancy incidence rate (449.0 per 100,000 patient-years [95% CI: 375.1-533.1]) was similar to rates in the general population (460.2 and 519.2 per 100,000 person-years); no trends between dosing and malignancy

incidence were observed. Six subjects experienced hepatotoxic events, including cytolytic hepatitis (n=2), liver injury (n=2), toxic hepatitis (n=1), and hepatocellular injury (n=1); most cases had clear evidence of alternative cause or ⩾1 confounder. Of 96 fatal events in 77 patients, most (91/96) were considered unlikely/not related to study drug or causality was not reported.

Conclusion: The nature, character, and rate of SAEs reported in this study of long-term safety data from natalizumab-treated patients in real-word settings are consistent with the drug's known safety profile.

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NL, JS: contractors for Biogen.

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MH: served on a medical advisory board for Biogen; serves on the editorial board of the *Multiple Sclerosis Journal*, has received speaker's honoraria from Bayer-Schering, Biogen, Novartis; receives research support from Dystonia Ireland, the European Dystonia Foundation, the Health Research Board of Ireland.

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P1230

Real world experience of fingolimod after switching multiple sclerosis (MS) therapy; focus on natalizumab naïve and experienced persons with MS, respectively

L. Forsberg[1], S. Johansson[1], T. Frisell[2], J. Hillert[1], P. Nilsson[3], C. Dahle[4], A. Sveningsson[5], J. Lycke[6], A.-M. Landtblom[7], J. Burman[7], F. Walentin[8], C. Martin[5], F. Piehl[1], T. Olsson[1]

[1]Department of Clinical Neuroscience, [2]Department of Medicine, Karolinska Institutet, Stockholm, [3]Department of Clinical Sciences, Neurology, Lund University, Lund, [4]Department of Clinical and Experimental Medicine, Linköping University, Linköping, [5]Department of Clinical Science, Danderyd Hospital, Stockholm, [6]Department of Clinical Neuroscience and Rehabilitation, University of Gothenburg, Gothenburg, [7]Department of Neuroscience, Uppsala University, Uppsala, [8]Örebro University Hospital, Örebro, Sweden

Introduction: Fingolimod (FGL) is a second line treatment in for patients with relapsing-remitting multiple sclerosis (RRMS). Strict inclusion criteria of randomized control trials make it difficult to predict how an unselected patient population will respond to a drug.

Aim: To report demographic and clinical characteristics of FGL patients treated in a real-world setting stratified by prior treatment with NTZ in relation to drug survival and clinical outcome scales.

Method: Both NTZ and FGL patients have been followed through a Swedish national post-marketing surveillance study; Immunomodulation and MS Epidemiology (IMSE). IMSE aims to include all patients, regardless of previous treatments, age or disease status.

IMSE includes clinical data on extended disability status scale (EDSS), MS severity scale (MSSS), symbol digit modalities test (SDMT), MS impact scale (MSIS-29), European quality five dimensions (EQ-5D) and the Visual Analog Scale (VAS). Statistical differences over time were analyzed using the Wilcoxon Signed Rank Test. Drug survival was measured using the Kaplan-Meier curve. The entire FGL cohort included 1,340 patients.

Results: In patients with at least 12 and 24 months of FGL treatment (N=944, and N=628) MSSS, MSIS-29 Psychological (PSY) and SDMT clinical test results improved significantly after 12 and 24 months.

Significant improvements were found in all tests in NTZ naïve patients after one year, EDSS worsened significantly in the NTZ experienced patients and only MSIS-29 PSY improved significantly. MSSS, MSIS-29 PSY and SDMT were still significantly improved after 24 months in the NTZ naïve group. NTZ experienced group results remained the same.

The one and two year discontinuation rates were 22% and 36%. Discontinuation was significantly more common among the NTZ experienced group.

Discussion: FGL patients displayed a satisfactory treatment response. However, a more complex picture emerged when the group was stratified for prior NTZ treatment.

A rebound effect upon discontinuation of NTZ has been suggested; however the NTZ group is selected for patients with higher disease activity. One interpretation is that FGL often has an insufficient effect in this group of patients.

Conclusion: FGL is efficacious in an unselected MS population over a longer follow up period. These effects were not seen in patients switching from NTZ to FGL.

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Jan Lycke has received travel support and/or lecture honoraria from Bayer Schering Pharma, Biogen, Novartis, Teva and Sanofi Genzyme; has served on scientific advisory boards for Almirall, Teva, Biogen, Novartis and Sanofi Genzyme; serves on the editorial board of the Acta Neurologica Scandinavica; has received unconditional research grants from Biogen, Novartis and Teva.

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P1231

National, real-time monitoring of MS-immunotherapy patterns with visualisation and analysis platform (VAP) implemented in swedish MS-registry

L. Stawiarz[1], E. Hagel[2], H. Eriksson[3], J. Hillert[4]
[1]Clinical Neuroscience (CNS), Karolinska Institutet, [2]Department of Learning, Informatics, Management and Ethics (LIME), Karolinska Insitutet, Stockholm, [3]Carmona AB, Halmstad, [4]Clinical Neuroscience (CNS), Karolinska Insitutet, Stockholm, Sweden

Background: MS patients can be offered a wide range of immunomodulating treatments (DMT) nowadays. Many new potential treatments for MS are in phase 2 or 3 clinical trials and will soon contribute to the broad choice of possible therapies. Disease modifying drugs (DMD) can be prescribed according to the individual neurologists' preferences with local limitations, traditional strategy of 1st or 2nd line treatments, tailored to an individual patient's medical status and predicted response, or be in line with MS guidelines. In such a situation, the space and time patterns of MS treatment are difficult to acquire.
Objectives: In the advances of treatment options, development of a real-time, easy and flexible monitoring system of DMD use, has been highly requested. Flexibility meant a possibility to select single or any group of DMDs with other parameters defining a particular subgroup. The intention was to implement both cross sectional comparisons and longitudinal follow-ups of treatment strategies. The aim of the project was to design a system, with an intuitive user interface, on-the-fly calculations and easy access.
Methods: All the neurological clinics in Sweden are involved in gathering DMT data on MS patients in Swedish MS Registry (SMSreg) on a regular, however not mandatory basis. SMSreg has over 82% coverage of prevalent MS patients i.e. 15.7 of 19.5 thousand estimated patients. Total number of registered DMDs is 28.7 thousand on 12.7 thousand unique MS patients with treatment data.
Results: Real-time monitoring of DMDs in VAP is divided into two groups of customizable diagrams for cross sectional comparisons (daily status) and longitudinal ones. The user can compare the drugs use in many ways. Started, discontinued and ongoing treatments can be selected. All, treatment-naïve or further treatment patients can be chosen. Divisions by gender, clinical course, disease duration and age groups are implemented. Monitoring can be done on five administrative levels from own neurologist's patients up to the country level. The system is available through an intuitive user interface supported with simple graphical selection tools.
Conclusions: Monitoring of DMT with the help of real-time VAP reports offers a wide range of flexible, real-time visualization and statistics on a national level. It satisfies the needs of providing detailed information on treatment patterns back to decision makers, clinicians and researchers, which are otherwise challenging to gather.

Disclosure

Leszek Stawiarz declares no conflict of interests.
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P1232

Durable improvement in clinical outcomes in treatment-naive patients with relapsing-remitting multiple sclerosis who switched from SC IFNB-1a to alemtuzumab (care-MS I extension study 4-year follow-up)

C. Oreja-Guevara[1], R. Alroughani[2], D. Brassat[3], A.N. Boyko[4], P. McCombe[5], B. Steingo[6], B. Van Wijmeersch[7], D.H. Margolin[8], K. Thangavelu[8], C.E. Rodriguez[8], P. Vermersch[9], on behalf of the CARE-MS I Investigators
[1]University Hospital San Carlos, Madrid, Spain, [2]Amiri Hospital, Sharq, Kuwait, [3]Purpan Hospital and Mixed Unit of Research 1043, University of Toulouse, Toulouse, France, [4]Pirogov Russian National Research University & Demyelinating Diseases Center, Usupov Hospital, Moscow, Russian Federation, [5]University of Queensland, Brisbane, QLD, Australia, [6]Fort Lauderdale Multiple Sclerosis Center, Fort Lauderdale, FL, United States, [7]Rehabilitation and MS Centre Overpelt BIOMED, University Hasselt, Hasselt, Belgium, [8]Sanofi Genzyme, Cambridge, MA, United States, [9]University of Lille, Lille, France

Background: In CARE-MS I (NCT00530348), alemtuzumab significantly reduced the annualised relapse rate (ARR) versus SC IFNB-1a over 2 years in treatment-naive patients with active relapsing-remitting multiple sclerosis (RRMS). Patients completing CARE-MS I could enter an extension study (NCT00930553), in which SC IFNB-1a-treated patients switched to alemtuzumab.
Goal: To evaluate 4-year efficacy and safety of alemtuzumab in patients who switched from SC IFNB-1a in CARE-MS I.
Methods: Following SC IFNB-1a discontinuation, patients received 2 courses of alemtuzumab 12 mg (Month 0: 5 days; Month 12: 3 days), followed by as-needed alemtuzumab for relapse or MRI activity or other DMT per investigator discretion. Assessments: ARR, 6-month confirmed disability worsening (CDW; ⩾1-point EDSS increase [⩾1.5-point if baseline EDSS=0]) and confirmed disability improvement (CDI; ⩾1-point EDSS decrease [baseline score ⩾2.0]), EDSS stability (⩽0.5-point change) or improvement (⩾1.0-point decrease), no evidence of disease activity (NEDA), and adverse events (AEs).
Results: 144/173 (83%) CARE-MS I SC IFNB-1a-treated patients enrolled in the extension; 125 (87%) remained on study 4

years later. ARR decreased from 0.39 during SC IFNB-1a treatment to 0.11 over the first 2 years after switching to alemtuzumab. Over 2 years after switching to alemtuzumab, the proportions of patients with no evidence of relapse increased from 60% after SC IFNB-1a treatment to 80% and the proportion achieving NEDA increased from 27% to 54%. In Year 4 after switching, ARR remained low (0.15), and the proportions with no evidence of relapse (86%) and achieving NEDA (54%) remained high. 86% of patients had improved/stable EDSS since switching to alemtuzumab. Over the 4 years since switching, 81% had no evidence of 6-month CDW; 24% had 6-month CDI. These results were achieved with most patients (75%) receiving no additional treatment after their initial 2 courses of alemtuzumab. The 4-year AE profile of alemtuzumab after switching was consistent with that of alemtuzumab-treated patients in the core study.

Conclusion: Alemtuzumab improved clinical outcomes in the first 2 years after switching from SC IFNB-1a; these improvements were durable over the following 2 years with most patients receiving no additional treatment. Based on these findings, alemtuzumab may provide a unique treatment approach with durable efficacy in the absence of continuous treatment for RRMS patients who switched from SC IFNB-1a.

Disclosure

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P1233

Efficacy and safety of Natalizumab treatment for relapsing-remitting multiple sclerosis: results from a retrospective French cohort

R. Beyrouti, S. Courtois, E. Penombre, S. Mostoufizadeh, E. Cohen

Neurology, Emile Muller Hospital, Mulhouse, France

Background: Natalizumab has been commercially available for almost a decade, with approximately 140,000 patients exposed and 400,000 patient-years (PYs) of exposure. The large exposure to Natalizumab, especially compared with more recently approved multiple sclerosis (MS) disease-modifying therapies, provides the opportunity to assess postmarketing data for evidence of rare and/or latent events.

Objective: Report the long-term effectiveness and safety of Natalizumab in a French Cohort of relapsing-remitting multiple sclerosis (RRMS) patients.

Methods: This retrospective study enrolled 120 MS patients under Natalizumab treatment in Mulhouse, France, over a period of ten years. Clinical and radiological disease activity was assessed compared to baseline: Expanded Disease Scale Score (EDSS), annualized relapse rate (ARR), no evidence of disease activity (NEDA) defined by absence of relapses, no sustained EDSS progression, and absence of active magnetic resonance imaging (MRI) characterized by new T2 or T1 gadolinium-enhancing lesions. Natalizumab therapy discontinuation and adverse events were recorded for safety and tolerability evaluation.

Results: The detailed study will be presented.

Conclusion: In this French cohort, Natalizumab is effective on ARR reduction, MRI stabilization with 2/3 of patients with NEDA. This clinical practice cohort is consistent with efficacy data from phase 3 trials. The frequency of side effects leading to cessation of treatment, was higher in clinical practice than in clinical trials.

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Elie Cohen: nothing to disclose

P1234

Long-term efficacy, safety, tolerability and quality of life with fingolimod treatment in patients with multiple sclerosis in real-world settings in France: VIRGILE one-year results

C. Papeix[1], C. Lebrun-Frenay[2], E. Leray[3], G. Kobelt[1,4], J.M. Visy[5], M. Coustans[6], M. Debouverie[7], S. Aly[8], I. Chouette[8]

[1]La Salpêtrière Hospital, Paris, [2]Pasteur Hospital, Nice, [3]EHESP Sorbonne, Paris Cite, France, [4]Lund University, Lund, Sweden, [5]SCP de neurologie, Reims, [6]Laënnec Hospital, Quimper, [7]Central Hospital, Nancy, [8]Novartis Pharma S.A.S., Rueil-Malmaison Cedex, France

Background: Fingolimod 0.5mg daily has an established efficacy, safety and tolerability profile in patients with relapsing-remitting multiple sclerosis (RRMS), with data from a large clinical development programme demonstrating its benefits on relapse rates, disability progression and imaging activity compared to placebo and/or IFNB-1a IM. However, more limited data is available in real-world settings, which include patients with a wider range of co-morbities and concomitant treatments. The French Health Authorities (HAS, CEPS) requested a pharmacoepidemiological study to assess the use and impact of fingolimod in the treatment of highly active forms of RRMS in France. They also requested that a natalizumab arm was included in the study.

Objective: To assess the effect of fingolimod 0.5mg on relapse activity, disability progression and quality of life in real-life practice. The study will also describe baseline characteristics of patients treated with fingolimod and natalizumab, and assess the

impact of fingolimod treatment on health resources consumptions in both groups.
Methods: This is a non-interventional, multicentre, post-authorisation, observational study with prospective follow up of patients treated with fingolimod or natalizumab for 3 years, and potentially an additional 2 years for patients in the fingolimod group. The primary endpoint is the change in annualised relapse rate (ARR) at 2 years compared to baseline (relapse rate in the year prior to treatment).
Results: A total of 1111 patients in the fingolimod arm and 334 patients in the natalizumab arm have been enrolled. Full efficacy and safety results (number of relapses, EDSS, tolerability) will be presented for patients who are at one-year follow up.
Conclusion: VIRGILE is the largest study in France to date evaluating the long-term efficacy, safety, and tolerability profiles of fingolimod in real-world settings. The one year data from this interim analysis supports the long-term efficacy and safety profile of fingolimod.

Disclosure

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CLF has received consultancy fees from Almirall, Merck, Novartis, Biogen, MEDDAY, Roche, Teva.·
GK has received consultancy fees from Biogen, Merck Serono, Novartis, Genzyme, Roche·
JMV has received compensation from Novartis for educational activity and consulting·
MC disclosures: Novartis, Biogen, Teva, Genzyme·
CP: has received compensation as a consultant, advisory board member or speaker for Roche, Novartis, Biogen idec, Teva Aventis, Genzyme- Sanofi.·
EL has received compensation as a consultant for Novartis, Biogen, medday·
SA and IC are employees of Novartis Pharma S.A.S·
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P1235

Long-term follow-up of patients treated with natalizumab: results from a single centre cohort

L. Midaglia[1], À. Vidal-Jordana[1], P. Mulero[1], M. Zuluaga[1], I. Galán[1], G. Arrambide[1], J. Río[1], C. Nos[1], J. Castilló[1], B. Rodríguez-Acevedo[1], M. Comabella[1], C. Auger[2], J. Sastre-Garriga[1], Á. Rovira[2], M. Tintoré[1], X. Montalban[1]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Dept & Epidemiology Dept, [2]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Natalizumab has demonstrated to be effective in controlling disease activity in relapsing-remitting multiple sclerosis (RRMS) patients. However, data regarding long-term efficacy are still needed.
Objective: To assess long-term natalizumab effectiveness in patients treated for ⩾ 5 years in a single MS centre.
Methods: From a prospective on-going cohort including all patients starting natalizumab in our centre, patients that started natalizumab ⩾ 5 years ago at the time of data collection were sellected. Patients are followed every 3 months, and presence of relapses and EDSS score is collected. Annualized relapse rate (ARR) in the 3 years prior to treatment onset and during natalizumab treatment was calculated (pre and on-ARR, respectively). Patients underwent MRI scans at baseline and yearly thereafter. Number of Gd-enhancing lesions was collected at each time point. Baseline characteristics and reasons leading to discontinuation are described. Clinico-radiological disease activity during the first 5 years of treatment is analyzed and compared to pre-treatment period.
Results: One hundred and sixty-two out of 220 patients should have received natalizumab ⩾ 5 years; 66 patients (40.7%) stopped treatment before this time point mainly due to PML risk (23.5%) or ineffectiveness (8.6%). Compared to patients who continued treatment, patients stopping natalizumab due to ineffectiveness had a longer disease duration (p=0.023) and a higher baseline EDSS (p=0.022). Sixty out of 96 patients who remained on natalizumab treatment ⩾5 years have been consecutively followed in our centre, without treatment withdrawals at any time and were included in the analysis. Mean follow-up time was 84.2 months (SD 12.3); at baseline mean age at treatment onset was 34.3 (SD 8.6), mean disease duration was 9.2 years (SD 5.6), mean pre-ARR was 1.3 (SD 1), and median EDSS was 4.0 (range 1-6.5). A 70.2% presented Gd-enhancing lesions at baseline MRI with a median number of 1 (range 0-40). ARR significantly decreased during natalizumab treatment (on-AAR 0.10; p< 0.001). A significant decrease of Gd-enhancing lesions were observed during the follow-up period (5.4% at year 1, 1.8% at year 2, 0% at year 3 and 4, and 1.8% at year 5; p< 0.001 for all comparisons). Treatment discontinuation ⩾ 5 years was uncommon (11.2%) mainly due to PML risk.
Conclusions: Natalizumab is effective in reducing disease activity in RRMS patients, and its effect is maintained for at least 5 years.

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participated in advisory boards of clinical trials in the past years with Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Receptos, Roche, Sanofi-Genzyme and Teva Pharmaceutical

P1236

Lymphopenia and eosinophilia in dimethyl fumarate treated patients

A. Vinagre Aragón, C. García Malo, S. Novo Ponte, L. Mena Romo, I. Moreno Torres, M.R. Blasco Quílez, A. García Merino
Neurology, Hospital Puerta de Hierro, Madrid, Spain

Background: Dimethyl fumarate (DMF) is an effective oral therapy for relapsing remitting multiple sclerosis with different biological effects on immunomodulation and neuroprotection.
Objectives: To analyse the impact of DMF therapy on blood counts in a group of patients treated over a 12 month period.
Methods: 106 patients were included in the study, 70% females, with a mean EDSS of 1.41. EDSS, number of relapses and adverse events were recorded every 3 months. Complete blood count (CBC), biochemical tests and urinanalysis were performed at months 1,2,3,6,9 and 12.
Results: 57% of patients developed lymphopenia: 67% mild (1300-800/uL), 21% moderate (800-500/uL) and 6% severe (< 500/uL) lymphopenia. Different patterns of lymphopenia were observed: progressive 8.4%, persistent 33% and transient 17%. There was no relation between those patterns and previous treatments. A striking finding was the frequent (24.5%) presence of eosinophilia, detected most often in the first month of therapy (80% of cases), with values ranging 500-5.300/uL. Eosinophilia was asymptomatic in all but one, and disappeared in 91% after 2 months. Treatment had to be withdrawn in 2 patients: in one case due to progressive severe lymphopenia and because of eosinophilia with urticaria in another patient. Compared to the rest of patients, those who developed early eosinophilia had an increased tendency to suffer lymphopenia more frequently.
Conclusions: DMF has a good tolerability profile. However, a significant percentage of patients develop lymphopenia. Different grades and patterns of lymphopenia have been observed in our series. In addition, eosinophilia, an observation generally unnoticed due to its early presentation, has been observed in a quarter of patients. The meaning of these observation is unclear. We could not establish a significant relation neither between eosinophilia and lymphopenia nor between previous treatments and the development of blood count disturbances. Clinical vigilance and periodic blood tests are mandatory.

Disclosure

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P1237

The value of PASAT short-term training: Only a ‚practice effect' or does it tell us more about MS?

M.P. Sormani[1], N. de Stefano[2], G. Giovannoni[3], D.W. Langdon[4], D. Piani Meier[5], D.A. Häring[5], D. Tomic[5], L. Kappos[6]
[1]University of Genoa, Genoa, [2]University of Siena, Siena, Italy, [3]Royal London Hospital, [4]Royal Holloway University of London, London, United Kingdom, [5]Novartis Pharma AG, [6]University Hospital, University of Basel, Basel, Switzerland

Background: Cognitive performance measured by Paced Auditory Serial Addition Test (PASAT) was shown to correlate with brain volume (BV), but is difficult to interpret longitudinally due to a practice effect. While BV loss (BVL) is increasingly recognized as predictor for disability progression, the association between learning ability (practice effect) with disease characteristics and long-term disease outcome is poorly investigated.
Objectives: To determine the correlation between practice effect and disease characteristics, and the relevance of practice effect and BV for future disability worsening and treatment impact.
Methods: In this posthoc analysis of data pooled from FREEDOMS and FREEDOMS II (n=1009, complete data set), practice effect was assessed by evaluating the change in PASAT score from screening (Day -14) to baseline (Day 0). High learners and low learners were defined as having a PASAT score change above or below the median of their screening PASAT quartile group. A multiple regression model was used to evaluate the correlation between practice effect and baseline disease characteristics, and a Cox regression hazard model to assess the impact of learning ability, baseline normalised BV (NBV) and treatment on BVL and 3-month confirmed disability progression (CDP) over 2 years.
Results: Mean screening PASAT score was 45.4, increasing on average by 3.2 from Day -14 to Day 0; change ranged from 5.0 (Q1) to 0.5 (Q4). Higher learners had higher NBV (p< 0.001), lower clinical and MRI disease burden (EDSS, p=0.031; T2LV, p=0.009) and younger age (p=0.003) at baseline. NBV was correlated with CDP (HR 0.758, p=0.006) but PASAT Day -14 (HR 0.990, p=0.151) or PASAT change (HR 0.953, p=0.779) did not correlate with CDP when adjusted for NBV. Fingolimod had an effect on BVL (difference 0.39%, p< 0.001), with low learners experiencing greater BVL at Month 24 than high learners (difference 0.17%, p=0.058). There was an effect of fingolimod on disability progression (HR 0.561, p=0.001), which was greater in high learners (HR 0.396, p< 0.001) than in low learners (HR 0.798, p=0.351), p for interaction=0.05.
Conclusions: The data suggest that short-term changes in PASAT are of clinical relevance and depend on NBV, disease severity and age. High learners had a lower rate of BVL and benefited more from treatment than low learners, supporting the early implementation of efficient treatment strategies that slow BVL for a favorable long-term prognosis.

Disclosure

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Nicola De Stefano has served on scientific advisory boards and steering committees of clinical trials for Merck Serono SA, Novartis Pharma AG and Teva and has received support for congress participation or speaker honoraria from Bayer Schering AG, Biogen Idec, Merck Serono SA, Novartis Pharma AG, Sanofi-Aventis and Teva
Daniela Piani Meier, **Dieter A Häring**, **Davorka Tomic** are employee of Novartis

P1238

Anti-JCV antibody serostatus in a long-term natalizumab infusing population

T. Hoyt, A. Christensen, R. Metzger, J.F. Foley
Rocky Mountain MS Research Group, Salt Lake City, UT, United States

Background: John Cunningham virus (JVC) antibody serostatus is being utilized to stratify risk of developing progressive multifocal leukoencephalopathy (PML) in natalizumab infusing patients with multiple sclerosis (MS). In the US prescribing information for natalizumab, seroconversion is reported to be 3-8% annually. Findings from recent studies are inconsistent regarding the impact of natalizumab therapy duration on the rate of JCV seroconversion and index values. The aim of this study was to characterize serostatus changes longitudinally in a long-term natalizumab treated US cohort.
Methods: A total of 981 patients were tested for anti-JCV antibodies using the STRATIFY JCV Gen2 assay between Jan 2013 and Mar 2016. Of these, 552 had a first and last test separated by at least 180 days. Patients were further divided into two infusing cohorts: Group 1 - First test occurring after the initiation of natalizumab (n = 411); Group 2 - First test occurring prior to the initiation of natalizumab (n = 141).
Results: At baseline, 981 patients were anti-JCV antibody seropositive (60%) and 393 (40%) were seronegative. For Group 1, the average time between the first and last test was 35.5 months and the natalizumab treatment duration was 81.7 months. During the testing period 222 patients remained positive (54.0%), 146 remained negative (35.5%), 31 switched from negative to positive (7.5%), and 12 switched from positive to negative (2.9%). For Group 2, the average time between the first and last test was 19 months and the natalizumab treatment duration was 15.1 months. During the testing period 58 remained positive (41.1%), 67 remained negative (47.5%), 11 switched from negative to positive (7.8%), and 5 switched from positive to negative (3.5%). The annualized seroconversion rates for Group 1 and Group 2 were 6.0% and 9.0%, respectively. Conversely, the annualized seroreversion rates were 1.8%, 5.1%, respectively.
Conclusion: Baseline seroprevalence, without respect to previous or current therapies, is similar to that reported in other MS populations. For both long-term natalizumab patients and those initiating therapy, the net change results in an annualized seroprevalence rate increase of 4.2% and 3.9%, respectively. Natalizumab therapy did not appear to alter the conversion rate. Further analysis of anti-JCV antibody index levels will also be reported.

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Ryan Metzger owns stock in Biogen.
Dr. Foley participates in the Speakers´ Bureaus for Biogen, Genentech-Roche, Genzyme and Accorda. Dr. Foley advises for Biogen, Genentech-Roche, and Genzyme.

Risk management for disease modifying treatments

P1239

TRUST-Study: methods of an optional MRI-safety surveillance for progressive multifocal leukoencephalopathy (PML) in relapsing remitting multiple sclerosis patients treated with Natalizumab

A. Gass[1], J. Würfel[2], I. Kompan[3], J. Gregori[3], T. Ziemssen[4], V. Limmroth[5], A. Bayas[6], J. Haas[7], R. Linker[8], M. Mäurer[9], M. Stangel[10], B. Tackenberg[11], M. Meergans[12], O. Harlin[13], H.-P. Hartung[14]
[1]Department of Neurology, University Medicine Mannheim UMM, University of Heidelberg, Mannheim, Germany, [2]Medical Image Analysis Center (MIAC AG), Basel, Switzerland, [3]mediri GmbH, Heidelberg, [4]MS Center Dresden, Center for Clinical Neuroscience, University Hospital Carl Gustav Carus, Dresden University of Technology, Dresden, [5]Department of Neurology, Cologne General Hospitals, University of Cologne, Cologne, [6]Department of Neurology, Hospital Augsburg, Augsburg, [7]Department of Neurology, Jewish Hospital Berlin, Berlin, [8]Department of Neurology, University Hospital Erlangen, Friedrich-Alexander-University, Erlangen, [9]Department of Neurology, Caritas-Hospital Bad Mergentheim, Bad Mergentheim, [10]Clinical Neuroimmunology and Neurochemistry, Department of Neurology, Hannover Medical School, Hannover, [11]Department of Neurology, Philipps-University and University Clinics Gießen and Marburg, Marburg, Germany, [12]Biogen, Zug, Switzerland, [13]Biogen, Ismaning, [14]Department of Neurology and Center for Neuropsychiatry, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany

Background: Signs of PML on MRI may occur before clinical manifestations; therefore early detection is crucial. As signs are initially subtle and may mimic existing MS-lesions, extensive experience is needed for identification. MRI-utilization and -reading experience are heterogeneous in daily practice and 2nd-opinion-reading by expert neuro-radiologists is not commonly practiced. Here we report methods and findings regarding PML-detection with obtaining optional MRI 2nd opinion.
Objectives: To investigate consequences of integrated patient-management in natalizumab (NTZ.) treated patients (pat.) as a

valuable approach to improve collaboration between neurologists, (neuro-) radiologists and MS-experts, potentially improving patient outcomes.
Methods: This non-interventional study aims to include 1260 pat. (≥12 months on NTZ prior study start;
3 years follow-up). Data are collected to capture in-practice MRI-procedures and patient-related data. An optional 2nd opinion expert read on MRI-scans, focusing on pharmacovigilance measures, is available. Radiology sites receive support to optimize MRI-quality if requested. Pseudonymized MRI-data are provided, followed by image quality-control and expert reading.
Results: Until December 6, 2015, 844 pat. have been included by 143 neurologists. 67 radiologists consulted for optional MRI 2nd opinion in 821 MRI-datasets representing 417 of the 844 pat. Recommended MRI-protocol was followed in 43.6% of cases, 98% of scans were of sufficient quality, earlier reference scans were provided in 14% of cases. Scans were evaluated regarding signs of PML and reports were sent to the sites within 3.3 (SD: 4.7) working days upon receipt of scans. 6 cases of suspected PML were reported within the study framework. Of those, 4 pat. were diagnosed with PML. MRI was provided from all 4 pat. for 2nd-opinion expert read. PML was detected in the 2nd option read in 2 pat. and was confirmed in the other 2 cases subsequently. One patient had been non-symptomatic to the PML lesion.
Conclusions: MRI-Safety surveillance in MS is a relatively new field and processes for optional patient care are still under development. Suspicion of PML and suggestion of extended diagnostic work-up can be initiated through an optional MRI-central reading. The initial results presented here emphasize the value of close interdisciplinary collaboration for patient surveillance, but needs to be proven in a larger setting.
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IK and JG: employees of *mediri GmbH, Heidelberg.*
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MMa: has received honoraria from Bayer HealthCare, Biogen, Genzyme, MerckSerono, Novartis, Roche, SanofiAventis, TEVA.
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MMe and OH: are employees and hold stocks/stock options in Biogen.
HPH: has received honoraria for consulting and speaking from Bayer Healthcare, Biogen, GeNeuro, Genzyme, Merck, Novartis, Octapharma, Opexa, Roche, Teva

P1240

Rituximab as an effective treatment option after natalizumab withdrawal

S. Malucchi, M. Capobianco, A. di Sapio, M. Lo Re, F. Sperli, M. Malentacchi, M. Matta, A. Oggero, A. Bertolotto
AOU San Luigi Gonzaga, Regional Multiple Sclerosis Center, Neuroscience Institute Cavalieri Ottolenghi, Orbassano, Italy

Background: Natalizumab is highly effective in reducing multiple sclerosis disease activity, however it carries a risk of progressive multifocal leukoencephalopathy (PML), that represents the major reason of treatment discontinuation. No guidelines about patients´ management after natalizumab withdrawal exist. In a previous study we presented our experience about the use of rituximab after natalizumab discontinuation in 10 patients. Here we describe a larger population treated with rituximab after natalizumab.
Aim of the study: To evaluate rituximab efficacy in controlling disease activity after natalizumab discontinuation.
Patients and methods: 29 relapsing remitting multiple sclerosis patients (22 female and 7 male) have been treated with natalizumab for a median number of 51 infusions (range 12-100). 28 patients stopped natalizumab due to the high risk of PML and 1 patient stopped it for convenience. Although in Italy the use of rituximab in multiple sclerosis is "off label", these patients have been proposed to switch to rituximab after a wash out period of about two months because of the lack of valid therapeutic options. Each patient underwent gadolinium-enhanced brain MRI scan after the last infusion of natalizumab and two months later, in order to exclude radiological signs suggestive for PML ; then brain MRI was performed every six months.

Median wash out period after natalizumab discontinuation was 3.3 months (1.4-7.9 months). At first Rituximab protocol was 375mg/mq once/week for 4 weeks (first cycle) and 1000mg at day 0 and day 15 in case of CD19 increase and/or clinical relapse or radiological reactivation (second cycle); subsequently the protocol has been changed in 1000mg at day 0 and day 15 every six months.
Results: During the wash out period disease stability was observed in all patients except the one with a wash out of 7.9months; radiological stability was observed at 6 months after rituximab administration in all the patients and at 12 months in 20 out of 29 patients with a follow up of one year. Exacerbation of

sensitive symptoms without evidence of brain MRI activity was observed in two patients during the follow up.
Conclusions: rituximab represents a valid and effective treatment option after natalizumab discontinuation; rituximab therapy must be started after a short wash out period.

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Oggero A, received speaking honoraria from Biogen
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P1241

Infection prevention protocols in the monographic alemtuzumab unit: towards improving safety

A. Domínguez Mayoral[1], S. Eichau Madueño[2], Z. Palacios[3], P.S. Soledad[2], I.A. Guillermo[1], Multiple Sclerosis Unit (Dr Izquierdo)
[1]Neurology, [2]Macarena Hospital, [3]Integral Medicine Unit, Macarena Hospital, Seville, Spain

Background: Alemtuzumab is one of the most promising drugs in Multiple Sclerosis. The aim is to asses if a protocols with Preventive and Infectious Unit could be useful for improving drug safety, following the example of other biologics drugs.
Methods: We collected data of 35 patients of our monographic Alemtuzumab Unit. The pre-screening included HIV, Varicella, Hepatitis, Measles, Mumps and Rubella serologies, QuantiFERON, Mantoux and chest radiography. Routine immunizations in the months prior to infusion were against pneumococcus, Haemophilus influenza, hepatitis A and B, meningoco and tetanus. Vaccination of measles, rubella, mumps and Varicella depended on the serological results. A checklist of adverse effects was applied monthly after the treatment. The second dose of vaccine as tetanus, hepatitis B or pneumococcus was measured when the drug lymphopenia is corrected.
Results: We detected 27 infections in our sample. All cases were resolved with treatment. We found 13 upper tract infections and 4 gastroenteritis and 2 patients with herpes labialis and urinary infection. We collected 3 cases of prolonged fever (all of them solved with Septrim or antibiotics). One case was reported of: fungal infection, infection cyst buccal mucosa, pneumonia, ear infections, onychomycosis and infectious cellulitis.
Conclusions: This protocol with Infectious and Preventive Unit can minimize infections incedence. Fever of unknown origin must be study properly in our patients. It must assess the prolongation of preventing with acyclovir if there are previous herpes and the need for prophylactic antibiotics in patients with recurrent respiratory infections. Futher studies to improve knowledge about immunization after vaccination are needed.

Disclosure

There are not conflict of interest and source of founding

P1242

Prospective, multicentric study of using JCV serology and L-selectin for PML risk assessment

N. Schwab[1], T. Schneider-Hohendorf[1], I. Meinl[2], S. Windhagen[3], T. Kümpfel[2], H. Wiendl[1]
[1]University of Muenster, Muenster, [2]Ludwig-Maximilians-University of Munich, Munich, [3]Clinics Osnabrueck, Osnabrueck, Germany

Background: With a PML incidence associated with natalizumab treatment of 4.11 / 1000 patients, there is a need for risk stratification biomarkers. To this end, the manufacturer has introduced the JCV index (= normalized anti-JCV antibody titer). Our group has previously shown that low levels of L-selectin (CD62L) might indicate a higher PML risk as well.
Patients and methods: Since 2011, 140 long-term (mean >4 years) natalizumab-treated patients from three German centers have been included in this prospective study (mean period of observation 3 years). Many of these patients were anti-JCV-positive (66%) with a high JCV index (2.2 in JCV+) and were, therefore, at high PML risk. They have given blood for CD62L measurements between 3 and 14 times (mean 4 times) to observe fluctuations over time and assess risk levels for PML. Enhanced PML risk was defined as at least one time point of CD62L below the threshold of 28.5 (%CD62L+ cells of CD4+ T cells) after thawing.
Results: While individual CD62L-levels fluctuated, over 5 years of observation only 21 of 140 patients (15%) were measured CD62L-low (< 28.5) at least once. Of these 21 patients, 18 were anti-JCV positive (86%). Of these 18 patients, 10 discontinued natalizumab-therapy due to fear of PML, 5 are still undergoing treatment, and 3 developed PML. There was one PML case, who was never measured CD62L-low. PML incidence and, therefore, potential risk in the group of JCV+ CD62L-low patients was 1:6. Current specificity in the ongoing study is 87% over five years and current sensitivity is 3 of 4 or 75%.
Conclusions: The prospective combination of anti-JCV antibody status/index and monitoring of CD62L identifies a group of patients with very high PML risk (1:6) with high specificity (87%) and sensitivity (75%).

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NS has received honoraria for advisory boards and travel expenses from Biogen Idec. TS-H has received travel expenses compensation from Biogen Idec. IM has received travel expenses from Bayer-Schering. SW has received honoraria for lecturing and travel expenses for attending meetings from Bayer-Schering, Biogen Idec, Merck-Serono, Novartis, Sanofi-Aventis, and Teva. TK has received travel expenses and personal compensations from Bayer-Healthcare, Teva, Merck-Serono, Novartis, Sanofi-Aventis, and

Biogen Idec as well as grant support from Bayer-Schering AG. HW has received honoraria and consultation fees from Bayer Healthcare, Biogen Idec, Fresenius Medical Care, GlaxoSmithKline, GW Pharmaceuticals, Merck- Serono, Novartis Pharma, Sanofi Genzyme, and Teva Pharma. NS, TS-H and HW are co-inventors of a patent related to the use of CD62L in PML risk stratification.

P1243

Very early immune thrombocytopenia (ITP) 2 months after first dosing in a patient treated with alemtuzumab for relapsing remitting MS - are our clinical vigilance methods adequate?

J. Haartsen, S. CM Lee, O. Skibina
Eastern Health, Melbourne, VIC, Australia

Introduction: Alemtuzumab is a humanized IgG1 kappa monoclonal antibody approved for treatment relapsing remitting Multiple Sclerosis (RRMS) in Australia. Immune thrombocytopenia (ITP) was recognised in both phase 2 and 3 clinical trials of alemtuzumab as a potential risk factor with this treatment. In the phase 2 clinical trial of annual alemtuzumab for treatment of RRMS, 6 of 216 patients (2.8%) developed ITP. Over mean follow-up of 4.5 years, the incidence rate of ITP was 6.2 (95% confidence interval, 2.3-13.3) per 1000 person-years. Median times from initial and last alemtuzumab exposure to ITP diagnosis were 24.5 and 10.5 months, respectively[1]. In the phase 3 trials CARE MS 1 and 2, the overall rate of ITP on Alemtuzumab 12mg annual dose was 1.6%. Previously ITP associated with alemtuzumab treatment was characterized by delayed presentation after drug exposure, responsiveness to conventional ITP therapies, and prolonged remission.
Study: We present a 42 year old woman with a diagnosis of RRMS in 2007, who was treated without complication in our hospital with first course alemtuzumab 22-26.6.2015. Her routine post Alemtuzumab monthly full blood examination on 20.8.2015 was normal, platelet count was 296. On 31.8.2015 she reported a single mouth lesion and small cluster of petechiae on chest, legs, and stomach. She was advised to have her platelets retested as soon as possible and on the following day the result was a count of 14 with no other abnormalities. She was immediately admitted to our hospital, and treated with weaning doses of oral prednisolone, starting dose of 75mg daily. Three days after her admission her platelets increased from 6 at admission to 33 and she was discharged. She was managed as an outpatient with weaning prednisolone over the next 4 months.
Conclusion: Our case highlights the need for clinicians to maintain a high level of vigilance and routine monitoring for ITP in patients treated with alemtuzumab. Routine pathology monitoring is recommended as monthly for 5 years with patients treated with alemtuzumab. However this case occurred outside the routine monitoring schedule, earlier than previously reported and with minor symptomatology. This case highlights the need for a comprehensive patient education approach and provision of services that enable prompt responses to patient's queries and concerns.

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P1244

The influence of information presentation formats on treatment understanding and decision-making in MS patients

G. Reen[1], E. Silber[2], D. Langdon[1]
[1]Psychology, RHUL, Egham, [2]King's College Hospital NHS Foundation Trust, London, United Kingdom

Background: Effective decision-making in Multiple Sclerosis (MS) requires patients to understand complex risk-benefit profiles of disease-modifying drugs (DMDs). Studies have shown the effects of presentation formats on understanding of treatment information, but with limited findings directly relevant to MS patients.
Goal. To identify numerical and graphical formats which facilitate DMD understanding in MS patients, and assess the effect of treatment understanding on confidence in their treatment decisions.
Method: 45 relapsing-remitting MS patients (mean age: 45.96, 34 females) were recruited. They were presented with hypothetical treatment information in differing formats. Decisional confidence was recorded (DCS). All patients were assessed for health literacy (REALM-R), numerical reasoning (VESPAR), pre-morbid IQ (WTAR), fatigue (FSS), depression and anxiety (HADS). Cognitive symptoms were assessed via BICAMS.
Results: Understanding of treatment information was significantly affected by different graphical formats (one-way ANOVA, ($F(1,44)=95.54$, $P< .001$). Treatment understanding was greatest for bar charts (relative to pictographs, $t(44)=3.93$, $p< .001$, and pie charts, $t(44)=16.88$, $p< .001$) and line graphs (relative to pictographs, $t(44)=3.93$, $p< .001$, and pie charts, $t(44)=3.93$, $p< .001$). Treatment understanding was lowest for pie charts.

Understanding of treatment information was also affected by different non-graphical formats ($F(1,44)=240.99$, $p< .001$). Treatment understanding was the greatest for frequencies (relative to percentages, $t(44)=5.86$, $p< .001$, and verbal descriptors, $t(44)=42.65$, $p< .001$). Treatment understanding was the lowest for verbal descriptors.

There were significant correlations between treatment understanding and health literacy ($r=.680$, $p< .001$), numerical reasoning ($r=.643$, $p< .001$), pre-morbid IQ ($r=.628$, $p< .001$), information processing speed ($r=.489$, $p< .01$), verbal memory ($r=.456$, $p< .01$) and visual memory ($r=.336$, $p< .05$).

There was no correlation between treatment understanding and scores of decisional confidence.
Conclusions: Presentation formats affect MS patients' understanding of treatment information. However, an increase in treatment understanding does not improve confidence in their treatment decisions.

Disclosure

GR nothing to disclose.
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P1245

Is Maraviroc useful in immune competent patients? Clinical and radiological features of four Natalizumab-related PML cases

N. De Rossi[1], C. Scarpazza[1], C. Cordioli[1], L. Prosperini[2], M. Capobianco[3], L. Moiola[4], P. Naldi[5], S. Gerevini[6], R. Capra[1]
[1]Multiple Sclerosis Centre, Spedali Civili Brescia, Montichiari, [2]Dept of Neurology and Psychiatry, Sapienza University, Viale Dell'Università, Rome, [3]SCDO Neurologia 2, Centro di Riferimento Regionale Sclerosi Multipla, AOU San Luigi Gonzaga, Orbassano, [4]Department of Neurology, San Raffaele Scientific Institute, Milan, [5]Multiple Sclerosis Centre, Clinica Neurologica, AOU 'Maggiore della Carità' Novara, Novara, [6]Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Background: Progressive Multifocal Leukoencephalopathy (PML) is an uncommon side effect caused by the JC virus, emerging in natalizumab treated multiple sclerosis (NTZ-MS) patients. Immune restoration at NTZ withdrawal can be followed an Immune Reconstitution Inflammatory Syndrome (IRIS), which causes additional damage of the nervous tissues. Although the established utility of corticosteroids in modulating IRIS once arisen, few anecdotal case reports support the possibility that Maraviroc may prevent IRIS and blunt its manifestation. However, Maraviroc efficacy is still controversial.
Goals: To evaluate the impact of Maraviroc in modifying the course of PML and IRIS in NTZ-MS.
Methods: Clinical and MRI data of 34 patients who developed PML were retrospectively collected from 25 Italian sites. Four of 34 patients were treated with Maraviroc. Their clinical course was described and their longitudinal disability scores, measured by means of EDSS, were compared with the clinical course of 19 patients who experienced IRIS without Maraviroc treatment.
Results: In all the patients, Maraviroc therapy was associated with a worsening clinical condition. Despite the use of Maraviroc, three out of four patients developed IRIS. In these patients, IRIS emerged 78.3 (mean) days after Natalizumab discontinuation. In the whole cohort (n=19), IRIS emerged 81.04 (mean) days after Natalizumab discontinuation. Thus, the use of Maraviroc did not change the clinical course of PML, neither in preventing IRIS, not in delaying it. Moreover, Maraviroc was not associated with a better clinical outcome since the difference between the EDSS score at PML onset and at 1 year follow up was 2 and 1.3 points for patients taking and not taking Maraviroc, respectively.
Conclusions: in NTZ-PML related patients, Maraviroc does not show a favorable impact on the management of IRIS and a clear advantage on steroid use.

Disclosure

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P1246

Effect of aspirin on flushing in relapsing-remitting multiple sclerosis patients receiving delayed-release dimethyl fumarate

D. Rog[1], S. Cader[2], T. Harrower[3], C. McGuigan[4], C. Young[5], J. Potts[6], J. Hanna[7]
[1]Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Manchester, [2]University Hospital, Southampton & Hampshire Hospitals Foundation Trust, Southampton, [3]Royal Devon and Exeter NHS Foundation Trust, Exeter, United Kingdom, [4]St. Vincent's University Hospital and University College, Dublin, Ireland, [5]Walton Centre NHS Foundation Trust, Liverpool, United Kingdom, [6]Biogen, Cambridge, MA, United States, [7]Biogen, Maidenhead, United Kingdom

Background: In clinical trials, delayed-release dimethyl fumarate (DMF; also known as gastro-resistant DMF) demonstrated efficacy and a favourable benefit-risk profile in patients with relapsing-remitting multiple sclerosis (RRMS). However, DMF treatment was associated with flushing events in some patients.
Objectives: This phase 4 study (ASSURE; NCT02090413) aimed to evaluate whether enteric-coated oral aspirin (acetylsalicylic acid; ASA) reduces the incidence and/or severity of flushing events in patients with RRMS treated with DMF in clinical practice.
Methods: A randomised, three-arm, multicentre study in the UK and Ireland in which 241 patients received DMF (120mg for 7 days; then 240mg) bd plus 150mg ASA bd (n=80) or 75mg ASA once daily and evening placebo (n=80) or placebo bd (n=81). The primary endpoint was the incidence and severity of patient-reported flushing events during weeks 1-4, captured with the Modified Global Flushing Severity Scale (MGFSS) and the Modified Flushing Severity Scale (MFSS). Post-hoc analyses examined weekly trends in prevalence of flushing events and evaluated the time-by-treatment interaction.
Results: The incidence of flushing events or severity did not show significant differences during weeks 1-4 combined. However, the incidence of MGFSS flushing events was lower with ASA 75mg at week 2 (-14.8%; 95% CI -29.2, -0.3) and week 3 (-17.6%; -32.8, -2.4) and with ASA 150mg bd at week 3 (-19.0%; -34.1,

-3.9) compared to placebo. MFSS flushing events were less common with ASA 150mg bd at weeks 3 (19.0%; -34.2, -3.8) and 4 (-17.6%; -33.7, -1.6) compared to placebo. Additionally, post-hoc analysis of MGFSS looking at the trend in flushing incidence and severity showed a significant treatment effect over time for both ASA doses compared to placebo, suggesting significantly lower rates of flushing and milder severity with ASA 75mg and 150mg bd compared to placebo over time (all $p < .04$). Rates of treatment discontinuation due to adverse events were 6.2% with placebo, 8.8% with ASA 75mg and 7.5% with ASA 150mg bd. Rates of treatment-emergent gastrointestinal disorders were 40.7% with placebo, 43.8% with ASA 75mg and 55.0% with ASA 150mg bd. No new safety concerns emerged.

Conclusions: While these data do not support routine ASA prophylaxis in DMF-treated patients, the results would suggest a role for ASA 75mg or 150mg bd in some RRMS patients with DMF-emergent bothersome flushing.

Disclosure

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James Potts is an employee of and holds stock/stock options in Biogen.

Jerome Hanna is an employee of and holds stock/stock options in Biogen.

P1247

CD62L and prediction of progressive multifocal leukoencephalopathy: the controversy might be time-and technology-related

B. Pignolet[1], N. Schwab[2], T. Schneider-Hohendorf[2], F. Bucciarelli[1], M. Comabella[3], C. Lebrun-Frenay[4], H. Wiendl[2], D. Brassat[1], BIONAT, SFSEP, BEST-MS

[1]Pôle Neurosciences, CHU Toulouse Purpan, Toulouse, France, [2]University of Münster, Münster, Germany, [3]VHIR, Barcelona, Spain, [4]CHU Nice, Nice, France

Background: Current Multiple Sclerosis (MS) treatment strategy is called "escalation" with first and second line therapy. Natalizumab (NTZ) is used as second line therapy essentially because of a higher risk of severe adverse effects. Indeed, concerns about safety appeared with cases of progressive multifocal encephalopathy (PML), a severe adverse effect due to JC virus infection. So, there is an urgent need to find biomarkers of PML risk to rationalize the use of NTZ. Recently, CD62L expression in peripheral blood mononuclear cells (PBMC) was proposed as a new risk minimization factor since a 9-fold lower percentage of CD62L was correlated with the risk of PML. It was later confirmed that low CD62L increased the relative risk 55-fold. In contrast a recent study stated that CD62L was not a reliable biomarker.

Objectives: To resolve the controversy in providing new set of data and confirm CD62L as a robust PML prediction marker when assessed at 2 years of NTZ.

Methods: The BIONAT cohort (1200 patients starting NTZ) with a prospective biological samples collection has been analyzed in a retrospective manner. Using flowcytometry, CD62L level on CD4 T cells derived from frozen PBMC was determined.

Results: Using the retrospective study in the BIONAT cohort, we confirmed that the low level of CD62L on CD4 T cells assessed at 2 years after NTZ initiation could be used as a biomarker of PML risk development ($p=0.0018$). The time-dependent ROC curves showed an excellent prognostic capacity of CD62L for PML prediction in the years following the test (AUC = 0.87), when assessed after two years of NTZ. A CD62L cut-off value of 10% gave the best compromise between sensitivity (80%) and specificity (85%). The hazard ratio was as high as 7 ($p=0.005$).

Conclusion: CD62L is a robust marker for stratifying PML risk in our cohort and may allow to reduce NTZ-related PML cases, when integrated in a stratification algorithm.

Disclosure

B. Pignolet, F. Bucciarelli, C. Lebrun-Frenay report no disclosure. N. Schwab received travel funding from Biogen, speaker honoraria from Novartis, holds a patent for usage of L-selectin as a predictive marker for PML, and received research support from DFG, University Munster. T. Schneider-Hohendorf received travel funding from Biogen, holds a patent for usage of L-selectin as a predictive marker for the risk to develop PML. H. Wiendl is on the scientific advisory board for Bayer Healthcare, Biogen Idec, Sanofi-Genzyme, Merck Serono, Novartis, Roche, and Teva, received travel funding and/or speaker honoraria from Bayer Vital GmbH, Bayer Schering AG, Biogen, CSL Behring, EMD Serono, Fresenius Medical Care, Sanofi-Genzyme, Merck Serono, OmniaMed, Novartis, and Teva, is on the editorial board for *Journal of Clinical Practice*, *Journal of Neuroinflammation*, and *PLoS One*, has consulted for Biogen Idec, Merck Serono, Novartis, OmniaMed, Roche, and Sanofi-Genzyme, received research support from Bayer Healthcare, Bayer Vital, Biogen Idec, Merck Serono, Novartis, Sanofi-Genzyme, Sanofi US, Teva Pharma. German Ministry for Education and Research, Deutsche Forschungsgesellschaft, European Union, Else Kroner Fresenius Foundation, Fresenius Foundation, Hertie Foundation, NRW Ministry of Education and Research, Interdisciplinary Center for Clinical Studies Muenster, RE Children´s Foundation, and Else Kroner Fresenius Foundation. D. Brassat receives travel funding and/or speaker honoraria from Biogen, Sanofi-Genzyme, Teva, Merck Serono, Bayer, and Almirall, received research support from the French Ministry of Health, French Multiple Sclerosis Society, and the European Union.

P1248

Infections and serious infections with ocrelizumab in relapsing multiple sclerosis and primary progressive multiple sclerosis

H.-P. Hartung[1], D.L. Arnold[2,3], A. Bar-Or[2], G. Comi[4], J. de Seze[5], G. Giovannoni[6], S.L. Hauser[7], B. Hemmer[8,9], L. Kappos[10], F. Lublin[11], X. Montalban[12], K.W. Rammohan[13], K. Selmaj[14], A. Traboulsee[15], P. Chin[16], C. Li[17], N. Mairon[17], J. Napieralski[17], J. Wolinsky[18]

[1]Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany, [2]McGill University, [3]NeuroRx Research, Montreal, QC, Canada, [4]University Vita-Salute San Raffaele, Milan, Italy, [5]University Hospital of Strasbourg, Strasbourg, France, [6]Queen Mary University of London, London, United Kingdom, [7]University of California, San Francisco, CA, United States, [8]Technische Universität München, [9]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, [10]University Hospital Basel, Basel, Switzerland, [11]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [12]Vall d'Hebron University Hospital, Barcelona, Spain, [13]University of Miami, Miami, FL, United States, [14]Medical University of Lodz, Lodz, Poland, [15]University of British Columbia, Vancouver, BC, Canada, [16]Genentech, Inc., South San Francisco, CA, United States, [17]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [18]University of Texas Health Science Center at Houston, Houston, TX, United States

Background: Increased risk of infection has been reported with multiple sclerosis (MS) disease-modifying treatments; assessment of infection is an important component of the ocrelizumab (OCR) safety profile. OCR was evaluated in patients with relapsing MS (RMS; two identical, Phase III, interferon beta-1a [IFNβ-1a]-controlled studies [OPERA I and II]) and primary progressive MS (PPMS; a Phase III, placebo [PBO] -controlled study [ORATORIO]).
Objective: To evaluate infections and serious infections in patients with RMS or PPMS treated with OCR.
Methods: In OPERA I and II, patients were randomised 1:1 to OCR 600mg via intravenous (IV) infusion every 24 weeks or IFNβ-1a 44μg three-times weekly for 96 weeks. In ORATORIO, patients were randomised 2:1 to OCR 600mg as two 300mg IV infusions 14 days apart, or matched PBO every 24 weeks for ⩾120 weeks. Infections were classified by the Medical Dictionary for Regulatory Activities system organ class and preferred term.
Results: In pooled analyses of OPERA, the proportion of patients reporting an infection was 58.4% and 52.4% in the OCR and IFNβ-1a groups, respectively; common infections (⩾10% in either group) reported more frequently in the OCR group were upper respiratory tract infections (URTI) and nasopharyngitis. Most infections were mild to moderate and recovered on treatment. Two OCR-treated patients (< 1%; both non-serious) withdrew due to infections. The proportion with any serious infection was 1.3% in the OCR group and 2.9% in the IFNβ-1a group. In ORATORIO, the proportion of patients reporting an infection was 69.8% and 67.8% in the OCR and PBO groups, respectively; common infections (⩾10% in either group) reported more frequently in the OCR group were URTI and influenza. Most infections were mild to moderate, and the rate of withdrawal due to infections was low (OCR, 0.8%; PBO, 1.3%).The proportion of patients with serious infections was 6.2% and 5.9% in the OCR and PBO groups, respectively. No opportunistic infections were reported in any study over the controlled treatment periods. There were no deaths related to infection in OPERA and two deaths (< 1%) in ORATORIO in the OCR group (pneumonia aspiration and pneumonia; unrelated to OCR per investigator and related per sponsor).
Conclusion: The proportion of serious infections was numerically lower in patients treated with OCR compared with IFNβ-1a in patients with RMS and similar compared with PBO in patients with PPMS.
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Disclosure

Douglas Arnold reports equity interest in NeuroRx Research, which performed the MRI analysis for the trial, and consultation fees from Acorda Therapeutics, Biogen, Genzyme, F. Hoffmann-La Roche Ltd., Innate Immunotherapeutics, MedImmune, Mitsubishi Pharma, Novartis, Receptos, Sanofi, and Teva.
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Xavier Montalban has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Almirall, Bayer, Biogen, Genzyme, Merck, Novartis, Octapharma, Receptos, F. Hoffmann-La Roche Ltd., Sanofi, Teva and Trophos.

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P1249

New algorithm to estimate risk of natalizumab-associated progressive multifocal leukoencephalopathy (PML) in anti-JCV antibody positive patients: analyses of clinical trial data to provide further temporal precision and inform clinical practice

H. Koendgen, I. Chang, B. Sperling, G. Bloomgren, B. Haddock, S. Richman, P.-R. Ho, N. Campbell
Biogen, Cambridge, MA, United States

Background: Previous PML risk estimates in natalizumab-treated patients using postmarketing data were stratified by 3 established risk factors: presence of anti-JCV antibodies, prior immunosuppressant (IS) use, and treatment duration. As individual risk factor information was not available for all patients, population-based assumptions were needed. While essential since 2012 in guiding patient care, these estimates can now be made more precise using patient-level clinical trial data to assess risk associated with anti-JCV antibody levels ("index").

Objective: To derive annual index-stratified PML risk estimates from clinical trials stratified by the 3 risk factors and based on individual patient data.

Methods: Data were pooled from the STRATIFY-2 (N=24,402), TOP (N=5691), TYGRIS (N=6489), and STRATA (N=1094) trials. The life-table method provided forward-looking PML risk estimates for anti-JCV antibody positive patients in yearly epochs. Further index-stratified risk estimates for patients without prior IS were derived by combining these risk estimates with the probability distribution of index values in patients with/without PML using Bayes rule.

Results: The pooled cohort comprised 37,249 natalizumab-treated patients, including 156 patients with confirmed PML. Patients received a median (range) of 42 (1-129) natalizumab doses, 58% were anti-JCV antibody positive, and 14% had prior IS use. For patients with index $\leqslant$0.9, estimated PML risks (per 1000 patients) in yearly epochs 1, 2, 3, 4, 5, and 6 of natalizumab exposure were 0.1, 0.1, 0.2, 0.4, 0.5, 0.6, respectively; for those with index >0.9 to $\leqslant$1.5, respective estimated risks were 0.1, 0.3, 0.8, 2, 2, 3; for those with index >1.5, respective estimated risks were 0.2, 0.9, 3, 7, 8, 10; for those with prior IS use, respective estimated risks were 0.3, 0.4, 4, 8, 8, 6. Cumulative PML risk over time will be presented.

Conclusions: Although consistent with previous risk estimates from postmarketing data, these updated risk estimates achieve greater temporal precision in yearly treatment epochs using individual patient data and do not require population-based assumptions. By incorporating index in the algorithm, PML risk can be further stratified for anti-JCV antibody positive patients without prior IS use. In the prior algorithm, the largest numeric increase in PML risk occurred after >2 years of treatment; with increased precision using clinical trial data, the largest increase is observed after >3 years.

Disclosure

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Bill Haddock: employee of and may hold stock and/or stock options in Biogen.
Sandra Richman: employee of and may hold stock and/or stock options in Biogen.
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P1250

Quantitative electroencephalography supports the diagnosis and predicts the functional outcome in natalizumab associated progressive multifocal leukoencephalopathy

G. Classen[1], R. Hoepner[2], C. Classen[3], A. Salmen[4], C. Brandt[5], R. Gold[2], A. Chan[4]
[1]Paediatric Neurology, Bethel Children´s Hospital, Bielefeld, [2]Neurology, St. Josef Hospital, Ruhr University Bochum, Bochum, [3]Computer Science, TU Dortmund University, Dortmund, Germany, [4]Neurology, Inselspital Bern, Bern, Switzerland, [5]General Epileptology, Bethel Epilepsy Center, Bielefeld, Germany

Background: Progressive multifocal leukoencephalopathy (PML) is a serious side effect of natalizumab (Nat). The value of electroencephalography (EEG) for diagnosis and prediction of Nat-PML outcome in MS patients is unclear.
Methods: Digital EEGs (according to the international 10/20-system) were obtained from two patient groups (Nat-PML (n=24) vs. relapsing MS (n=22)). In Nat-PML patients, EEGs were recorded at diagnosis, one and two years after virus elimination. EEGs were analysed during wakefulness in resting state with closed eyes. The first epoch of two seconds without artefacts was chosen from every minute of the recording. The relative spectral magnitude (RSM) for each frequency band (beta (β): 14-30Hz; alpha (α): 8-13.5Hz; theta (θ): 4-7.5Hz; delta (δ): 1-3.5Hz) was calculated by discrete fourier transform. Disability was assessed by EDSS.
Results: Age and gender were equally distributed between groups. However, MS patients showed lower disability compared to Nat-PML patients (difference of mean EDSS: 2.12; Mann-Whitney-Test (MWT): $p < 0.05$). At diagnosis, Nat-PML patients demonstrated a significantly higher RSM of slow frequencies (θ: 1.3-fold; δ: 1.4-fold) and lower RSM of α (0.6-fold) and β (0.8-fold) bands compared to MS controls (MWT: each $p \leq 0.01$). RSM of θ and β frequencies correlated with expansion of Nat-PML lesions on MRI at diagnosis (Spearman´s Rho: θ corr. 0.51; β corr. -0.62; each $p < 0.05$). Further RSM of θ and α frequencies correlated with EDSS at all time points of Nat-PML (Spearman´s Rho: θ corr. 0.44; α corr. -0.42; each $p \leq 0.01$). Finally using the following cut-off for RSM of θ and δ frequencies (δ≥28% or θ>21%) for the first recorded EEG during Nat-PML, the EDSS 1-2 years after virus elimination could be predicted (odds ratio (EDSS≥4) 17.6 (95%CI 1.2-250.4)).
Conclusion: To our knowledge, this study is the first to show, that quantitative EEG analysis can be used to support PML diagnosis and is the first objective parameter predicting Nat-PML outcome.

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P1251

Natalizumab extended interval dosing reduces serum trough natalizumab concentrations and a4 integrin receptor occupancy

J.F. Foley[1], T. Hoyt[1], A. Christensen[1], E. Riddle[2], T. Plavina[2], L. Seawright[1], R. Metzger[1]
[1]Rocky Mountain MS Research Group, Salt Lake City, UT, [2]Biogen, Cambridge, MA, United States

Background: Blockade of the α4 integrin by natalizumab (NTZ) affects immune cell trafficking into the central nervous system (CNS). Extended interval dosing (EID) has been proposed as a potential risk mitigation strategy for NTZ induced progressive multifocal leukoencephalopathy (PML), with maintained efficacy and a trend toward reduced PML risk observed in a retrospective multi-center trial. The pharmacological response of NTZ EID remains poorly characterized.
Methods: A total of 445 NTZ-infusing patients were evaluated, with 323 on standard interval dosing (SID; every 28-30 days), and 122 on EID (every 33-51 days). NTZ serum concentrations and α4 integrin occupancy were measured at dosing trough prior to infusion in all patients, and at additional timepoints between infusions in a subset of patients.
Results: At 2 hours after NTZ administration, NTZ serum concentrations were similar between the SID and EID cohorts (median=120.5 versus 138.0 mg/ml, respectively; p=0.304), and receptor occupancy was also not different between the two cohorts (median=97% for both; p=0.821). At 4 weeks post-infusion, NTZ concentration remained similar in SID versus EID patients (median= 27.7 versus 25.6 mg/ml, respectively; p= 0.117), as did receptor occupancy (median= 89 versus 88%, respectively; p=0.700). However, by weeks 5 and 6, EID patients exhibited lower trough NTZ concentration (median=16.4 mg/ml) and receptor occupancy (median=80%) compared to that observed at 4 weeks (trough) in SID patients ($p < 0.001$ for both comparisons). Also, the proportion of patients with maximal α4 integrin occupancy (at least 95% saturation) was 3-fold lower at trough EID

timepoints versus the trough timepoint for SID (9% versus 24%, respectively; p= 0.013).
Conclusions: EID reduces both NTZ serum concentrations and α4 integrin occupancy levels at trough timepoints, though receptor occupancy was still generally maintained within the range considered to be protective against disease. Further research is needed to determine if these reductions lead to an increase in immunological trafficking into the CNS, and could serve as a potential mechanism to reduce PML risk.

Disclosure

John F. Foley Dr. Foley participates in the Speakers´ Bureaus for Biogen, Genentech-Roche, Genzyme and Accorda. Dr. Foley advises for Biogen, Genentech-Roche, and Genzyme.
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Ryan Metzger owns stock in Biogen.
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P1252

Efficacy and safety of fingolimod 0.5 mg every-other-day in multiple sclerosis patients who presented severe adverse events during conventional fingolimod treatment

C. Zecca[1], A. Merlini[2], G. Disanto[1], L. Panicari[1], M. Rodegher[3], M. Romeo[2], M.J. Messina[3], L. Moiola[2], C. Stefanin[4], A. Ghezzi[4], P. Perrone[5], F. Patti[6], G. Comi[2], C. Gobbi[1], V. Martinelli[2]
[1]Neurocenter of Southern Switzerland, Lugano, Switzerland, [2]Department of Neurology, San Raffaele Scientific Institute, [3]San Donato Hospital, Milan, [4]Multiple Sclerosis Study Center, Gallarate Hospital, Gallarate, [5]Legnano Hospital, Legnano, [6]Department of Neuroscience, University of Catania, Catania, Italy

Introduction: Fingolimod 0.5 mg every day (FTY-ED) is an approved treatment for relapsing-remitting multiple sclerosis. In the case of severe adverse events, treatment discontinuation is recommended, depriving patients of a potentially effective therapy. We investigated whether FTY 0.5 mg every-other-day (FTY-EOD) could prevent severe adverse events in at risk patients while at the same time maintaining efficacy against disease activity.
Methods: Multicentre observational study. We included 60 consecutive FTY-EOD (mean follow-up 12.4 (7.6) months) and 63 FTY-ED (mean follow-up 22.9 (12.2) months) treated patients. Univariate and multivariate logistic regression identified the variables associated with a switch to FTY-EOD. Risk of disease progression (new relapses and/or increase in lesion load at MRI) was assessed with Cox regression models.
Results: The main reason to switch from FTY-ED to FTY-EOD was persistent lymphopenia and/or leucopenia, which occurred in 75% of patients, followed by increased liver enzymes at routine laboratory testing (21,7%). At multivariate analysis, low weight was associated with the risk of being switched to FTY-EOD (OR=0.94, 95%CI=0.89-0.99, p=0.026), while female patients (OR=20.44, 95%CI= 2.06-202.78, p=0.009) were more likely to switch to FTY-EOD due to lymphopenia. FTY-EOD patients were at higher risk of developing relapses as well as the combined outcome relapses and/or new T2 lesions and/or Gd+ lesions in survival analyses (HR=3.27, 95%CI=1.27-8.44, p=0.014 and HR=2.19, 95%CI=1.17-4.09, p=0.014, respectively). Treatment with FTY-EOD was associated with an increase of lymphocyte count above 200/ul in the majority of lymphopenic patients (n=42, 93.3%). Twenty patients out of 60 discontinued FTY-EOD treatment during the follow-up, mostly because of insufficient efficacy (n=10) or persistent leuco-lymphopenia (n=4). No serious adverse events were observed during the study.
Conclusions: According to our multicenter observational study, the strategy to reduce the dose of FTY-ED to FTY-EOD to overcome severe adverse events is safe but associated with increased risk of disease reactivation, independently of lymphocyte count.

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P1253

Use of AAN PML diagnostic criteria in dutch-belgian natalizumab-associated PML cohort

M.T. Wijburg[1,2], C. Warnke[3], J. Killestein[2], M.P. Wattjes[1]
[1]Department of Radiology & Nuclear Medicine, Neuroscience Amsterdam, VUmc MS Center Amsterdam, [2]Department of Neurology, Neuroscience Amsterdam, VUmc MS Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands, [3]Department of Neurology, University of Düsseldorf, Düsseldorf, Germany

Background: The diagnosis of natalizumab-associated progressive multifocal leukoencephalopathy (NTZ-PML) is, if not biopsy proven, based on the combination of PML lesion identification on magnetic resonance imaging (MRI), presence of clinical PML symptoms, and detection of JC virus (JCV) DNA by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF). In 2013, the AAN Neuroinfectious Disease Section introduced PML diagnostic criteria proposing categories of diagnostic certainty depending on the presence or absence of these features. However, at the time of NTZ-PML suspicion, patients often lack PML symptoms due to early PML lesion detection on MRI (as recommended recently by the European Medicines Agency), and JCV DNA can be undetectable in their CSF, hampering the diagnosis of NTZ-PML.
Objective: To investigate the diagnostic performance of the AAN PML diagnostic criteria in early NTZ-PML patients.
Methods: For all patients in the Dutch-Belgian NTZ-PML cohort, data on the presence or absence of the diagnostic features were

collected from the time of the first NTZ-PML diagnostic work-up. Diagnosis was based on JCV DNA detection in CSF or PML lesion evolution on MRI, including PML immune reconstitution inflammatory syndrome at later stages. The AAN PML diagnostic categories are: "definite PML" (PML lesion on MRI, PML symptoms, and positive JCV PCR), "probable PML" (PML lesion on MRI and positive JCV PCR, but no PML symptoms), "possible PML" (PML lesion on MRI and PML symptoms, but negative JCV PCR), "not PML" (PML lesion on MRI, but no PML symptoms and negative JCV PCR). Frequencies and percentages of the patients for each category are presented.

Results: Of the 28 NTZ-PML patients included, 10 patients (35.7%) met the criteria for "definite PML", 8 patients (28.6%) met the criteria for "probable PML", 6 patients (21.4%) met the criteria for "possible PML", and 4 patients (14.3%) met the criteria for "not PML", at the time of first diagnostic work-up. There were no significant differences between the categories in terms of age, gender, or natalizumab treatment duration.

Conclusion: A larger proportion of NTZ-PML patients of our cohort did not fulfil diagnostic criteria for "definite PML" or even "probable PML" at the time of first PML suspicion, which is likely the result of early PML lesion detection on MRI. Thus, the AAN PML diagnostic criteria may not be applicable to early NTZ-PML patients, and a revision of the NTZ-PML case definition may be warranted.

Disclosure

Potential conflict of interest

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P1254

An observational, multicentre, one-day study to assess demographic, clinical and neurovegetative characteristics of patients requiring extended cardiac monitoring following administration of the first dose of fingolimod

G.L. Mancardi[1], G. De Angelis[2], N. Montano[3,4], E. Vanoli[5,6], M. Mirabella[7], S. Bonavita[8], F. Patti[9], F. Frigerio[10], M. Bartezaghi[10], R. Turrini[10]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Maternal and Child Health, University of Genoa, Genoa, Italy, [2]U.O.C. Cardiology ASST Rhodense, Rho- Milan, Italy, [3]Department of Internal Medicine, Ca' Granda IRCCS Foundation, Ospedale Maggiore Policlinico, [4]Department of Biomedical and Clinical Sciences, L. Sacco Hospital, University of Milan, Milan, Italy, [5]Cardiovascular Department, IRCCS Multimedica, Sesto S. Giovanni, Milan, Italy, [6]; Department of Molecular Medicine, University of Pavia, Pavia, Italy, [7]Institute of Neurology, Fondazione Policlinico Universitario "A. Gemelli", UCSC, Rome, Italy, [8]I Clinic of Neurology, Second University of Naples, Naples, Italy, [9]Department of Medical and Surgery Sciences and Advanced Technologies, GF Ingrassia, Section of Neurosciences, MS Center, University of Catania, Catania, Italy, [10]Novartis Farma S.p.A, Origgio, Italy

Background: Fingolimod is an oral immunomodulator exerting its therapeutic effects in multiple sclerosis via sphingosine-1P receptors (S1PR). S1PR are also expressed in the heart, mainly in atrial myocytes, and mediate cardiovascular (CV) effects. Effects of fingolimod first dose (FFD) on heart rate (HR) and atroventricular (AV) conduction are well defined, and the recommended FFD continuous 6-hours (hrs) ECG monitoring can be extended until the day after in case given conditions occur. Understanding potential interactions of preexisting individual autonomic profile with the FFD effects may add novel safety information and help explain the cases requiring extension of the 6-hrs period

Objectives: To characterize the patient population treated with FFD according to EMA label and clinical practice, in terms of baseline demographics, clinical and neurovegetative status and probability of extension of the continuous ECG monitoring

Methods

Observational, prospective study of 6 (up to 24) hrs. ECG was recorded for 15 min before FFD administration and for 6 hrs after. Heart Rate and HR Variability (HRV) in the frequency domain were derived from the ECG traces by a specialized software

Results: 625 patients were enrolled in 59 Italian centres. Of these, 580 (92.8%) patients were discharged at the 6th hour after FFD administration, while 45 (7.2%) required monitoring extension. Ten (1.6%) patients showed an AV block (3 of 1st degree, 7 of 2nd), all benign and reversible. The mean max percentage reduction in HR was 17.6±8.4. Normalized spectral power (norm units, nu) in the Low Frequency band (LFnu; marker of sympathetic modulation) < 75.2 (OR=0.47; 95%CI: 0.23-0.94), nu power in the High Frequency band (HFnu; marker of vagal modulation) < 19.4 (OR=2.07; 95%IC: 1.04-4.12) and previous annualized relapse rate 0 vs ⩾2 (OR=0.25; 95%CI: 0.08-0.75) were correlated with the probability of discharge at 6 hrs (which was not correlated with demographic or other clinical variables). With regard to HRV and the max HR reduction, coefficients indicated a weak positive correlation between the latter and LFnu and LF/HF ratio, whereas HFnu showed a weak negative correlation

Conclusions: Data confirm the well known and manageable CV profile of FFD. An individual higher vagal tone at baseline may contribute to the chances of extending CV monitoring. The potentially synergistic effects of FFD and individual inherent vagal tone were not associated with clinically significant cardiac events

Disclosure

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P1255

Inflammatory natalizumab-associated PML: baseline characteristics, lesion evolution and relation with PML-IRIS

M.T. Wijburg[1,2], J. van Eijk[3], S. Frequin[4], R.R. Hupperts[5], C. Tiu[6], J. de Graaf[7], J. Killestein[2], M.P. Wattjes[1]
[1]Department of Radiology & Nuclear Medicine, Neuroscience Amsterdam, VUmc MS Center Amsterdam, [2]Department of Neurology, Neuroscience Amsterdam, VUmc MS Center Amsterdam, VU University Medical Center, Amsterdam, [3]Department of Neurology, Jeroen Bosch Hospital, 's Hertogenbosch, [4]Department of Neurology, St. Antonius Hospital, Nieuwegein, [5]Department of Neurology, Orbis Medical Center, Sittard, The Netherlands, [6]Department of Neurology, University Hospital Bucharest, Bucharest, Romania, [7]Department of Neurology, Isala Hospital, Zwolle, The Netherlands

Background: Approximately 30% of natalizumab-associated progressive multifocal leukoencephalopathy (NTZ-PML) patients present with imaging findings suggestive of inflammation, such as contrast-enhancement, at the time of PML diagnosis. The histopathological background and clinical relevance of these inflammatory PML lesions are not understood. After the diagnosis of PML and natalizumab discontinuation, these inflammatory lesions have to be differentiated from inflammation related to immune reconstitution inflammatory syndrome (IRIS) lesions.
Objective: To investigate the imaging characteristics of inflammatory PML lesion at diagnosis and during follow-up and to determine whether these inflammatory lesions are linked to inflammatory lesions seen at PML-IRIS stage.
Methods: We screened 46 of our local and referred NTZ-PML patients for signs of inflammation on brain MRI (contrast enhancement, signs of mass effect and/or edema, and perivascular T2 lesions) at PML diagnosis. Contrast-enhancement was further classified according to location (center of the PML lesions, border of the PML lesions, outside of the PML lesions either with or without a perivascular spread) and the enhancement pattern (punctuate, homogeneous, patchy). All follow-up MRI scans including those at the PML-IRIS were analyzed.
Results: Thirteen patients showed signs of inflammation at PML diagnosis, of whom ten had follow-up MRIs at the time of PML-IRIS available. Contrast-enhancement was the leading imaging sign in inflammatory PML (92.3%) and PML-IRIS (100%), mostly with a patchy appearance in the periphery of the lesions. The most relevant discriminative factor was swelling with mass effect, exclusively being present at the PML-IRIS (60%) but not in the inflammatory PML stage. Signs of perivascular inflammation with perivascular T2 lesions were more frequent present at the PML-IRIS stage (80%) compared to the inflammatory PML stage (46.%). Nine inflammatory PML patients (90%) showed similar patterns of inflammation at PML-IRIS stage as at diagnosis of inflammatory PML.
Conclusion: Inflammatory PML lesions share the same imaging characteristics as PML-IRIS lesion. In the majority of patients, inflammatory PML lesions are linked to PML-IRIS lesions with respect to inflammation evolution during follow-up. This suggests a shared pathological mechanism of inflammation such as cellular immune response against the JC virus, even at the time of PML diagnosis.

Disclosure

Potential conflict of interest

MTW, SF, CT and JdG do not report any competing interest.
JvE has received consultancy fees from Biogen, Merck-Serono, Teva, Novartis, and Sanofi.
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MPW has received consultancy fees from Biogen and Roche.

P1256

Analysis of CD4+CD62L+ peripheral blood T-cells in patients with multiple sclerosis - correlation with disease modifying treatment and anti-JCV antibody index

M.K. Boziki, G. Papadopoulos, R. Lagoudaki, E. Polychroniadou, C. Bakirtzis, N. Grigoriadis, D. Karacostas
2nd Neurology Department, Aristotle University of Thessaloniki, Thessaloniki, Greece

Background: CD62L, a molecule also referred as L-selectin, expressed on CD4+ peripheral blood lymphocytes, has recently drawn attention due to its possible relevance as a biomarker predictive of progressive multifocal leukoencephalitis (PML) in patients with multiple sclerosis (MS) under natalizumab, especially when combined with anti-JC virus (JCV) antibody index.
Aim: The present study addresses possible correlation between CD62L expression and anti-JCV antibody index in multiple sclerosis patients under first- and second line disease modifying treatments.
Methods: Forty-four patients under first- (interferon-β, glatiramer acetate) (m:f 13:31, age 41.54 ± 10.19) and 41 patients under second-line (natalizumab, fingolimod) treatment (m:f 13:28, age 40.04±9.95) were included. Frequency of peripheral blood CD62L+ cells (% of CD4+ T-cells), as well as CD62L mean fluorescence intensity (MFI) on CD4+ T-cells were analysed by flow cytometry. Anti-JCV antibody serology was conducted by standard ELISA techniques.
Results: Groups were gender ($p=0.83$) and age ($p=0.5$) matched. Patients under second-line treatment exhibited lower mean anti-JCV antibody index compared to first-line treatment group (1.04±1.11 versus 1.93±1.37, $p=0.001$). Frequency of CD4+CD62L+ T-cells was significantly lower in patients under second- compared to first-line treatment (67.17±18.18 versus 79.79±8.45, respectively, $p< 0.001$). Also CD62L MFI on CD4+ T-cells was significantly lower in patients under second- compared to first-line treatment (54.96±21.9 versus 72.31±37.33, respectively, $p=0.01$). In patients under first - line treatment, frequency of CD4+CD62L+ T-cells, as well as CD62L MFI on

CD4+ T-cells, did not correlate with anti-JCV antibody index (Pearson's r=0,14, p=0.35 and Pearson's r=0.008, p=0.958, respectively). In patients under second-line treatment frequency of CD4+CD62L+ T-cells exhibited a significant negative correlation with anti-JCV antibody index, whereas CD62L MFI on CD4+ T-cells did not show significant correlation (Pearson's r=-0.571, p< 0.001 and Pearson's r=0,046, p=0,779, respectively).
Conclusion: These data provide evidence of an inverse association between CD62L expression on T-cells and anti-JCV antibody index in patients under second-line disease modifying treatment. Further prospective studies are needed in order to elucidate potential clinical application of CD62L expression analysis on PML risk prediction, in addition to anti-JCV antibody index.

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P1257

Nail loss: a new adverse event of teriflunomide treatment?

L. Mancinelli[1], M. di Ioia[1], V. Di Tommaso[1], E. Pietrolongo[1], D. Farina[1], D. Travaglini[1], G. De Luca[1], P. Amerio[2], A. Lugaresi[3,4]
[1]Dept. of Neuroscience, Imaging and Clinical Sciences, [2]Dept. of Dermatology and Venereology, University 'G. d'Annunzio', Chieti, [3]Dept. of Biomedical and NeuroMotor Sciences (DIBINEM), Alma mater studiorium - Università di Bologna, [4]IRCCS Istituto delle Scienze Neurologiche - 'UOSI Riabilitazione Sclerosi Multipla', Bologna, Italy

Background: Teriflunomide is a new oral treatment for Relapsing Remitting Multiple Sclerosis, showing a similar efficacy to subcutaneous Interferon β-1a (IFNB1a) 3-times weekly in the phase three clinical trial "TENERE".
Case report: A 55 years old woman with MS, started teriflunomide in May 2015, shifting from IFNB1a. After an initial period of good tolerability, in August 2015 she began to complain of hair loss (a known side effect of teriflunomide) scarcely noticeable at examination. Two months later she complained about progressive loss of hand nails occurring in the last few weeks. At examination two nails in her right hand had dropped off (one of these presenting in a regrowth phase), whereas two in the left hand presented lack of growth with consequent void at the nail matrix. Some of the remaining nails showed thinning and progressive detachment from their bed. The patient also reported persistent hair loss and denied use of new drugs or different soap or other cosmetic products. At referral an expert dermatologist excluded nail mycosis, psoriasis and other possible causes of nail dystrophy, and confirmed that the hypothesis of a causal relationship with teriflunomide was highly probable. Hence, the drug was discontinued and the patient underwent the accelerated removal procedure with oral colestiramine. A few weeks later she started therapy with dimethyl-fumarate, that was well tolerated. In the following months her nails showed progressive regrowth and normalization.
Discussion: We could not find any published reports of nail loss associated with teriflunomide treatment. We believe this represents a new adverse event of teriflunomide treatment based on the following: time relationship between event onset and starting treatment, a progressive development consistent with nail matrix growth; absence of any other change in the patient's life such as new drugs, new diet, new cosmetics; simultaneous presence of hair loss, which presumably shares the same pathophysiological mechanism; exclusion of other possible etiologies by the dermatologist and, finally, reversibility at drug discontinuation.
Conclusion: MS specialists should be aware of this potential adverse event, which might represent a new cause of teriflunomide discontinuation.

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P1258

Multiple sclerosis disease rebound after treatment switch from fingolimod to alemtuzumab

M. Willis[1], O. Pearson[2], Z. Illes[3], C. Nielsen[3], T. Sejbaek[3], M. Duddy[4], K. Petheram[5], C. van Munster[6], J. Killestein[6], B. Uitdehaag[6], C. Malmestrom[7], E. Tallantyre[1], N. Robertson[1]
[1]Cardiff University, Cardiff, [2]Morriston Hospital, Swansea, United Kingdom, [3]University of Southern Denmark, Odense, Denmark, [4]Royal Victoria Infirmary, Newcastle, [5]Sunderland Royal Hospital, Sunderland, United Kingdom, [6]VU University Medical Center, Amsterdam, The Netherlands, [7]Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Background and goals: The landscape of therapies available to treat relapsing multiple sclerosis (MS) continues to expand. As a result clinicians are faced with significant challenges in deciding optimum treatment strategies for individual patients which is influenced by a number of factors including the degree of clinical and radiological disease activity, JC virus antibody status, potential adverse effects of drugs and sequential treatment risks. We report a case series of 9 patients treated with alemtuzumab after discontinuation of fingolimod with significant early rebound disease activity. We suggest potential underlying mechanisms and highlight the importance of this phenomenon for patient management.
Methods: Patients with relapsing MS treated with fingolimod and subsequently alemtuzumab were identified by personal communication with 6 European neuroscience centres. History was obtained by clinical note review.
Results: 9 patients (5 female, median follow-up 15 months (range 8-22)) were identified who had received alemtuzumab following fingolimod. All patients had undergone a therapeutic escalation strategy prior to treatment with fingolimod with 8/9 also having previously received natalizumab. In 5/9 patients lymphocyte counts had not recovered to normal range prior to alemtuzumab and in 4 patients lymphocytes reconstituted more rapidly than expected. 8/9 patients experienced at least one clinical relapse soon after starting alemtuzumab, with active radiological disease seen in all patients.
Conclusions: We postulate that rebound activity in these patients is caused by a significant number of lymphocytes remaining 'hidden' from the usual intravascular therapeutic effects of alemtuzumab as a result of selective lymphoid sequestration. Subsequent CD52 positive lymphocyte egress from lymph nodes then initiates the observed rebound inflammatory disease activity. The repopulating immune repertoire is also likely to be considerably different to that normally observed post alemtuzumab. Further systematic observational studies are required to confirm these phenomena. In addition future trials addressing longer-term outcomes of induction and escalation paradigms need to be designed in order to guide clinicians on strategies for treatment switches. In particular, careful consideration needs to be given to mode of action of individual therapies and sequential treatment effects.

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P1259

Progressive multifocal leukoencephalopathy in a JCV seronegative patient treated by natalizumab : a new case report

N. Hadhoum[1], V. Neuville[2], P. Vermersch[3]
[1]Neurology, Roger Salengro Hospital, Lille University Hospital, Lille, [2]Maubeuge Hospital, Maubeuge, [3]Roger Salengro Hospital, Lille University Hospital, Lille, France

Background: the prediction of the risk of progressive multifocal leukoencephalopathy (PML) is crucial to guide natalizumab (NTZ) prescription and ensure a higher safety use. The JCV index (a corollary to antibody titer) is a predictive factor of PML.
Case presentation: here we report a case of a 55-year-old female diagnosed with multiple sclerosis in 1996. Because of a continued clinical disease activity despite interferon, she was switched to NTZ. A total of 84 infusions were administered between 2011 and 2016. She never received any prior immunosuppressor and has been tested negative for anti-JCV antibodies: index at 0.22 in 06/2014 and 0.11 in 06/2015 and 10/2015. The annual MRI were strictly stable. During a routine follow-up, the patient complained of a right-sided lower limb paresis. NTZ was immediately stopped. Brain magnetic resonance imaging revealed a sub-cortical white matter lesion, hypoT1, hyperT2 in the left parietal lobe invading the U-fibers in DIR sequence. PML was suspected then confirmed by detection of JCV-DNA in the CSF (2 analyses: 11 then 68 copies/ml). The peripheral CD4+ T-cell count was 1149/mm3, CD8+ at 395/mm3. Note that the JCV index was still negative at the diagnosis and 15 days later. We investigate the lymphopenia and found a probable common variable immune deficiency (CVID) with severe hypogammaglobulinemia (3g/dL), surprisingly asymptomatic until now. A JCV seroconversion was noted at 3 months (index at 3.48).
Discussion: it is well-known that PML risk is influenced by NTZ duration, prior use of immunosuppressors and seropositivity for the JCV. The JCV seronegativity status does not allow to exclude any risk of PML. Indeed, de novo infection with seroconversion is theoretically possible and underestimate rate of infection appears likely (in case of low viremia). One recent publication reports a NTZ-related PML diagnosed 2 weeks after negative anti-JCV antibody assay and 2 others PML due to NTZ were tested negative (prior to diagnostic) among the 541 reported cases. In our case, we can hypothesize that the JCV index were false negative results as the asymptomatic CVID imply a fail in humoral responses.
Conclusion: this case must not undermine the central role of the JCV index in predicting the risk of PML. However, it seems wise to regularly control the blood lymphocyte phenotype and immunoglobulins. CVID is the one of the most common causes of adult immunodeficiency.

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P1260

Alemtuzumab-induced idiopathic thrombocytopaenic purpura in three regional UK MS treatment centres

A. Pace[1], D. Rog[1], P. Talbot[1], T. Mihalova[1], N. Sharaf[1], S. Ravenscroft[2], M. Wilson[3], M. Willis[4], N. Robertson[4]
[1]Greater Manchester Neurosciences Centre, [2]Department of Haematology, Salford Royal NHS Foundation Trust, Salford, [3]Walton Centre NHS Foundation Trust, Liverpool, [4]Institute of Psychological Medicine and Clinical Neuroscience, Cardiff University, Cardiff, United Kingdom

Background: Alemtuzumab is a highly effective therapy for active relapsing remitting multiple sclerosis (MS) but may induce de-novo autoimmune disease, including immune thrombocytopaenic purpura (ITP) in 1-2% of treated patients. Currently there is little available data on clinical presentation and long-term outcomes of these patients outside clinical trials.
Objective: To describe the collective experience on ITP following alemtuzumab treatment across three regional UK multiple sclerosis treatment centres.
Methods: Cases identified in the MS centres in Greater Manchester, Liverpool and Cardiff were pooled for this study. ITP was identified via centre-specific monitoring protocols that included regular platelet counts and review of patient reported symptoms suggesting impaired haemostasis.
Results: Six patients (F:M=4:2) were identified across a combined treated cohort of 235 (2.6%). Mean age at treatment was 32.5 years (range 20-42). One patient was treated at diagnosis, two were treatment-naïve but received alemtuzumab 2 and 8 years after diagnosis, and three had previously been treated with other licensed MS drugs. Patients had very active disease, with a mean 4 relapses (range 2-8) in the two years pre-treatment. Baseline EDSS scores indicate accrual of significant disability by time of treatment initiation (mean 4.8, range 3.5-6.5). All pre-treatment platelet counts were normal (range 184-334). Thrombocytopaenia occurred at a median 6 months following most recent infusion (range 1-24). Platelet counts at nadir ranged widely (4 to $41x10^3$) and 4 patients developed severe thrombocytopaenia ($< 20x10^3$). Three patients required treatment with standard first line ITP therapy, while platelet counts recovered spontaneously in the remainer. There were no haemorrhagic complications (including one ITP case during pregnancy) and all 6 patients achieved remission. However 3 patients relapsed, 2 cases requiring further therapy. Two patients developed additional autoimmune comorbidities.
Conclusions: A robust surveillance programme with monthly platelet counts, patient/ physician education on vigilance to relevant signs and symptoms, and involvement of local haematology expertise are integral to a safe alemtuzumab service for MS, allowing for early detection and management of ITP. Our patient experience suggests sustained remission after ITP therapy is not always the norm and that ITP may be followed by other autoimmune adverse events in some cases.

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P1261

Transgenic overexpression reveals a direct dose-dependent role for interferon in the pathogenesis of thrombotic microangiopathy, with implications for risk mitigation

D. Hunt[1], D. Kavanagh[2], A. Jackson[1], I. Campbell[3], S. Chandran[4]
[1]MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, [2]Newcastle University, Newcastle, United Kingdom, [3]University of Sydney, Sydney, NSW, Australia, [4]Anne Rowling Clinic, University of Edinburgh, Edinburgh, United Kingdom

Background: An association between interferon-beta therapy and thrombotic microangiopathy has been the subject of a recent international drug safety alert. There is a need to understand the nature of this serious adverse reaction, and to consider whether the risk to patients can be reduced.
Methods: We analysed new cases of interferon-beta associated thrombotic microangiopathy referred to the national renal thrombotic microangiopathy centre in the UK (n=8), comparing pathological microvascular changes seen in patient biopsies to microvascular changes in a novel transgenic model of interferon overexpression.
Results: Detailed clinical evaluation of new cases, combined with analysis of national safety data, is consistent with a direct drug-induce thrombotic microangiopathy. This evolves over months (7/8 cases) and typically presents at a late stage to an intensive care setting with fulminant organ failure.
We demonstrate that chronic exposure to interferon causes small vessel damage in a novel transgenic model of interferon toxicity, whereby interferon is overexpressed at zero, moderate and high levels. In this model system, a dose-dependent microangiopathy is observed using both standard histopathological techniques and scanning electron microscopy of microvascular casts (Three groups: Wildtype, interferon moderate overexpression, interferon high overexpression: $P< 0.001$ ANOVA). These microvascular changes include specific pathological changes seen in patient biopsies, such as endothelial hyperplasia and microaneursym formation. The microvascular phenotype was fully rescued in IFN^{High} x $IFNAR^{-/-}$ mice, demonstrating the critical role of downstream interferon signalling in the mediation of disease.
We show these mechanistic insights have two important implications for patient safety. Firstly, multiple sclerosis patients treated with high-dose recombinant interferon-beta are at particular risk of this serious complication, with 93% of UK patients treated with the highest available dose. Secondly targeted monitoring of high

risk patients shows it may be possible to identify early signs of this complication and stop the drug prior to the development of fulminant organ failure.
Conclusion: Interferon causes a dose-dependent thrombotic microangiopathy. It can evolve over months and may be detected early in high-risk patients, prior to the development of permanent organ failure.

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Tools for detecting therapeutic response

P1262

Ambulatory motor dysfunction in MS assessed by wearable inertial sensor metrics during the timed-up-and-go task (TUG)

C. Oberndorfer[1], J. Barth[1,2], J.H. Guppy[3], J. Bush[3], R. Needham[4], A. Healy[4], N. Chockalingam[4], C. Herberz[2], C.E.I. Westling[5], B.M. Eskofier[1], D. Roggen[5], J. Klucken[6], W. Rashid[7], H.J. Witchel[3]
[1]Universität Erlangen-Nürnberg, [2]ASTRUM IT, GmbH, Erlangen, Germany, [3]Brighton and Sussex Medical School, Brighton, [4]CSHER, Staffordshire University, Stoke-on-Trent, [5]University of Sussex, Brighton, United Kingdom, [6]Universitätsklinikum Erlangen, Erlangen, Germany, [7]Hurstwood Park Neurosciences Centre, Haywards Heath, United Kingdom

Background: Individuals with MS suffer from ambulatory motor dysfunction; recently the timed-up-and-go (TUG) test has been shown to relate to ambulatory dysfunction (as judged by EDSS). To complement patient reports in the elderly, a range of objective performance metrics based on ambulation have been demonstrated as feasible, including the sit-to-stand transition time. These TUG metrics have not yet been applied to multiple sclerosis patients.
Methods: Fully-ambulatory persons with multiple sclerosis whose Hauser Ambulatory Index (HAI) was 2 or less (PwMS, N=17) and age-matched healthy volunteers (N=24) were instrumented with 7 inertial sensors with 3 axes of gyroscopy and accelerometry recording at 128 Hz. Participants performed the timed-up-and-go twice, and transition times between sitting and standing were calculated as described previously; in this study we focused only on the data from the sensor placed on the lumbar spine.
Results: PwMS reported their walking to be significantly more affected (according to the MSWS-12) than age-matched healthy controls (50.99±4.69 vs. 0, P< 0.001, unpaired t test), and their walking time in the timed 25 foot walk (T25FW) reflected this (6.09±0.27 seconds vs. 4.45±0.15, P< 0.001, unpaired t test). In the stopwatch measured TUG, significant differences were detected between PwMS and age-matched, healthy volunteers, (12.33±0.59 seconds vs. 10.04±0.33, P< 0.01). Similarly, the duration of the TUG as measured by the sensors was longer for PwMS than for the healthy volunteers (13.86±1.09 seconds vs. 10.19 ± 0.36, P< 0.01), and the transition times for sit-to-stand (PwMS 0.81±0.09 seconds vs. healthy 0.67±0.03) and stand-to-sit (PwMS 1.03±0.11 seconds vs. healthy 0.92±0.05) were longer for PwMS, but not significantly (P>0.1 for both). The range of the raw angular acceleration (in the pitch orientation) of the lumbar segment was significantly lower in PwMS (153.4±8.9 deg/second vs. 204.7±6.5, P< 0.001).
Conclusions: In this group (HAI< 2), traditional measures of ambulatory dysfunction (e.g. T25FW) are quite sensitive to multiple sclerosis. Wearable inertial sensors have the potential to provide specific metrics of ambulatory dysfunction (e.g. weakness) in MS with good face value. Future studies using these sensors have the potential to realise additional information on movement dysfunction, including specific deficits such as difficulties executing sitting and standing associated with disease progression.

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P1263

INSPIRATION-MRI: standardized acquisition and centralized quantitative reading of MRI scans of RRMS patients in German daily clinical practice

A. Gass[1], S. Hoffmann[2], J. Gregori[2], A. Fuchs[3], C. Cornelissen[3]
[1]Klinik für Neurologie, Universitätsklinikum Mannheim, Mannheim, [2]mediri GmbH, Heidelberg, [3]Novartis Pharma GmbH, Nuremberg, Germany

Background: INSPIRATION is a non-interventional study, conducted in Germany, to validate the feasibility and potential benefit of standardized MRI-acquisition and central-quantitative MRI-reading in clinical practice for RRMS-patients.
Objective: MRI has become an integral part of MS-patient management. However, quantitative analysis of lesion-load is not trivial and has mainly been realized in clinical trials. We investigate whether additional quantitative information and visualization

of lesion-load is regarded useful in the daily management of RRMS-patients.

Methods: INSPIRATION included 253 patients in 15 centers. Sites underwent expert training and standardized sequence implementation. A centralized quantitative MRI-data analysis is performed (volume of T2-lesions, T1-hypointense and contrast-enhancing lesions, percentage of brain volume change). The results are visualized and provided to the physicians.

Results: 392 of 394 (99.5%) data sets passed the quality analysis. 2 cases were excluded because of missing sequences. 7 cases led to site queries (0.02%). 34.7% of the patients were treated with fingolimod upon study inclusion (21.5% interferons, 17.9% dimethylfumarate, 7.6% copaxone, 6.8 % natalizumab, , 10.8% no/other). The mean number (±SD)/ml volume (±SD) of T2 lesions at baseline was 30.1 (±2.8)/11033.1 (±1578.9), of black holes 4.0 (±0.9)/490.3 (±135.5) and of Gd+ lesions 0.4 (±0.2)/31.1 (±20.3). 103 patients had a 12 months follow-up MRI documented. The mean number (±SD)/ml volume (±SD) of T2 lesions after 12 months was 32.5 (±4.7)/11634.4 (±2297.4), of black holes 4.3 (±1.4)/547.4 (±210.0) and of Gd+ lesions 0.2 (±0.1)/18.0 (±14.1). The lesion count of T2 lesions differed between neurologists (no/missing: 12.8%/10.4%; 1-2: 2.4%; 3-9: 20.4%; ⩾9: 48.2%), radiologists (no/missing: 8.4%/1.6%; 1-2: 2.8%; 3-9: 14.3%; ⩾9: 72.9%) and central reading (no/missing: 1.6%/0.4%; 1-2: 2.4%; 3-9: 14.3%; ⩾9: 81.3%).

Conclusions: More sophisticated, additional quantitative MRI-analysis is provided in a real world situation. A common standardized analysis of MRI data for several centers revealed differences between the estimation of lesion numbers by the centers and the quantitative approach. A centralized approach might improve the comparability of MRI scans. The quantitation of lesion load and volumes and visualization of MRI-abnormalities may facilitate MRI-data use by the responsible neurologist to support patient management.

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P1264

Usefulness in clinical practice of 1-year magnims scoring system to predict response to glatiramer acetate

M. Romeo[1], M.P. Sormani[2], A. Merlini[1], M.J. Messina[1], R. Messina[1], L. Moiola[1], A. Nuara[1], P. Preziosa[1], M. Radaelli[1], M.A. Rocca[1], M. Rodegher[1], F. Sangalli[1], B. Colombo[1], G. Dalla Costa[1], L. Ferrè[1], F. Martinelli Boneschi[1], G. Comi[1], V. Martinelli[1]
[1]Neurology, San Raffaele Hospital, Milan, [2]Department of Health Sciences, University of Genoa, Genoa, Italy

Objectives: The MAGNIMS score is a new scoring system able to predict disability progression in relapsing remitting multiple sclerosis (RRMS) patients according to their disease activity during the first year of treatment with interferon-beta (IFN-β). This scoring system has not yet validated in patients treated with glatiramer acetate (GA). The objective of our study was to evaluate the use of MAGNIMS score on an Italian cohort of RRMS patients treated with GA in daily clinical practice.

Materials: This is an observational, single-centre, 4-year study carried out on RRMS patients who started GA treatment between January 2000 and December 2011. The MAGNIMS score was obtained by a combination of relapse and new T2-weighted lesions at brain MRI scan after 1-year of therapy (Sormani et al, Neurology 2016). Hazard ratios (HR) were used to evaluate the ability of scores to predict the suboptimal response (defined by the presence of at least 1 positive parameter among new relapse, any MRI active lesion or EDSS progression) and disability worsening (defined by EDSS progression 1.5 points for patients with EDSS at 1 year = 0, 1 point for EDSS of 1.0-5.0 and 0.5 for EDSS >= 5.5 sustained over at least 6 months and confirmed at the end of the follow-up; or switching to other therapy for lack of efficacy in the subsequent 3 years.

Results: We have considered 253 patients; 10 patients with no adherence to therapy were excluded and then 243 patients have been evaluated. During the following 3 years, 77 patients (32%) had a disability worsening and 141 patients (58%) were suboptimal responders. After 1-year follow-up the risk of disability worsening was 27% in patients with no relapse and less than 3 brain MRI lesions (score 0) in the first year and 55% in patients with 1 relapse and at least 3 MRI lesions or more than 1 relapse (score 2) in the first year (HR 2.4; CI 1.2-4.6, p.0.01).

In the subsequent 3 years, 47% of patients with score 0 in the first year was NEDA3 vs 27% of the remaining patients with score 1-2. Patients with a score 0 or 1-2 had a suboptimal response probability of 53% or 73 %, respectively (HR 1.8; 95% CI 1.3-2.6; p: 0.001).

Conclusions: Our study confirms the usefulness of 1-year MAGNIMS scoring system to evaluate treatment response in the following 3 years also in patients treated with GA.

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P1265

Improved cerebral blood flow after natalizumab treatment in multiple sclerosis

C. Record, S. De Simoni, C. Feeney, D. Sharp, R. Nicholas, J. Raffel
Imperial College London, London, United Kingdom

Introduction: Alterations in cerebral arterial blood flow have been previously reported in people with multiple sclerosis (pwMS). The pathophysiology is unknown, but may be related to inflammation in the CNS vasculature. If this were the case, cerebral blood flow would likely improve with effective disease modifying treatment.
Methods: This study used pulsed arterial spin labelling (PASL) magnetic resonance imaging (MRI) as a surrogate for cerebral blood flow (CBF). We compared grey matter CBF in eight healthy controls (HCs) with seventeen pwMS. CBF was also compared before and after three months of natalizumab treatment in fifteen pwMS.
Results: pwMS (n=17, mean age 41.4 yrs) showed significantly decreased CBF in the hypothalamic region, anterior cingulate gyrus, caudate nucleus and medial frontal gyrus (all $p< 0.05$) compared with HCs (n=8, mean age 41.9 yrs). CBF improved significantly three months after commencing natalizumab in the following regions: middle frontal gyrus, inferior frontal gyrus, insular cortex, opercular cortex, putamen, anterior cingulate gyrus, paracingulate gyrus and frontal pole (all $p< 0.05$). Correlations with baseline functional status, lesion volume and clinical response to natalizumab will also be presented.
Conclusion: As previously reported, PASL MRI demonstrates decreased CBF in pwMS compared with HCs. We have shown for the first time that CBF improves after disease modifying treatment, suggesting that decreased cerebral blood flow may be related to inflammation. ASL should be further investigated as a putative marker of response to treatment in MS.

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P1266

Permeability of the blood-brain barrier in normal appearing white and grey matter predicts early inadequate treatment response to fingolimod og natalizumab

S.P. Cramer[1], H.J. Simonsen[1], J.L. Frederiksen[2,3], H.B.W. Larsson[1,3]
[1]Functional Imaging Unit, Department of Clinical Physiology/ Nuclear Medicine, [2]Department of Neurology, University of Copenhagen, Glostrup, [3]The Faculty of Health Science, Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Purpose: We have previously shown that permeability of the blood-brain barrier, measured as the transfer constant K_{trans} (ml/100g/min) by dynamic contrast-enhanced MRI (DCE-MRI) is linked to the degree of inflammation in MS patients, and thus could provide a quantitative measure of the current level of disease activity (Cramer, SP 2014 and 2015). Many efficacious treatment options have emerged in recent years, however detecting an unfavourable treatment response remains a challenge due to lack of quantitative methods. This study aimed to investigate whether K_{trans} measured in the normal appearing white (NAWM) and grey matter (NAGM) can predict early inadequate response to second-line treatment (Fingolimod or Natalizumab, at the time of study initiation).
Methods: Sixty relapsing remitting MS patients were included in the study protocol consisting of a DCE-MRI at baseline (pre-treatment), and again three and six months post-treatment. Of these, thirty-four patients initiated second-line treatment for clinical reasons and completed the study protocol. Treatment effect after one year was assessed according to the international No Evidence of Disease Activity (NEDA) criteria by an experienced MS clinician, blinded to the DCE-MRI results.
Results: Baseline K_{trans} in NAWM was inversely correlated with increasing baseline treatment intensity (categorical variable: (a) no treatment, (b) interferon-beta/glatiramer acetate or (c) prednisolone treatment after relapse within the last month) and positively correlated with 2) presence of relapse within three months (linear regression, model $r^2=0.35$, $p=0.0001$). There was no effect of time in the linear regression analysis. We observed a significantly higher average K_{trans} in the treatment period in both NAWM and NAGM (Student´s t-test; $p=0.01$ and $p=0.007$, respectively), in the patients who did not have NEDA (equal to high disease activity despite treatment; n=15 out of 34). A logistic regression analysis showed that average K_{trans} in the treatment period in both NAWM and NAGM predicted NEDA at one year ($r^2=0.27$, $p=0.04$ and $r^2=0.33$, $p=0.03$, respectively).
Conclusions: Here, for the first time we show that permeability of the blood-brain barrier measured by DCE-MRI holds important clinical information, which could be highly useful in clinical management of MS patients. Being able to detect early inadequate treatment response could potentially save MS patients from both relapses, and side-effects of an inefficacious treatment.

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P1267

Observational study to identify biomarkers for treatment response in dimethylfumarate treated MS patients

M. Diebold[1], C. Sievers[2], N. Sanderson[2], M. Meira[2], L. Kappos[2], R.L.P. Lindberg[2], T. Derfuss[2]
[1]Biomedicine and Neurology, Universtity Hospital and University of Basel, [2]University Hospital and University of Basel, Basel, Switzerland

Background: Dimethylfumarate (DMF) is an immunomodulatory treatment for relapsing-remitting multiple sclerosis (RRMS). The mode of action of DMF has not been fully elucidated yet.
Objectives: To characterize in-vivo and in-vitro effects of dimethylfumarate on the composition, phenotype, and function of lymphocyte subsets.
Methods: Peripheral blood mononuclear cells (PBMC) were collected from 20 well-characterized RRMS patients at baseline and after 3 months of dimethylfumarate treatment and an age- and gender-matched cohort of healthy individuals at 0 and 3 months. Absolute and relative values of lymphocyte subpopulations from all patients were obtained for B-cells, T-cells, T_H-polarisation, regulatory T-cells and NK-cells longitudinally. An analysis of cytosolic and mitochondrial reactive oxygen species (ROS) levels was conducted by flow cytometry. Viability after oxidative stress induction was assessed in PBMCs with/without in-vitro DMF by flow cytometry. Response of PBMCs to in-vitro stimulation was examined regarding proliferation rate, cell viability and T-cell-subsets. Cytokine expression of PBMCs with/without in-vitro stimulation were analysed by multiplex ELISA.
Results: Absolute lymphocyte counts (subpopulations of B-cells, T-cells and NK-cells) were decreased after 3 months of treatment with dimethylfumarate compared to baseline. CD4:CD8-ratio increased indicating a relatively more pronounced decrease of CD8+ T-cells. Preliminary findings indicate that anti-CD3/CD28 mediated proliferation is reduced by in vitro pre-treatment with DMF. There is also a trend for a change in cytokine pattern during DMF treatment.
Conclusions: Our findings on the immunomodulatory properties of dimethylfumarate are in line with effects described in the literature. In-depth analysis of proliferation, oxidative stress profiles and cytokine expression may allow to group patients into different categories of treatment response.

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P1268

Plasma cytokine concentration changes in multiple sclerosis patients after treatment with dimethyl fumarate

A.R. Gafson[1], R. Nicholas[1], G. Giovannoni[2], P.M. Matthews[1]
[1]Imperial College London, Hammersmith Hospital, [2]Queen Mary University London, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, United Kingdom

Background: Plasma cytokines concentrations provide markers of inflammatory response in relapsing-remitting multiple sclerosis (RR-MS) patients.
Objective: Here we explore pharmacodynamic effects of dimethylfumarate (DMF) on plasma cytokines. We have tested specifically for decreases in Th1- and Th17- associated cytokines and increases in those associated with the Th2- response.
Methods: Whole blood was taken at baseline and 6 weeks post treatment with dimethyl fumarate from 31 relapsing-remitting MS patients (RR-MS). Blood also was taken from 10 age- and sex-matched volunteers at the same times. Plasma was extracted and cytokine and inflammatory markers were measured using the Meso Scale Discovery (MSD) V-PLEX Human Biomarker 40-Plex Kit. Paired analyses were performed using nonparametric Wilcoxon 2-sample test. Comparisons between groups were performed using Student's t-test with a significance threshold of p-value < 0.05.
Results: At baseline, patients had higher plasma concentrations of IL-2 than did the healthy volunteers ([0.56 pg/ml vs 0.29 pg/ml], 1.9-fold difference, $p < 0.05$).
An increase in cytokine expression of IL-4 (36%) [0.05 pg/ml (pre), 0.07 pg/ml (post)] and IL-13 (21%) [1.5 pg/ml (pre), 1.8 pg/ml (post)] were found after treatment with dimethyl fumarate ($p < 0.05$). Significant decreases in IFNγ (a marker of Th1 activity) or IL-17, GM-CSF or IL-22 (markers of Th17 response) were not found.
Conclusion: Increases in the Th2 associated plasma cytokines IL-4 and IL-13 were found with short-term dimethyl fumarate treatment. We did not find evidence for concomitant decreases in Th1 and Th17 inflammatory markers. Further work is needed to

assess whether the peripheral Th2 cytokine changes are sustained or associated directly with clinical responses.

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P1269

Differential effects of fingolimod on NKs and B cells subsets of relapsing-remitting multiple sclerosis patients

I. Moreno Torres[1], A. Sánchez López[1], A. García Grande[2], C. González García[1], L. Campos Ruíz[1], L. Rodríguez Esparragoza[1], R. García Hernández[1], V. Elvira[3], A. García-Merino[1]
[1]Neuroimmunology, [2]Flow Cytometry Unit, Institute for Biomedical Research of 'Puerta de Hierro' University Hospital, Majadahonda, [3]Signal Theory and Communications Department, University Carlos III of Madrid, Madrid, Spain

Background: Lymphopenia in fingolimod treated patients is due to decreased egress of CCR7(+) lymphocytes from lymph nodes. We aimed to clarify the changes in peripheral blood of Natural Killer cells (NKs) and B cell subsets at 6 months of treatment and the association with efficacy parameters defined by no evidence of disease activity´ (NEDA) at 1 year.
Materials and methods: Patients 18 to 55 years of age with relapsing-remitting MS according to Mc Donald 2010 criteria, and Expanded Disability Status Scale (EDSS) score of 0 to 5.0 were enrolled. Samples were obtained from 10 healthy controls and 30 patients before starting fingolimod and 6 months later. The following lymphocyte subsets were measured by flow cytometry: central memory (TCM) and effector memory (TEM) T cells, naive (TN) and regulatory T cells , NK^{dim}, NK^{bright} and NK cells, NKTs , memory B, naive LB, Plasmablasts, LB1 cells, regulatory LB cells, CD5+ and CD5- B cells. EDSS was calculated at baseline, 6 and 12 months. Basal Gadolinium-enhanced (GdE+), new GdE+ and T2-weighted lesions were analyzed at baseline and 6 months. NEDA status at 1 year was determined for all patients. Mann-Whitney U test compared data before and after treatment; correlation between two variables was expressed using Spearman´s rho.
Results: An increase of NK bright > 10% of the NKs at baseline and a lack of decrease in LB1 CD11b+ and plasmablasts at 6 months were all associated with poor efficacy at 1 year (p=0.035964, p= 0.042182 and p=0.005678 respectively). Regulatory LBs increased significantly only in NEDA patients (p=0.0011963). CD20+CD5+ increased in all patients (p=0.000018), but elevations >25% associated with poor efficacy at 1 year (p=0.0029526).
Interpretation: In addition to the well known effects of fingolimod on CD4+ T cell subsets our findings highlight effects on additional lymphocyte subpopulations (NK bright, LB1 CD11b, plasmablasts and regulatory LB) that can be relevant and which can to be used to predict treatment response

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P1270

Sustained disability improvement in patients with secondary progressive multiple sclerosis (SPMS) assessed by a multicomponent endpoint: a post hoc analysis from the ASCEND study

G. Giovannoni[1], D. Steiner[2], F. Sellebjerg[3], S. Cohan[4], D. Jeffery[5], D. Rog[6], Y. Chen[2], Q. Dong[2], P.-R. Ho[2], D. Cadavid[2], D. Amarante[2]
[1]Barts and the London School of Medicine and Dentistry, London, United Kingdom, [2]Biogen, Cambridge, MA, United States, [3]Danish Multiple Sclerosis Center, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark, [4]Providence Brain and Spine Institute, St. Vincent Medical Center, Portand, OR, [5]Piedmont HealthCare, Mooresville, NC, United States, [6]Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, United Kingdom

Background: As most trials for MS disease-modifying therapies focus on disability progression, a robustly defined endpoint related to disability improvement does not exist. Given the limited data and the complexity of MS, identifying and assessing improvement of disability and functional impairment in treated MS patients can be challenging. Previous analyses in relapsing-remitting MS patients have demonstrated natalizumab treatment effects on improvement of baseline disability and functional impairment, but such outcomes have never been explored in patients with advanced SPMS such as the ASCEND study population.
Objectives: To examine sustained disability improvement in ASCEND.
Methods: ASCEND, a multicenter, double-blind, phase 3 trial, enrolled natalizumab-naive patients diagnosed with SPMS for ⩾2 years and disability progression unrelated to clinical relapses in the past year; patients were randomized to 300 mg natalizumab (n=439) or placebo (n=448) IV treatment for 2 years. Disability improvement was defined as a multicomponent endpoint of improvement on ⩾1 of 3 components (Expanded Disability Status Scale [EDSS; ⩾0.5-point decrease from baseline score of 6.0-6.5 or ⩾1.0-point decrease from baseline score of 3.0-5.5], Timed 25-Foot Walk [T25FW; ⩾15% decrease from

baseline], or 9-Hole Peg Test [9HPT; ⩾15% decrease from baseline on either hand]) confirmed at 6 months and sustained at week 96/last assessment. Data were analyzed via logistic regression model adjusted for baseline EDSS/T25FW/9HPT.
Results: Most participants had advanced disability at baseline (63% had EDSS scores of 6.0-6.5), and 71% had no relapses within 2 years pre-enrollment. Significantly more participants treated with natalizumab (33%) than placebo (23%) met the multicomponent criteria (OR=1.67 [95% CI 1.23-2.26]; P=0.001). Analysis of the individual components showed improvement on all components, most prominently on T25FW (natalizumab 15% vs placebo 9%; OR=1.75 [95% CI 1.16-2.68]; P=0.009). Among those meeting T25FW or 9HPT improvement criteria, the average magnitudes of improvement from baseline were 12.4%-16.3% at week 12 and reached 27.1%-28.2% by week 96.
Conclusion: This post hoc analysis indicates that natalizumab was associated with disability improvement over 2 years in an SPMS population with severe baseline disability, suggesting additional benefits beyond the treatment effect observed on slowing disability progression on the 9HPT component of the study's primary endpoint.

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P1271

High sensitivity measurement of neurofilament-light levels in plasma demonstrates a significant reduction in multiple sclerosis patients starting fingolimod

F. Piehl[1], I. Kockum[1], M. Khademi[1], K. Blennow[2], N. Norgren[3], H. Zetterberg[2,4], T. Olsson[1]
[1]Clinical neuroscience, Karolinska Institutet, Stockholm, [2]Psychiatry and Neurochemistry, University of Gothenburg, Gothenburg, [3]Uman Diagnsotics, Umeå, Sweden, [4]Molecular Neuroscience, UCL Institute of Neurology, London, United Kingdom

Background: An increasing body of evidence suggests neuroaxonal damage to be the main determinant of long term disability. Among different markers of neuroaxonal damage neurofilament light (NFL) has emerged as a promising biomarker candidate. Still, an important obstacle for a wider introduction into clinical practice is that such analyses have required access to cerebrospinal fluid (CSF). Detection of NFL in serum or plasma have been reported previously, however, most technical platforms have an analytical sensitivity limit above levels normally seen in healthy controls and with a significant overlap with levels seen in MS patients.
Objective: To (i) determine the correlation between NFL in CSF and serum/plasma in a pilot cohort of MS patients and controls, and (ii) to determine levels of NFL in plasma at baseline and at 12 months of patients starting treatment with fingolimod (Gilenya).
Methods: We applied the Single Molecule Array (Simoa) technology for ultrasensitive detection of NFL using antibodies from UmanDiagnostics (UmanDiagnostics, Umeå, Sweden) transferred onto the Simoa platform using a homebrew kit (Quanterix Corp, Boston, MA, USA). The lower limit of quantification (LLoQ), determined by the blank mean signal + 10 SD was 1.95 pg/ml.
Results: The correlation between serum and CSF levels was high both in controls with non-inflammatory neurological conditions (Spearman rank test, Sr=0.759; p< 0.0001; n=27) and MS patients (Sr=0.5776; p< 0.0001; n=46). Furthermore, plasma and serum levels in MS patients were also highly correlated (Sr=0.684; p< 0.007; n=14). In patients being either treatment naïve or switching from injectable disease modulatory treatments the plasma level of NFL decreased significantly (baseline mean 26.4 ± 6.81 pg/ml, 12 months mean 22.3 ± 5.81; Paired T test, two tailed, p=0.004; n=30). Additional data on a cohort of 200 patients with correlation to clinical and treatment related outcomes will be included in the final presentation.
Conclusions: We here report a high correlation of CSF NFL levels in CSF and plasma/serum of MS patients and controls using an ultrasensitive analysis platform. Furthermore, plasma levels of NFL were significantly reduced at 12 months compared with baseline in MS patients initiating fingolimod treatment. The results suggest that NFL levels in plasma can be used to monitor treatment effectiveness in MS patients.

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P1272

Adding brain volume changes to Non-evidence of Disease Activity (NEDA) criteria and to Rio score for predicting treatment response after interferon-beta therapy

F. Pérez-Miralles[1], J. Sastre-Garriga[1], J. Río[1], À. Vidal-Jordana[1], D. Pareto[2], M. Tintoré[1], C. Auger[2], Á. Rovira[2], X. Montalban[1]
[1]Multiple Sclerosis Centre of Catalonia/Neuroimmunology Department, [2]MRI Unit, Radiology Dept, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Brain volume changes on therapy with disease-modifying drugs are being considered as potentially useful to monitor treatment response at an individual level, alone and in combination with other clinical and radiological parameters, but more evidence is needed to support this claim.
Objective: To investigate whether brain volume changes improve the predictive ability of the (No) Evidence of Disease Activity (EDA) and Río Score (RS) criteria for mid-term EDSS progression in patients treated with interferon-beta.
Methods: One hundred and twenty-four patients treated with interferon-beta were assessed for brain volume changes, presence of new lesions (⩾1 for EDA / ⩾3 for RS), relapses and confirmed EDSS worsening after one year. Different cut-off points for brain volume changes were evaluated: -1.2, -1.0, -0.86 (selected from a previous published work), -0.6, -0.4 and -0.2% brain volume loss per year. EDSS scores were obtained at four years. Original EDA (EDA-3) and RS (Río-3) as well as EDA and RS including brain volume changes (EDA-4 and Río-4) were comparatively evaluated.
Results: One hundred and one patients had their EDSS and the presence of further relapses assessed at four years and had a complete MRI evaluation (both presence of new lesions and brain volume changes). Sensitivity, specificity and positive and negative predictive values for EDA-3 and EDA-4 (expressed as range for all cut-off points) were respectively (%): 85/90-95, 40/7-30, 26/20-24 and 91/86-92. Same parameters for Río-3 and Río-4 (in both cases with a cut-off of 2 out of 4 criteria / expressed as range for all cut-off points) were: 55/80, 95/79-89, 73/48-64 and 90/94-95. OR for predicting confirmed EDSS worsening was significant for EDA-3 (3.701, p=0.050), but not for all EDA-4 cut-off points, whereas both Río-3 (23.528, p< 0.001) and Río-4 for all cut-off points (OR range 15.06 - 32.00, p< 0,001). Río-4 shows a larger area under the curve for prediction of disability at 4 years than Río-3 (0.84 versus 0.82).
Conclusions: Addition of brain volume changes to Río-3 criteria (Río-4) improves its prediction of response to interferon-beta. Brain volume changes could be incorporated as a monitoring parameter in treatment-response criteria.

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P1273

Treatment response to dimethyl fumarate is characterized by CD8+ T cell reduction in multiple sclerosis

F. Luessi[1], V. Fleischer[1], M. Friedrich[1], A. Rezk[2], U. Bühler[1], E. Witsch[1], T. Uphaus[1], S. Bittner[1], S. Groppa[1], A. Bar-Or[2], F. Zipp[1]
[1]Dept. of Neurology, University Medical Center Mainz, Mainz, Germany, [2]Neuroimmunology Unit, Montreal Neurological Institute, McGill University, Montreal, QC, Canada

Background: Dimethyl fumarate (DMF) alters the composition of circulating immune cells and induces lymphopenia in a subpopulation of treated multiple sclerosis (MS) patients.
Objective: To investigate the relationship between the leukocyte composition in DMF-treated MS patients and their disease activity in the first year of therapy.
Methods: Peripheral blood samples from 91 relapsing-remitting MS patients were immunophenotyped using flow cytometry. The lymphocyte subset analysis included $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ and $CD56^+$ subpopulations. We compared untreated MS patients (n=40) with DMF-treated MS patients (n=51) 6 months after treatment onset. Disease activity of DMF-treated patients was then longitudinally assessed and defined as MRI activity and/or clinical relapse in the first year under DMF treatment (mean follow-up 11.5 months).
Results: MS patients without evidence of disease activity showed significantly lower absolute counts of total CD3+ T cells (p< 0.002), including CD4+ (p< 0.032) and CD8+ T cells (p< 0.001), as well as CD19+ B cells (p< 0.021) in comparison to MS patients with disease activity under DMF treatment. In addition, patients without disease activity demonstrated an increased CD4+/CD8+ ratio (p< 0.025) indicating a disproportionate reduction of CD8+ T cells relative to CD4+ T cells. The degree of CD8+ T cell reduction at 6 months after commencement of DMF enabled prediction of the treatment response in the first year (area under the receiver operating characteristic (ROC) curve 0.767 [0.633 - 0.901]).
Conclusion: DMF treatment response is associated with lower circulating T cells and B cells, and particularly characterized by a disproportionate reduction of CD8+ T cells. Changes in the cellular immune profiles during DMF treatment are clinically relevant and might be used to predict clinical response to DMF treatment.

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P1274

Deploying the MS Bioscreen in the clinic: towards real-world precision medicine

R. Bove, A. Lizee, P. Garcha, S.L. Hauser, UCSF MS-EPIC Team, UCSF MS Bioscreen Team
Neurology, University of California, San Francisco, San Francisco, CA, United States

Background: The MS Bioscreen (MSB) was developed as a translational digital tool to meet the challenges of dynamic management of a complex chronic disease. Its back-end manages data; computes quantified insight; and serves the front-end, a tablet-powered application used at the point-of-care by the neurologist.
Goals: Our first goal was to pilot the integration of data obtained both from a large research database (EPIC) and a real-world clinical medical record into a real-time platform used during the clinical encounter.
Our second goal was to examine the impact of the MSB on two aspects of the clinical encounter: (1) patient and provider satisfaction, and (2) clinical decision-making.
Methods: One hundred patients with a diagnosis of MS/CIS, presenting for scheduled visits with one of 6 UCSF MS expert clinicians, are assigned to visits during which the clinician either does (MSB+) or does not (MSB-) use MSB. Questionnaires are completed before (patients) and after (patients and clinicians) individual visits. During MSB+ visits, patient-specific clinical and neuroimaging data imported from EMR and/or from the research database are visualized and contextualized within a reference dataset.
Results: First, we will describe the effect of MSB deployment on patient's evaluation of the patient-doctor encounter, their perception of the clinician as an MS expert, their understanding of the disease process, and their autonomy in participating in their MS care. We will report mitigating factors (patient education and goals for encounter).

Second, we will describe the effect of MSB deployment on clinician's reported time taken pre-encounter to review patient data, and their satisfaction with their communication with patients surrounding disease course and personalized recommendations.
Finally, we will examine the impact of MSB on clinical decision-making in three unique scenarios: (1) initial MS presentation, (2) breakthrough disease on current therapy, and (3) indolently progressive clinical disease and/or accelerating rate of brain atrophy.
Conclusion: The clinical deployment of the MSB represents the ultimate phase in the development of a real-world precision medicine tool for complex chronic disease management.

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P1275

Therapeutic use of anti-α4 integrin antibodies in Rasmussen's encephalitis

H. Kebir[1,2], L. Carmant[3,4,5], F. Fontaine[3], K. Béland[3], C. Bosoi[3], N. Sanon[3], J.I. Alvarez[6], S. Desgent[3], C. Pittet[7], D. Hébert[3], M.-J.

Langlois[3], R.-M. Rébillard[4], D.K. Nguyen[5,7], C. Cieuta[8], G.L. Holmes[9], H.P. Goodkin[10], J.R. Mytinger[10], M.B. Connolly[11], E. Haddad[2,3,4], A. Prat[5,7]
[1]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), [2]Microbiology, Infectiology and Immunology, Université de Montréal, [3]Centre de Recherche du Centre Hospitalier Universitaire Sainte-Justine, [4]Pediatrics, [5]Neurosciences, Université de Montréal, Montreal, QC, Canada, [6]University of Pennsylvania, Philadelphia, PA, United States, [7]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, [8]Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, QC, Canada, [9]Dartmouth-Hitchcock Medical Center, Dartmouth University, Lebanon, NH, [10]Fontaine Research Park, University of Virginia, Charlottesville, VA, United States, [11]B.C. Children's Hospital, University of British Columbia, Vancouver, BC, Canada

Rasmussen´s encephalitis (RE) is a chronic smoldering unilateral inflammatory brain disorder that mainly affects children between 14 months and 14 years of age. Surgical hemispherectomy remains, to date, the only definitive treatment for this refractory epileptic syndrome. In view of the belief that RE is an immune-mediated disease associated with trafficking of reactive T cells into the CNS, α4 integrin blockade, a highly effective therapy for relapsing-remitting multiple sclerosis, was recently suggested as a potential alternative approach to treat RE. Unfortunately, the absence of an animal model of disease has hampered the development and testing of new therapies for RE.

In this study, we describe an experimental model of RE that shares several clinical and pathological features with the human disease. Immunodeficient NOD/SCID/IL2Rγ_c(null) mice injected with peripheral blood mononuclear cells (PBMCs) of 9 RE patients and 6 control subjects were monitored by electroencephalography. Mice injected with PBMCs from RE patients developed severe seizures of cortical origin, displayed intense astrogliosis and increased numbers of human IFN-γ- and granzyme B-expressing T lymphocytes in the brain, as compared to mice injected with control PBMCs. α4 integrin blockade dramatically reduced seizure frequency and lymphocyte recruitment into the brain.

Our findings validate the T cell-mediated immune hypothesis of RE and describe a valuable *in vivo* model to understand the pathology of this disease and to develop patient-tailored experimental therapeutics.

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P1276

Increased IFN-beta binding antibody levels in non-responding MS patients - a Hungarian multicentre study

C. Rajda[1], T. Csépány[2], M. Keresztes[3], H. Polyák[1], A. Kiss[1], K. Bencsik[1], Z. Szolnoki[4], L. Tóth[5], C. Rózsa[6], J. Semjén[7], E. Bense[8], Z. Simon[9], E. Dobos[10], N. Tegze[11], G. Jakab[12], G. Katona[12,13], Z. Lohner[14], J. Füvesi[1], L. Vécsei[1]
[1]Department of Neurology, University of Szeged, Szeged, [2]Department of Neurology, University of Debrecen, Debrecen, [3]Department of Biochemistry, University of Szeged, Szeged, [4]Department of Neurology, Pándy Kálmán County Hospital, Gyula, [5]Department of Neurology, Hetényi Géza Hospital and Outpatient Clinic, Szolnok, [6]Department of Neurology, Jahn Ferenc Dél-Pest Hospital and Outpatient Clinic, Budapest, [7]Department of Neurology, Markhot Ferenc Teaching County Hospital and Outpatient Clinic, Eger, [8]Department of Neurology, Kenézy Gyula Hospital and Outpatient Clinic, Debrecen, [9]Department of Neurology, Szent János Hospital and merged hospitals in North Buda, [10]Department of Neurology, Szent Imre University Teaching Hospital, [11]Department of Neurology, Semmelweis University, Kútvölgyi Clinical Centre, [12]Department of Neurology, Semmelweis University, Uzsoki Hospital, [13]National Institute of Rheumatology and Physiotherapy, [14]Department of Neurology, Military Hospital, Róbert Károly Boulevard Place, Budapest, Hungary

Introduction: The immunogenicity of interferon-beta (IFN-beta) treatment is well known. The formation of antibodies against the drug diminishes treatment efficacy. IFN-beta, which belongs to the first line MS treatments are known to decrease the relapse rate by 1/3.
Methods: The high levels of binding IFN-beta antibodies correlated well with therapeutic effectiveness and can be useful among the other parameters when considering switching. Sixteen of the Hungarian MS centres took part in the trial of detecting binding antibodies in patients treated with IFN-beta. The 289 sera samples were measured by capture ELISA assay. The blood samples were collected at the 12th and 18th month of IFN-beta treatment and in case of therapeutic inefficacy. Patients with short follow-up period (< 2 years) were excluded, and the data were calculated for the 109 remaining patients.
Results: Thirty-two percent of the patients were treatment responders in the last 2-5 years, 50.5% were non-responders and 17.5% switched to other treatment because of side effects. In 5 patients (9%) the transition to secondary progressive form was the reason of non-responsiveness. In the remaining cases disease breakthrough was responsible for treatment failure. High binding antibody level was found in 8 patients (15%) of the non-responders, all had to change treatment because of relapses.
Conclusion: Our results support the earlier finding that high levels of binding antibodies in the sera correlate well with the presence of neutralizing antibodies, which are reliable also at negative values. The method of detection of binding antibodies seems to be reliable and reproducible.

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Treatment of progressive MS

P1277

Importance of upper limb function in advanced multiple sclerosis

A. Thomson[1], G. Giovannoni[2], M. Marta[1], S. Gnanpavan[1], B. Turner[1], D. Baker[1], K. Schmierer[1]
[1]Queen Mary University London, Barts and the London School of Medicine and Dentistry, [2]Barts and The London School of Medicine, London, United Kingdom

Background: The recent emphasis on early disease modifying treatment (DMT) of people with MS (pwMS) has consolidated the concept that once pwMS enter an advanced stage ("progressive MS") their MS does not respond to existing DMTs. Results of the natalizumab (Nz) in secondary progressive MS (ASCEND study, NCT01416181) challenges this concept. Although ASCEND's primary outcome was negative, pwMS treated with Nz were significantly less likely to develop confirmed progression at 12 weeks when using the 9-hole peg test (9HPT) of upper limb (UL) function.
Objectives: To present results of a online survey of pwMS exploring their views on the importance of UL function to maintain independence.
Methods: Using an infographic and the BartsMS blog (www.ms-res.org), a social media platform for pwMS with over 6,000 hits/day, we asked pwMS to rate the importance of UL function, and whether pwMS who are dependent on a wheelchair for mobility should be excluded from clinical trials of DMTs. The importance of UL (compared to lower limb) function was assessed using a Likert scale from 0 (UL function unimportant compared to walking) to 10 (UL function critically important, i.e. more important than walking in terms of staying independent).
Results: There were 130 responses to the survey. Sixty-nine respondents (53%) chose the maximum score on the Likert scale, and 117 respondents (90%) selected a score of 7 or greater thus ranking UL function well above lower limb function in staying independent. Ninety-five percent of responders felt that pwMS in wheelchairs should not be excluded from future progressive MS trials.
Conclusions: pwMS overwhelmingly consider UL function as superior compared to lower limb function in terms of staying independent. Results of the ASCEND trial suggest that worsening UL function in pwMS may be modifiable even at an advanced stage of the disease, indicating new trial designs based on this new evidence as well as the needs of pwMS are warranted. The discrepancy between apparent lack of effect on lower limb function but positive effect on UL function in advanced MS suggest greater functional reserve for the latter over the former.

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David Baker has received research support from Sanofi-Genzyme and is founder, shareholder and consultant to Canbex Therapeutics.
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Baseline assessment of fatigue and health-related quality of life in patients with primary progressive multiple sclerosis in the ORATORIO study

J. Wolinsky[1], F. McDougall[2], E. Lentz[3], G. Deol-Bhullar[2], X. Montalban[4]
[1]University of Texas Health Science Center at Houston, Houston, TX, United States, [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [3]Genentech, Inc., South San Francisco, CA, United States, [4]Hospital Vall d'Hebron University, Barcelona, Spain

Background: Multiple sclerosis (MS) is a chronic disease, resulting in long-term accumulation of physical and cognitive disability that negatively impacts patients' quality of life (QoL). Patient-reported outcomes provide insight into the humanistic burden of diseases. Limited patient-reported data are available in primary progressive MS (PPMS), highlighting the need to understand the patient's perception of their disease.
Objective: To assess baseline fatigue and health-related QoL in patients enrolled in ORATORIO, a Phase III, randomised, double-blind, placebo-controlled study of ocrelizumab in PPMS.
Methods: The Modified Fatigue Impact Scale (MFIS) assesses the effects of fatigue on physical, cognitive and psychosocial functioning. The MFIS is scored on a 0-84 scale and scores $\geqslant$38 indicate a clinically important level of fatigue. The Short Form-36 (SF-36) assesses patients' perception of health and well-being across 8 health concepts: 1) general health perceptions; 2) physical functioning; 3) role limitations due to physical problems; 4) bodily pain; 5) mental health; 6) role limitations due to emotional problems; 7) vitality; 8) social functioning. A Physical Component Summary (PCS) and Mental Component Summary (MCS) score can also be calculated. The SF-36 is scored on a 0-100 scale, and

lower scores reflect poorer QoL. T scores for SF-36 were calculated using the 2009 US Normative data; a mean (SD) score of 50 (10) corresponds to that of the general US population. MFIS and SF-36 were assessed at baseline in ORATORIO patients.
Results: In ORATORIO, the mean (SD) MFIS score was 41.6 (17.2) at baseline, with 62.7% of patients scoring above the threshold for clinically important symptoms. Baseline mean (SD) SF-36 PCS and MCS were 37.9 (8.6) and 44.2 (11.2), respectively, indicating their HRQoL was below that of the general US population. The baseline mean (SD) SF-36 subscale scores were as follows: general health perceptions, 40.8 (9.4); physical functioning, 34.6 (9.4); role limitations due to physical problems, 35.6 (10.2); bodily pain, 45.4 (11.3); mental health 43.9 (10.6); role-limitations due to emotional problems, 39.7 (12.8); vitality, 42.5 (9.4); and social functioning, 40.7 (10.5).
Conclusion: In ORATORIO, a high prevalence of fatigue and diminished HRQoL were reported at baseline by patients with PPMS, highlighting the unmet need for treatments that improve QoL and fatigue in this chronic, disabling disease.
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Fiona McDougall is an employee of F. Hoffmann-La Roche Ltd.
Ellen Lentz is an employee of Genentech, Inc.
Gurpreet Deol-Bhullar is an employee of F. Hoffmann-La Roche Ltd.
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P1279

Patient-reported outcomes in the phase III double-blind, placebo-controlled ORATORIO study of ocrelizumab in primary progressive multiple sclerosis

J. de Seze[1], X. Montalban[2], F. McDougall[3], A. Sauter[3], G. Deol-Bhullar[3], J. Wolinsky[4]
[1]University Hospital of Strasbourg, Strasbourg, France, [2]Vall d'Hebron University Hospital, Barcelona, Spain, [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [4]University of Texas Health Science Center at Houston, Houston, TX, United States

Background: Patient-reported outcomes (PROs) comprise a diverse range of measures that assess the impact of disease and therapeutic efficacy from the patient's perspective. ORATORIO was a randomised, double-blind, placebo-controlled Phase III study that evaluated the efficacy and safety of ocrelizumab (OCR), a humanised monoclonal antibody that selectively targets $CD20^+$ B cells, in primary progressive multiple sclerosis (PPMS).
Objective: To evaluate the effect of OCR on two PROs, the Short Form-36 (SF-36) and Modified Fatigue Impact Scale (MFIS), in patients with PPMS.
Methods: The SF-36 assesses patients' perception of functional health across 8 concepts that can be reported individually or combined to provide a Physical Component Summary (PCS) and a Mental Component Summary (MCS). The MFIS assesses the effects of fatigue on physical, cognitive and psychosocial functioning. In ORATORIO, patients were randomised (2:1) to receive OCR 600 mg or placebo intravenously as two 300 mg infusions 14 days apart, every 24 weeks for ⩾120 weeks until a prespecified number of 12-week confirmed disability progression events occurred. The SF-36 and MFIS were administered at baseline, Week 48 and Week 120. Change in SF-36 PCS and changes in SF-36 MCS and MFIS total score from baseline to Week 120 were assessed secondary and exploratory endpoints, respectively. T scores for SF-36 were calculated using the 2009 US Normative data; a mean (SD) score of 50 (10) corresponds to that of the general US population.
Results: There was no statistically significant difference in the decline in SF-36 PCS in the OCR group vs the placebo group (adjusted mean -0.688 with OCR vs -1.086 with placebo [p=0.5576]). However, OCR significantly improved SF-36 MCS compared with placebo (adjusted mean 1.577 with OCR vs -1.483 with placebo [p=0.0006]) from baseline to Week 120. Further, OCR significantly improved the MFIS total score compared with placebo (adjusted mean -0.462 with OCR vs 2.994 with placebo [p=0.0091]) and performed better than placebo for all three MFIS subscale components from baseline to Week 120.
Conclusions: In patients with PPMS, ocrelizumab reduced physical, cognitive and psychosocial aspects of fatigue and improved the mental well-being component of health-related quality of life compared with placebo, as measured from the patients' perspective. There was no difference observed between ocrelizumab and placebo groups in the SF-36 PCS.
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Fiona McDougall is an employee of F. Hoffmann-La Roche Ltd.
Annette Sauter is an employee and shareholder of F. Hoffmann-La Roche Ltd. **Gurpreet Deol-Bhullar** is an employee of F. Hoffmann-La Roche Ltd.
Jerry Wolinsky in the last 3 years has received compensation for service on steering committees or data monitoring boards for F. Hoffmann-La Roche Ltd., Medday Pharmaceuticals, Novartis,

Sanofi Genzyme and Teva Pharmaceuticals; consultant fees from AbbVie, Actelion, Alkermes, EMD Serono, Forward Pharma, Genentech, Inc., F. Hoffmann-La Roche Ltd., Novartis, Sanofi Genzyme, Takeda, Teva, and XenoPort; research support from, Sanofi Genzyme, the NIH and the NMSS through the University of Texas Health Science Center at Houston (UTHSCH) and royalties for monoclonal antibodies out-licensed to Chemicon International through UTHSCH.

P1280

A small molecule therapy for MS patients appears to override inhibitors of oligodendrogenesis to induce remyelination

S.H. Nye, J.G. Yarger
Discovery, ENDECE, LLC, Mequon, WI, United States

Background: There is an unmet need for remyelinating therapies to treat multiple sclerosis (MS) patients. NDC-1308 is an analog of estradiol (E2) that harnesses the body's natural remyelinating system to drive oligodendrogenesis, a process resulting in mature, myelinating oligodendrocytes (OLs) that can repair damaged myelin sheaths. NDC-1308 was previously shown in mouse oligodendrocyte progenitor cell (OPC) cultures to induce a 3-fold increase in OLs compared to vehicle. Structurally related estrogens, E2 and estriol, do not possess this activity. Side-by-side comparison of NDC-1308 and E2 activity, following chronic treatment in the cuprizone mouse model of demyelination, showed only NDC-1308 could significantly repair the myelin sheath (44% increase in hippocampus). NDC-1308 can apparently accomplish this by overriding inhibitors of oligodendrogenesis, such as Lingo-1.
Objectives: We investigated how NDC-1308 has gained the biological activity to repair demyelinated axons, but lost the deleterious side-effects commonly associated with estrogens.
Methods: Intracellular pathway activation by NDC-1308 and E2 was compared in human cell lines using real-time qPCR. Potential safety concerns for NDC-1308 were addressed. Estrogenicity was directly measured in a mouse uterotrophic assay since E2 treatment is known to cause a rapid and dramatic increase in uterine weight in this assay. Mutagenicity (Ames assay) and genotoxicity (micronucleus assay) was assessed. Biomarker development was initiated using human PBMCs.
Results: While NDC-1308 and E2 are both ER agonists, the remyelinating activity of NDC-1308 can be traced back to its unique ability to significantly up-regulate key genes (OLIG2, DNER, MOG and MBP) for oligodendrogenesis. Real-time qPCR analysis showed these same genes are up-regulated 2-3 fold in human PBMCs treated for 12 hours with NDC-1308, suggesting they could serve as potential therapeutic biomarkers. Unlike E2, NDC-1308 was not found to be estrogenic in the mouse uterotrophic assay. Further testing revealed that NDC-1308 is not mutagenic and not genotoxic. The OPC pool remained intact after 6 weeks of chronic NDC-1308 treatment, demonstrating that it can serve as a renewable source for sustaining oligodendrogenesis.
Conclusion: NDC-1308 is a potential first-in-class remyelinating therapy that possesses many key qualities needed to effectively treat secondary progress (SPMS) and relapsing-remitting (RRMS) MS patients.

Disclosure

Steven Nye is an employee and shareholder of ENDECE.
James Yarger is an employee and shareholder of ENDECE.

P1281

Effectiveness of autologous bone marrow mesenchymal stem cells intrathecal transplantation in patients with secondary progressive multiple sclerosis

M. Swiderek-Matysiak[1], J. Wojtkiewicz[2], A. Habich[2], I. Selmaj[1], W. Maksymowicz[2], K. Selmaj[1]
[1]Medical University of Lodz, Department of Neurology, Lodz, [2]University of Warmia and Mazury, Department of Neurosurgery, Olsztyn, Poland

Objective: To assess safety and therapeutic benefit of intrathecal administration of autologous mesenchymal stem cells (MSCs) in patients with secondary progressive multiple sclerosis (MS) who failed on previous therapies.
Methods: Twelve MS patients with disability progression by 1.0 point in the EDSS (Expanded Disability Status Scale) in past 12 months were included in the study. Mean EDSS score at baseline was 7.33 point, disease duration 9 to 20 years. Mean patients age was 48,1 years and gender ratio female/male 5/7. MSCs (CD 73, CD 90, CD 105 positive) were isolated from bone marrow and cultured for 4-5 weeks. After four passages, 20-25x10^6 of fresh MSCs were injected in single intrathecal infusion. Patients underwent a neurological assessment at baseline, 3, 6 and 12 months post-injection including EDSS, MSFC (Multiple Sclerosis Functional Composite) and SDMT (Symbol Digit Modalities Test).
Results: Six patients had injection-related adverse events of mild intensity (headache, backache). No major adverse effects were reported during 12 months of study follow-up. The mean EDSS improved during 1 year of follow-up by 0,25. At the end of 12 month follow-up, the EDSS score remained unchanged in 6 patients and was reduced by 0.5 degree in the other 6 patients compare to baseline. Cognitive function in SDMT was tested in 9 patients and showed improvement in 6, stabilization in 2 and worsening in 1 patient.
Conclusion: Intrathecal administration of autologous MSCs in patients with secondary progressive multiple sclerosis was safe well tolerated procedure and showed modest clinical benefit.

Disclosure

Nothing to disclose

P1282

Results of a pilot trial of lithium in progressive multiple sclerosis

J.R. Rinker[1,2], W. Meador[1], V. Sung[1,2], A. Nicholas[1,2], G. Cutter[3]
[1]Neurology, University of Alabama at Birmingham, [2]Neurology, Birmingham VA Medical Center, [3]Biostatistics, University of Alabama at Birmingham, Birmingham, AL, United States

Background: Progression in multiple sclerosis (MS) denotes the insidious accumulation of disability over time, driven by inflammatory demyelination and neurodegeneration. Current immune modulating drugs have shown little effect in progressive MS, so novel pharmacologic approaches to treat progression are needed.

Lithium carbonate (Li) is a pharmacologically active cation which distributes widely throughout the brain and has been shown to impart neuroprotective effects in several models of degenerative diseases. Li also ameliorates inflammatory demyelination in murine models of MS. Presented here are the results of a pilot trial designed to test the safety, feasibility, and efficacy of Li in a progressive MS cohort.

Methods: Subjects consented to a 2-year, open-label crossover trial of adjunct Li vs. standard care. Subjects were randomly assigned to take up to 300 mg Li daily in year 1 or 2. Annual clinical, radiological, and laboratory assessments were used to assess the primary outcomes of safety/tolerability and change in brain parenchymal fraction (BPF). Secondary outcome measures included relapse rates, changes in expanded disability status scale (EDSS) and MS functional composite, and scales of depression, fatigue, and quality of life.

Results: Of 23 consented subjects, 17 completed the 2-year study. Two of 6 subjects discontinued due to Li-intolerance (worsening gait), while 4 discontinued for personal or medical reasons unrelated to the study. Mean age at enrollment was 51 ± 7.8 years, and mean duration of disease was 14 ± 10.5 years. Median baseline EDSS was 4.

The most commonly reported side effects included increased thirst (n=11), polyuria (n=9), and fatigue (n=7). Myoclonic jerks or tremor affected 5 subjects but did not limit treatment. Two subjects experienced asymptomatic increases in thyroid stimulating hormone which resolved upon Li cessation. Relapse rates and change in EDSS did not significantly differ between on- and off-Li time periods.

Twenty three of 34 MRI pairs were available for change in BPF comparison at the time of publication. During Li treatment, BPF increased by a mean of 0.560 ± 0.379%, compared to 0.139 ± 0.304% during standard care (p=0.399).

Conclusions: In a progressive MS cohort, low-dose Li was well-tolerated and preliminary analysis does not rule out a benefit on brain volume compared to standard care. Future studies designed around efficacy should better clarify Li's role as a treatment for progressive MS.

Disclosure

Funding for the trial was provided through the Department of Veterans Affairs, CDA2-003-10S.

Dr. Rinker reports no conflicts of interest related to the conduct of the study.

Dr. Meador reports no conflicts of interest related to the conduct of the study.

Dr. Sung reports no conflicts of interest related to the conduct of the study.

Dr. Nicholas reports no conflicts of interest related to the conduct of the study.

Dr. Cutter reports no conflicts of interest related to the conduct of the study.

P1283

Fingolimod effect on disability progression in primary progressive multiple sclerosis patients with inflammatory activity: A post-hoc subgroup analysis of the INFORMS study

J.S. Wolinsky[1], B.A.C. Cree[2], M.S. Freedman[3], H.-P. Hartung[4], F. Lublin[5], D.H. Miller[6], X. Montalban[7], B. Uitdehaag[8], H. Weiner[9], C. Lubetzki[10], N. Putzki[11], B. Li[12], D.A. Häring[11], M. Merschhemke[11], L. Kappos[13]

[1]Texas Health Science Center, Houston, TX, [2]Multiple Sclerosis Center, University of California, San Francisco, CA, United States, [3]The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada, [4]Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany, [5]Icahn School of Medicine at Mount Sinai, New York, NY, United States, [6]Queen Square MS Centre, UCL Institute of Neurology, London, United Kingdom, [7]Hospital San Pedro Universitari Vall d'Hebron, Barcelina, Spain, [8]VU University Medical Center, Amsterdam, The Netherlands, [9]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States, [10]University Paris 6, Salpêtrière Hospital, Paris, France, [11]Novartis Pharma AG, Basel, Switzerland, [12]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States, [13]University Hospital, University of Basel, Basel, Switzerland

Background: Fingolimod, an oral sphingosine 1-phosphate receptor modulator that showed significant benefits in suppressing disease activity and slowing disease progression in relapsing multiple sclerosis (RMS), was evaluated for primary progressive MS (PPMS) in the INFORMS study. In the overall study population there was no effect of fingolimod on disease progression, in spite of a significant reduction in inflammatory MRI activity. However, the level of inflammatory activity in INFORMS was very low, with 13% of patients having Gd+ lesions at baseline, and 6% relapsing during the study.

Objective: To assess the potential benefit of fingolimod 0.5 mg on disease progression in PPMS patients with inflammatory activity, including the subgroup of younger patients.

Methods: Time to 3-month confirmed disability progression was assessed in patients with one or more Gd+ lesion at baseline (Gd+ patients) (n=107) vs those without Gd+ lesion at baseline (Gd- patients) (n=713), based on the composite endpoint of change from baseline in Expanded Disability Status Scale (EDSS), 25-Foot Timed-Walk Test or 9-Hole Peg Test. A key secondary endpoint was disability progression as assessed by EDSS. Subgroups of Gd+ patients ⩽ 50 years (n=76) vs Gd-patients >50 years (n=311), and of relapsing (n=47) vs non-relapsing (n=776) patients were also analysed. A Cox regression model was used to estimate treatment effect vs placebo.

Results: Risk reduction [RR] for disease progression compared to placebo was 7.10% (p=0.750) and 2.65% (p=0.770) in Gd+ and Gd- patients, respectively, for the composite endpoint, and 25.31% (p=0.274) and 6.91% (p=0.523) by EDSS. RR was 8.48% (p=0.739) and -9.45% (p=0.517) in Gd+ patients ⩽50 and Gd- patients >50, respectively, for the composite endpoint, and 36.15% (p=0.145) and -6.68% (p=0.712) by EDSS. A weak trend for RR was also observed in the subgroup of relapsing patients for EDSS [relapsing: 19.50% (p=0.725); non-relapsing: 9.06% (p=0.370)].

Conclusion: The effects of fingolimod in this post hoc subgroup analysis indicate a possibility of a treatment effect in younger patients with Gd+ lesions or relapses, which can only be validated in a further trial, more focused on such patients. This observation is consistent with other studies in PPMS and suggests that in a subgroup of PPMS patients controlling for inflammatory disease activity may have some impact on progression.

Disclosure

Fred Lublin has received compensation for service on steering committees, data monitoring boards or as a consultant for Bayer

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Others

P1284

Risk perception and propensity and its influences on treatment of Italian Multiple Sclerosis patients

F. Sangalli, E. Minacapelli, M. Radaelli, M. Falautano, L. Moiola, G. Comi, V. Martinelli
San Raffaele Scientific Institute, Milano, Italy

Background: Nowadays the treatment of Multiple Sclerosis (MS) makes neurologists and patients choose between many disease modifying therapies (DMT) with different efficacy and safety profiles. Patients are willing to take more responsibility for clinical choices, thus physicians need to understand patients' preferences to identify aspects that could guide them, such as patients' risk perception and their willingness to take risks.

Objectives: To evaluate in a cohort of Italian MS patients the willingness to accept risks associated with treatments in order to obtain improvement in disease outcomes.

Methods: We subdivided patients into two groups: group A consists of recently diagnosed patients diagnosed who start DMT; group B consists of patients treated with DMT for more than 6 months who are about to change treatment for inefficacy/intolerance. These patients completed a questionnaire to evaluate patients risk perceptions and propensity. Moreover we collect data on demographic, cultural and socioeconomic characteristics as well as personality and clinical aspects.

Results: We enrolled 355 patients, almost equally subdivided into the two subgroups. On average patients felt significantly less fortunate and optimist and more depressed after MS diagnosis. To gain 2 years of disease stability patients are willing to accept a therapy with a risk of severe disability and death of 1% and 0.5%, respectively. These percentages significantly raise to 1.5% and 0.9% if the proposed therapy can assure 4 years of disease stability. Considering only group B, patients were willing to take significantly higher risks for longer disease stability if they were changing therapy due to failure of previous treatment. The risk that most worried our patients was PML (48.3%), followed by risks related to MS; indeed disease progression and relapses were pointed out as the most preoccupying events by 20.3% and 16.3% of patients respectively. DISCUSSION**:** Generally patients showed preference to lower levels of risk and, among possible adverse events patients, PML is perceived as the most worrying followed by leukaemia. On the other hand, patients were also concerned about relapses and progression and they seem disposed to accept higher risks to obtain longer disease stability. Interestingly patients who previously failed to DMT were more willing to take risks in order to receive more effective treatment.

Disclosure

Dr Martinelli received travel supports and speaker fees for activities with Biogen Dompe, Merck-Serono, Bayer Schering, TEVA and Sanofi Aventis as a speaker.

Prof Comi received personal compensation for activities such as advisory board and consultant with the following companies: Novartis, Teva, Sanofi-Aventis, Merck Serono and Bayer Schering and for speaking with the following companies: Novartis, Teva, Sanofi-Aventis, Merck Serono, Biogen-Dompè and Bayer Schering.

Dr. L. Moiola received personal compensation for speaking activity from Biogen Dompè and Sanofi-Aventis.

Dr. F. Sangalli, Dr. E. Minacapelli, Dr. M Falautano and Dr. M. Radaelli have nothing to disclose.

P1285

Non-interventional post-authorization safety study to prospectively evaluate the safety and tolerability profile of Rebif® HSA-free scIFNβ-1a in naive relapsing remitting multiple sclerosis subjects: STEP study

A. Bertolotto[1], M. Caldano[2], P. Tortorella[3], V. Annibali[4], M. Capobianco[1], S. Cottone[5], P. Sola[6], A. Ghezzi[7], C. Solaro[8], G. Fenu[9], R. Mantegazza[10], P. Perrone[11], A. Bosco[12], A. Visconti[4], step study group

[1]AO S Luigi Gonzaga Neurologia 2 Cresm, [2]Lab Neurobiologia Clinica San Luigi Gonzaga, Orbassano, [3]Merck, Milano, [4]Merck, Roma, [5]Unità di neuroimmunologia ospedale villa sofia, Palermo, [6]Dipartimento di Neuroscienze uo Neurologia Ospedale Civile s Agostino Estense, modena, [7]AO S. Antonio Abate, Multiple Sclerosis Study Center, Gallarate, [8]Unità di neurologia dipartimento testa-collo asl3 genovese, Genova, [9]Dipartimento di Scienze Mediche Università di Cagliari, Cagliari, [10]Dipartimento di Neuroimmunologia e malattie neuromuscolari IRCCS Carlo Besta, Milano, [11]UO Neurologia, AO Ospedali Civile, Legnano, [12]Clinica Neurologica, Trieste, Italy

Background: Multiple sclerosis is a chronic, inflammatory, autoimmune disease of the central nervous system. Rebif® HSA-free scIFNβ-1a has been developed without human albumin and foetal calf serum to improve drug tolerability and to reduce immunogenicity. This work reports data from a post-authorization, 36 months, multicenter, non- interventional, safety study using HSA-free scIFNβ-1a.

Methods: 202 RRMS naïve patients were enrolled (44% with 44 µg and 52% with 22 µg HSA-free scIFNβ-1a). Visits were performed at baseline and at months 6, 12, 18, 24, 30 and 36. All adverse drug reactions (ADRs), the percentage of developing Binding Antibodies (Babs) and Neutralizing Antibodies (Nabs), MS relapse rate, and EDSS, Fatigue Severity Scale (FSS), MS International Quality of Life and Injection Device (RebiSmart) Satisfaction Questionnaire scores were measured at each visit.

Results: 44% of the patients suffered at least one ADR. 1 patient reported a grade 4 ADR. Flu-like syndrome was the most frequent ADR with significant differences between the patients with high vs low doses. 13% of patients showed 2 consecutive NAB positive tests at year 1, final results are ongoing. EDSS remained stable between 1.4 and 1.5 points. FSS score reached its maximum at month 24 (mean score 3 for all patients). 70% of patients was relapse-free at the end of the study. The ARR was 0.2 relapses. The mean time to first relapse was 3 years for both patient groups. Regarding Quality of Life, higher doses showed higher improvements in many dimensions, compared to lower doses. The scores of RebiSmart Questionnaire at month 36 were positive.

Conclusions: The product shows a safe profile and good tolerability. The dose of treatment was the predisposing factor for ADRs (in accordance with the SmPC information). Higher doses group showed a better performance in quality of life questionnaires and there were no differences regarding RR between different doses groups.

Disclosure

Dr. Antonio Bertolotto received honoraria for serving in the scientific advisory boards of Sanofi-Genzyme, with approval by the Director of AOU San Luigi University Hospital, and received speaker honoraria from Biogen, Genzyme, Novartis, TEVA; his institution has received grant support from Almirall, Biogen, Genzyme, Merck, Novartis, TEVA, from the Italian Multiple Sclerosis Society, Fondazione Associazione Ricerca Biomedica ONLUS and San Luigi ONLUS
Marzia Caldano: nothing to discose
Marco Capobianco:
Salvatore Cottone: nothing to discose
Patrizia Sola:
Paola Perrone:
Antonio Bosco:
Claudio Solaro: have received honoraria and travel grants from Merck-Serono, Biogen, Almirall, Genzyme, Novartis, Teva
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Maria Giovanna Marrosu:

P1286

Decision Coaching In Multiple Sclerosis (DECIMS) - pilot randomised controlled trial and process evaluation

A.C. Rahn[1,2], S. Köpke[3], I. Backhus[1], J. Kasper[4], A. Krützelmann[1], I. Kleiter[5], I. Mühlhauser[2], C. Heesen[1]

[1]Institute for Neuroimmunology and Multiple Sclerosis, Department of Neurology, University Medical Centre Hamburg-Eppendorf, [2]Unit of Health Sciences and Education, University of Hamburg, Hamburg, [3]Nursing Research Unit, Institute of Social Medicine and Epidemiology, University of Lübeck, Lübeck, Germany, [4]Department of Health and Care Sciences, University of Tromsø, Tromsø, Norway, [5]Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Bochum, Germany

Background: The "nurse decision coach" intervention (DECIMS) aims to redistribute health professionals' tasks in supporting immunotherapy decision making processes by people with multiple sclerosis (PwMS), following the principles of shared decision making. Currently, a multi-centre randomised controlled trial (RCT) is performed to test the intervention's efficacy. This pilot study aimed to test the randomisation procedure and to gather data on feasibility to inform the main trial.

Methods: Programme development followed the MRC framework for developing and evaluating complex interventions and was evaluated through a pilot-RCT and an embedded process evaluation. A convenient sample of 75 PwMS (age ⩾ 18 y) with suspected or relapsing-remitting MS facing an immunotherapy treatment decision was recruited in two German MS centres between March 2014 and June 2015. PwMS were randomised to the intervention (IG) or control group (CG). PwMS in the IG received decision coaching by a trained nurse, in the CG care as usual. Both groups had access to an evidence-based online information platform. Nurses were not blinded to group assignment, while PwMS and physicians were kept blinded. Primary outcome was 'informed choice', using a multi-dimensional measure including the sub-dimensions risk knowledge (questionnaire assessed after 14 days), attitude concerning immunotherapy (one question assessed after physician consultation), and treatment uptake (survey after six months). Secondary outcomes included an analysis of videotaped coaching videos assessing shared decision making.

Results: In total 73 PwMS were included, 38 in the IG and 35 in the CG. Groups were comparable at baseline. Data of 49 PwMS

were available for the primary endpoint calculation. A difference was shown with 15 of 29 (52%) PwMS in the IG achieving informed choice after six months compared with 6 of 20 (30%) PwMS in the CG, which was not significant. Analysis of coaching videos showed good levels of PwMS involvement in the coaching process. Process evaluation analysis showed a positive response of PwMS, nurses and physicians towards the intervention.
Conclusions: The innovative approach of delegating treatment information provision to trained nurses using evidence-based patient information has the potential to change current doctor-focussed practice in Germany.
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P1287

Tuberculosis pachymeningitis during natalizumab therapy for multiple sclerosis

A.C. Piccolo, S.M.D. Brucki, S.M.G. Rocha
Neurologia, Hospital Santa Marcelina, Sao Pablo, Brazil

Introduction: Natalizumab has been used to treat multiple sclerosis (MS) and has achieved relapse control, injury burden reduction, fewer new lesions on brain MRI, and fewer sequelae in patients with high disease activity who fail to respond to immunomodulation. Here, we describe a novel case of natalizumab-associated CNS tuberculosis.
Case report: A 54-year-old female was diagnosed with secondary progressive MS in February 2012, with a history of two previous relapses (2010 and 2011). Her clinical condition deteriorated over the last year with a global cerebellar syndrome, and cognitive impairment. Her EDSS score was 6.0. Natalizumab monthly therapy was initiated after considering clinical involvement, and elevated lesion burden on MRI. She did not have antibodies anti JCV, and a chest X-ray was normal. During follow-up, the patient showed stable disease with no clinical relapses, discrete improvement on cognition, and stable lesion burden on annual cranial MRI.

After 22 natalizumab infusions, the patient was taken to the emergency department after two seizures, and a subsequently low consciousness level. MRI showed a hypointense lesion on T2 and FLAIR in the left frontal region adjacent to the meninges, and gadolinium-enhancement on T1. CSF testing showed mild pleocytosis (four cells), protein of 46 mg/dL, and hypoglicorrhachia (CSF glucose, 59 mg/dL; serum glucose, 125 mg/dL). Syphilis and cryptococci tests and bacterioscopy were negative, as were CSF cultures for bacteria, fungus, and *Mycobacterium tuberculosis* negative. She had not been vaccinated with BCG. A biopsy of the meningeal lesion was performed after 3 weeks of initiation of oral empirical treatment for tuberculosis (isoniazid, rifampicin, pyrazinamide, and ethambutol). Meningeal biopsy confirmed caseous necrosis with granuloma formation, and she was diagnosed with tuberculosis pachymeningitis, although PCR was negative in this issue, and no bacillus was determined . The patient showed a good response to treatment with progressive neurological and MRI improvement, and no recurrence after one year of follow-up.
Conclusion: Besides natalizumab related progressive multifocal leukoencephalopathy, there are reported cases of neoplastic lesions and other infections related to its use. To the best of our knowledge, this is the first case of CNS tuberculosis associated with natalizumab treatment. Screening for pulmonary tuberculosis has been recommended, mainly in endemic areas.

Disclosure

Speaker in Board: Noovartis, Biogen, Merck-Serono, Genzyme, Pfizer, Teva and Boheringer;
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P1289

Subgroup analyses in phase III trials of therapeutics for multiple sclerosis: a closer look

A. Shirani[1], G. Cutter[2], O. Stuve[1]
[1]Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, Dallas, TX, [2]Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, United States

Subgroup analyses of clinical trials to assess the heterogeneity of treatment effects may provide important information for facilitating a personalized treatment approach, as well as for planning future studies. Yet, subgroup analyses can introduce methodological challenges and should be interpreted with caution. We are investigating the appropriateness of the use, reporting, and interpretation of subgroup analyses of clinical trials in multiple sclerosis (MS) over the past decade. We searched PubMed from January 2005 to March 2016 for phase III randomized clinical trials (RCTs) of disease modifying therapies for MS. Reports from a total of 24 RCTs were included. Information related to the subgroup analyses including pre-specification and number of subgroups, subgroup factors, analytical methods, and claims of subgroup differences were reviewed. There was substantial heterogeneity in the conduct and reporting of subgroup analysis in published RCTs in MS. We further compared the results to the subgroups pre-specified in ClinicalTrials.Gov versus other subgroups. Given the potential significance and impact of subgroup analyses results for evidence-based medicine and guiding therapeutic decision making, a more uniform framework for subgroup analysis should be encouraged or acknowledgement of the importance of unanticipated findings.

Disclosure

A.S. has no disclosures. G.C.'s consulting and/or DSMB commitments in past 12 months include the followings: Participation of Data and Safety Monitoring Committees (All of the below organizations are focused on medical research): Apotek, Biogen-Idec, Cleveland Clinic(Vivus), Glaxo Smith Klein Pharmaceuticals, Gilead Pharmaceuticals, Horizon Pharmaceuticals, Modigenetech/ Prolor, Merck/Ono Pharmaceuticals, Merck/Pfizer, Neuren, Sanofi-Aventis, Teva, NHLBI (Protocol Review Committee), NICHD (OPRU oversight committee); Consulting, Speaking fees & Advisory Boards: Cerespir Inc, Consortium of MS Centers (grant), D3 (Drug Discovery and Development), Genzyme, Genentech, Innate Therapeutics, Jannsen Pharmaceuticals, Klein-Buendel Incorporated, Medimmune, Novartis, Opexa Therapeutics, Receptos, Roche, Savara Inc., Spiniflex Pharmaceuticals, Somahlution, Teva pharmaceuticals, Transparency Life Sciences. G.C. is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham AL. O.S. serves on the editorial boards of JAMA Neurology, Multiple Sclerosis Journal, and Therapeutic Advances in Neurological Disorders. O.S. has served on data monitoring committees for Pfizer and Sanofi-Aventis without monetary compensation. O.S. collaborated with Medscape on educational initiatives. O.S. represented Novartis in front of a Scientific Advisory Group at the European Medicines Agency (EMA). O.S. has advised Genentech and Sanofi-Aventis. O.S. has participated in a Teva-sponsored meeting. O.S. has consulted for Huron Life Sciences and Navigant Consulting. O.S. currently receives grant support from Teva Pharmaceuticals and Opexa Therapeutics. O.S. received travel support from Pfizer. O.S. is funded by a Merit grant from the US Department of Veterans Affairs.

P1290

Phase II double blind trial to investigate the efficacy and the optimal way of administration (clinical, neurophysiological and neuroradiological effects) of autologous mesenchymal bone marrow stem cells in active and progressive Multiple Sclerosis

P. Petrou[1], I. Kassis[1], N. Levin[1], N. Raz[1], T. Ben Hur[2], A. Ginzberg[1], D. Karussis[1]
[1]Neuroimmunology and Cell Therapy Unit, Neurology Department, Hadassah University Hospital, Ein Kerem, [2]Neuroimmunology and Cell Therapy Unit, Neurology Department, Hadassah, Jerusalem, Israel

Objective: To evaluate the safety and efficacy of transplantation of autologous bone marrow-derived mesenchymal stem cells (MSC), in MS.
Background: MSCs have been shown to possess neurotrophic and neuroprotective effects. Two prior pilot studies in our center showed that a single intrathecal(IT), or IV administration of MSCs was safe and well tolerated, and provided indications of clinical efficacy in MS and ALS.
Design/Methods: The current study involves a double-blind crossover design that will enroll upon completion 48 progressive MS-patients. The study started in February-2015 and till the day of this abstract, 29 patients have already been included. During the 2-month run-in period, functional evaluations (EDSS, MSFC, neurocognitive evaluation, quantitative/functional MRI, OCT, dynamic visual and neurophysiological tests) were performed monthly before the transplantation. Bone marrow-derived MSC ($1x10^6$/Kg) or placebo were injected to the patients, IT or IV. At 6-months the patients are treated with a second injection of MSC/ placebo and are followed for safety and all the efficacy measures for 12 months. The study was approved by the Ethics committee and MOH and is monitored by an external CRO and a safety committee.
Results: No serious treatment-related adverse events have been observed this far. Until today 25 patients received the first transplantation and 13 also the second treatment. One patient already completed study.
Conclusions: IT and IM administration of autologous MSCs seems till now to be well-tolerated. Our trial, uniquely, uses the intrathecal way of administration and for the first time a rigorous double blind design utilizing extensive surrogate markers to detect possible clinical effects of regeneration. In addition, this study is the first to try to evaluate the optimal way of administration of stem cells in MS and to evaluate the possible additional benefit of a repeated injection. Detailed and updated safety data will be provided upon presentation (NCT02166021).
Keywords: Multiple Sclerosis (MS), Stem Cells, Mesenchymal Stromal Cells (MSC), Clinical Trial, Transplantation, Autologous, Intrathecal

Disclosure

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P1291

Comparision of clinical characteristics of patients in NMO &NMOSD

E. Yilmaz, S. Okar, G. Sayat, A. Tuncer, R. Karabudak
Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, Turkey

Objective: NeuromyelitisOptica (NMO)/ NeuromyelitisOptica Spectrum (NMOSD) encompass astrocytopatic and immune-mediated chronicinflammatory disease of the central nervous system(CNS). Unlike patients with MS, NMOSD attacks are more severe with predominance in spinal cord and optic nerves. In this study we evaluated our NMO/NMOSDpatients diagnosed according to the international criteria 2015.
Material and method: Demographic,clinical,laboratory and MRI features in 46 NMOSD patients who have been followed up in our center between 2002-2016 were documented. Age, gender, comorbidities, AQP4 antibodies,autoimmune and serologic markers, initial symptoms, number of attacks, long term treatment responses, MRI findings were analyzedin relation to their prognosis and outcomes.
Results: 46 patientswere evaluated(40 women-6 men) mean age at onset 36.8. Among them 26 were AQP4-Antibody positive.

11 patients have other autoimmune diseases such as Sjögren syndrome(n=7), Hashimoto thyroiditis(n=2) myasthenia gravis(n=1) idiopathic thrombocytopenic purpura(n=1) autoimmune hepatitis (n=1).7 of this 11 patients were AQP4-Antibody positive.

16 patients had antibodies associated with connective tissue disorders such as ANA ENA, antiphospholipid antibodies, ANCA. 4 patients who have AQP4-Ab negative NMO had antibodies to myelin oligodendrocyte glycoprotein(MOG).

Clinically, 34 NMOSD patients startedmonosymptomatic(ON), others hadmultiple symptomatology. Theirmean EDSS score was 3.5 and their mean number of attacks were3.4.

MRI findings were classified in four categories; Supratentorial(n=15), Optic nerve(n=11), Brainstem(n=16), Longitudinally extended tranvers myelitis(LETM)(n=40).

I.V. methylprednisolone(n=43), IVIg(n=3) and therapeutic plasma exchange(n=16)were selected for treatment of acute episodes. Azathioprine(n=25), cyclophosphamide(n=12), oral steroids(n=8),rituximab(n=4),methotrexate(n=1),eculizumab(n=1) were used for long term treatment.

Conclusion: We evaluated and compared NMO and NMOSD patients for their similarities and differences. The prognosis and outcomes were not different between the two groups.

However,in NMOSD patients monosymptomaticonset demonstrated significantly lower EDSSlevels compared to polysymptomaticonset; this difference was reflected on the disease progression index(Diseaseduration / EDSS).

Disclosure

EzgiYilmaz: nothing to disclose

Treatment of specific symptoms

P1292

Nabiximols has a beneficial effect on self report of MS related spasticity

S. De Trane, K. Buchanan, L. Keenan, C. Valentine, M. Liddicut, V. Stevenson, R. Farrell
UCLH, London, United Kingdom

Spasticity is a frequent and distressing symptom related to multiple sclerosis (MS). Nabiximols (Sativex®) was licensed in the UK in 2010 as an add-on treatment for MS-related spasticity in people with intolerable side effects (SEs) or inadequate response to other treatments.

Objective: This is a prospective observational cohort study to evaluate efficacy of Nabiximols for drug-resistant MS-spasticity.

Methods: Data was collected prospectively from subjects attending the spasticity service since 2011. Baseline measures included demographics, Numeric Rating Scale spasticity (NRS), Multiple Sclerosis Spasticity Scale-88 (MSSS-88). Subjects commenced 4 week trial of Nabiximols, telephone review at ~2 weeks, review at ~4 weeks. Clinically meaningful response was defined by ⩾20% reduction in NRS score. Follow up (FU) was at ~6 monthly intervals. Non responders (NR) considered subsequent treatment options included Intrathecal Bacofen Therapy (ITB).

Results: 102 people (95 progressive, 7 relapsing-remitting MS) were treated, 19 were unable to complete the NRS / MSSS-88 reliably. At baseline mean NRS= 7.3, MSSS-88= 233. After 2 weeks 78 reported benefit and returned for FU. Responders n=33 (32.3%), partial responders (< 20% change) n=6 (5.9%), non responders n=20 (19.6%). NRS reduced from 7.2 to 3.9 in CR (-3.3, p< 0.001), in partial responders 7.3 to 6.3 (-1, ns), and unchanged in NRS NR. MSSS-88 decreased by 51.3 in responders (p< 0.001), in NR (-3, ns). Change in NRS correlated with change in MSSS-88 (R=0.61, p< 0.001). Mean dose 7.6 (2-12) sprays daily. Long term treatment: 42 (41.2%) sustained NRS response (p< 0.005) at 6 months, 27 (26.5%) at 12 months and 15 > 24 months. Mean time to discontinuation was 3.8 months in those who stopped early < 6 months and 18.8 months in long term treated patients. 32 subjects (31.4%) had an ITB trial and 24 proceeded with pump. Side effects were mild 48% and 6 people (5.9%) experienced serious AE. Other reported benefits: improved spasm, pain, bladder control and sleep.

Conclusions: In a cohort of people with treatment-resistant MS-related spasticity, Nabiximols provided symptomatic relief in and delayed or avoided the need to proceed with an ITB pump in a proportion. Using the NRS as an outcome measure is challenging in an advanced MS cohort due to cognitive impairment.

Disclosure

Claire Valentine, Michelle Liddicut, Stefania De Trane, Liz Keenan, Katrina Buchanan, Val Stevenson have nothing to disclose.

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P1293

Long-term efficacy of intrathecal baclofen to manage severe spasticity in MS patients

Y. Sammaraiee[1], M. Yardley[1], L. Keenan[2], K. Buchanan[2], V. Stevenson[2], R. Farrell[2,3]
[1]University College London Medical School, [2]National Hospital for Neurology and Neurosurgery, [3]Institute of Neurology, London, United Kingdom

Background: Spasticity is a disabling symptom in people with MS. Oral treatments are effective however refractory drug resistant spasticity may require treatment escalation. Intrathecal baclofen (ITB) is an effective alternative.

Study aim: To evaluate long-term efficacy and safety of ITB in a cohort with MS related spasticity over 20 years (1994-2015).

Methods: A single centre observational cohort study was performed. Data collected by review of local ITB database. Baseline data was acquired pre trial (bolus dose ITB). Treatment effect noted at 4 hours. Responders proceeded to pump implantation. Baseline demographics, Ashworth spasticity scores, stiffness (NRS), Penn spasm score Penn, pain and discomfort (VAS), passive range of movement, mobility, spasticity treatment, trial data, and ITB doses were collected. Data was collected annually from pump implantation. Results analysed using paired t-test for pre and post-trial data.

Results: 106 people with MS were treated with ITB. Mean age 48.67 years (26-71); ten deceased at review. Seventeen were

receiving disease modifying therapy and all on oral spasticity agents. Baseline stiffness (NRS) was 7.81 (0-10), pain (VAS) 5.41 (0-10), comfort (VAS) 6.13 (0-10),Penn score 3.5(0-4) and Ashworth score was 1.57 (0-3.5). Post-trial scores: Ashworth (0.34, $p< 0.001$), Penn score
(1.00, $p< 0.001$) and VAS Scores (Pain: 1.71, Stiffness: 2.55, Comfort: 1.81; all $p< 0.001$). 85% maintained or increased passive range of movement after ITB trial. Sustained efficacy was reported on Ashworth, Penn and VAS/NRS mean scores up to 5 years. After 1 year, 73 (69%) discontinued oral anti-spasticity medication. Over 20 years, 69 (65%) had pump for 1-5 years, 28 (26%) for 6-10 years and 9 (8%) more than 10 years, some having 2-3 pumps (33%). Complications rates were low and mostly procedure or catheter related; incidence of 1.23 complications per 20 pump-years. In 9 ambulatory subjects, 7 (78%) continued to walk one year after pump insertion, 6 (67%) continue to walk at the time of analysis (mean follow up 3.4 years) and 3 (33%) remained ambulatory for an average of 30 months (maximum 4 years).
Conclusions: ITB has been used since 1994 in this centre. It is highly effective and safe long term treatment for refractory spasticity due to MS. Sustained effect noted on Ashworth score, VAS/NRS scores, Penn score. In a small cohort of ambulatory patients ability to walk was preserved indicating it should be considered in these patients.

Disclosure

Y Sammaraiee, Martin Yardley, Liz Keenan, Katrina Buchanan and Val Stevenson have nothing to disclose.
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P1294

The Effects of modified-release fampridine on upper limb impairment in multiple sclerosis

M. Simpson[1], L. Churilov[2], B. Bardsley[1], E. Heriot[1], J. Dimovitis[1], L. Carey[3], R. Macdonell[1]
[1]Austin Health, Univ. of Melbourne, [2]Statistics, [3]University of Melbourne, Melbourne, VIC, Australia

Background: Modified-release 4-aminopyridine (fampridine-MR) is used as symptomatic treatment of walking disability in patients with multiple sclerosis (MS). Its potential for use in other MS symptoms remains unproven and its mode of action in this context is uncertain.
Hypotheses: (1) Fampridine-MR improves upper limb function in patients with MS and upper limb impairment. (2) Treatment with fampridine-MR is associated with measurable alterations in objective electrophysiological parameters (evoked potentials and transcranial magnetic stimulation (TMS))
Methods: Study population: patients with MS of any disease subtype, duration and severity who have symptomatic impairment of one or both upper limbs. Study design: randomised double blind placebo-controlled trial. Treatment details: participants allocated to either fampridine-MR 10mg bd or placebo of identical appearance for 8 weeks. Primary outcome: performance on 9-hole peg test (9HPT). Secondary outcomes: grip strength; visual acuity and contrast sensitivity; modified fatigue impact scale score; sensory discrimination capacity; visual, somatosensory and motor evoked potentials; resting motor threshold; paired-pulse TMS; peripheral nerve conduction studies. A group of healthy control subjects was included for validation of electrophysiological measures
Results: 40 patients with MS (60% female, median age 52, median disease duration 13.5 years, median EDSS 6.0) and 20 healthy controls (60% female, median age 53) were enrolled. Treatment with fampridine was not associated with any effect on upper limb function as measured by the clinical primary or secondary outcomes. Treatment with fampridine was not associated with any measurable difference in the electrophysiological parameters tested. This held true after adjustment for hand dominance, disease duration and severity. 4 patients withdrew from the trial because of lack of efficacy or side-effects; all were in the placebo arm. Three patients were admitted to hospital during the study period; one with MS exacerbation (placebo), one with syncope (drug) and one with UTI (drug); otherwise there were no serious adverse events.
Conclusion: Treatment with fampridine was well-tolerated but did not produce clinical benefit for upper limb function, vision or fatigue, nor any measurable effect on electrophysiological parameters.

Disclosure

All authors: nothing to disclose

P1295

Lack of improvement in quantitative gait analysis after Botulinum toxin injection in patients with multiple sclerosis

G. Coghe[1], M. Pau[2], F. Corona[3], S. Caggiari[3], J. Frau[4], C. Inglese[5], L. Lorefice[6], G. Fenu[1], M.G. Marrosu[7], E. Cocco[1]
[1]Department of public health, clinical and molecular medicine, [2]Department of Mechanical, Chemical and Materials Engineering, [3]University of Cagliari, Cagliari, [4]Department of public health, clinical and molecular medicine, University of Cagliari, cagliari, [5]ASL 8 Cagliari, [6]department of public health, clinical and molecular medicine, [7]Department of medical sciences, University of Cagliari, Cagliari, Italy

Background: There are limited evidences regarding the impact of BT therapy for spasticity on active function in patients with MS. The effects of BT therapy on gait and walking performance have been studied in stroke patients. However, since MS has a peculiar spasticity pattern, the stroke studies cannot be extrapolated to the MS.
Objective: To quantitatively assess the functional modifications in gait induced by BT in MS.
Methods: A group of patients were enrolled. Inclusion criteria were a diagnosis of MS according to the 2010 McDonald criteria, being able to walk for at least 10m regardless of the use of aids. Moreover all participants were valid candidates to TB with the following pattern of infiltration: tibial posterior, soleus, gastrocnemius lateralis and medialis according to medical judgment. For each patient was evaluated, NRS, three-dimensional gait analysis (spatial-temporal and kinematic) at baseline and one month after the TB injection. For statistical analysis only the parameters of the treated leg were considered. Kinematic data were expressed by means of Gait Profile Score (GPS). Variation of each parameter was evaluated by means of two-way repeated measures ANOVA.
Results: Fourteen patients were enrolled (10 female and 4 male); Mean age was 50.4 (SD ±12.3) mean EDSS was 4.9 (SD ±1.3).

The statistical analysis was carried out on 16 treated legs. Mean reduction of NRS after TB injection was 1.14 (SD ±1.16) (not statistically significant). Out of 14 patients 8 referred an improvement. None of the gait spatial-temporal parameters revealed an improvement after treatment. In particular speed (p=0.367) and stride length (p=0.671). Regarding the kinematics data nor the GPS (p=0.676) neither the GVS of targeted joints (knee flex ext p=0.606 and ankle plantar-dorsal-flexion p= 0.973) reduced after treatment.
Conclusion: To our knowledge this is one of the first studies specifically targeting objective gait data on MS after treatment with BT injection. Despite the subjective improvement reported and the reduction of muscle tone, it remains impossible to demonstrate a quantifiable gain of function on gait patterns either in spatial temporal data and kinematics.

Disclosure

The authors report no financial or other conflict of interest relevant to the subject of this article.

P1296

The use of medical-grade Cannabis (Bedrocan®) in patients non-responders to nabiximols (sativex®)

F. Saccà[1], C. Pane[1], A. Carotenuto[1], M. Massarelli[1], R. Lanzillo[1], E.B. Florio[2], V. Brescia Morra[1]
[1]Department of Neuroscience, Reproductive, and Odontostomatological Sciences, Federico II University, [2]Farmacia Florio Dr. Ettore SNC, Napoli, Italy

Introduction: Spasticity is one of the most common symptoms in Multiple sclerosis (MS). It causes disability, and is chronically present. Historical treatment includes several drugs with very limited patient and physician satisfaction. Nabiximols (Sativex®) is a cannabis extract containing a 1:1 ratio of delta-9-tetrahydrocannabinol to Cannabidiol. Several studies showed its superiority over placebo in reducing the Numeric Rating Scale (NRS). Unfortunately, half of treated patients do not respond to Nabiximols and for them therapeutic options are absent.
Methods: We retrospectively enrolled patients that had been treated with Nabiximols (Sativex®) for 28 days and were judged non-responders (reduction < 20% from baseline NRS), and were subsequently treated with medical-grade cannabis (Bedrocan®) for at least 28 days. Bedrocan was fractionized at authorized ISO 9001:2008 pharmacies into 50 mg sachets. Patients were instructed to take Bedrocan at a dose of 50-100 mg /day.
Results: We found 13 patients (Table 1) corresponding to our inclusion criteria. Non-response to Nabiximols was caused by insufficient NRS reduction for all patients. Bedrocan was administered orally to eleven patients, and through smoking for two. Mean NRS for Nabiximols Baseline was 7.6±1.5 and 7.4±1.6 after 28 days (-0.2; CI -0.65, +0.15; p=0.493). Mean NRS for Bedrocan baseline was 7.6±1.8 and 5.3±2.4 after 28 days (-2.3; CI -3.58, -1.12; p< 0.001). Patients continued Bedrocan administration for 205±182 days (range 46-700). Two patients suspended therapy, one for the onset of dizziness, and the other for the drug's cost. Mean NRS at follow-up was 5.6±2.3, resulting in a significant reduction as compared to baseline (-2.0; CI -.2.9, -1.2; p< 0.001). During Bedrocan therapy, only 3 AEs were reported in three patients, as compared to 15 AEs in 11 patients during Nabiximols treatment (Odds Ratio 5.0; CI 1.45, 17.27; p< 0.02).
Discussion: This is the first study that investigates rescue strategies for Nabiximols non-responders. Bedrocan was very well tolerated with 85% responders at 28 days and 70% at the end of the individual follow-up. This is a high response rate if compared to previous trials. Future randomized, placebo-controlled studies are necessary to conclude, at a higher class of evidence, that medicinal-grade cannabis is a good option for Nabiximols non-responders.

Disclosure

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P1297

Nabixol (Sativex) in spasticity responders multiple sclerosis patients is effective on subjective but not on objective measures of walking ability

C. Solaro[1], E. Trabucco[2], M. Cella[1], A. Mattioda[3], S. Masera[3], P. Cavalla[3]
[1]ASL3 Genovese, genova, [2]Università di genova, of Experimental Medicine, Section of Diagnostic Radiology, [3]Centro SM, Dep. of Neuroscience, AOU Città della Salute e della scienza, torino, Italy

Background: Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) [Sativex(®)] is an oromucosal spray formulation is approved in a number of countries, included Italy, as add-on therapy for moderate-to-severe multiple sclerosis (MS) treatment-resistant spasticity symptoms.
Objective: The aim of the study is to provide real- life observational data of effect of Sativex on walking objective measures and patients' perceptions of the impact of MS on walking ability
Materials and methods: This was an observational, prospective study conducted in 2 italian MS centres. Patients with moderate to severe spasticity, with a score at the numerical rating scale (NRS) greater than 4 were included in the study. A battery of tests including Symbol Digit (SDT), Nine Hole Peg Test (9HPT), Fatigue Severity Scale (FSS), 12-item Multiple Sclerosis Walking Scale (MSWS-12), Two Minutes Walking Test (2MWT) and Timed 25-foot Walk (T25FW) was performed at baseline (T0) and 30 days later (T1). Responders had been defined by the literature as subjects with an improvement at the NRS score for spasticity greater than 20%
Results: Out of 75 subjects enrolled 33 were female and 42 male. Mean age was 53.7 years (range 28.26 - 81.43) , mean disease duration 13 years (range 0.7 - 39), 25 (29.3%) subjects had relapsing remitting, 34 (45.3%) secondary progressive and 19 (25.4%) had primary progressive disease course. Mean EDSS score was 6.2 (range 4 - 8.5).

A significant improvement (>20%) at NRS was observed in 49 patients (responders), 26 patients were classified as "no responders".

Considering patients able to walk (EDSS < = 6.5, n°32) mean NRS for spasticity at T0 was 7.9 (range 1-10) in 20/32 patients mean score decreased greater than >40%. MSWS-12 score decreased more than 6 points in 19/32 patients and an improvement (>20%) in FSS was reported in 5/32 subjects.

An improvement (>20%) in walking speed (T25FW) was observed in 2/32 patient and in endurance (2MWT) in only 1/32 patients. No patients improved in 9HPT and SDT

Conclusions: Real-life data confirm Sativex(®) as an effective on spasticity (65.3% responders) and well tolerated treatment option for MS patients. A positive effect was highlighted on measuring patients' perceptions of walking scale such as fatigue and MS12 while an effect on objective measures on walking performance was not found.

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Dr. Trabucco Erika: nothing to disclose
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Dr. Masera: nothing to disclose
Dr. Cavalla: nothing to disclose

P1298

Comparative effectiveness of natalizumab and fingolimod treatment on cognitive functions in relapsing multiple sclerosis

P. Iaffaldano[1], R.G. Viterbo[1], G. Lucisano[1,2], M. Trojano[1]
[1]University of Bari Aldo Moro, Bari, [2]Coresearch, Pescara, Italy

Background: Natalizumab (NTZ) exerts a positive impact on cognitive functions in Relapsing Multiple Sclerosis (RRMS). Little is known about the effect of Fingolimod (FIN) on these functions.

Objectives: to compare the effect on cognitive functions of 1-year treatment with FIN or NTZ.

Methods: All consecutive RRMS scheduled for treatment with NTZ or FIN underwent neuropsychological evaluations using the Brief Repeatable Battery, Stroop Test, Fatigue Severity Scale (FSS) and Beck Depression Inventory (BDI) at baseline and every 12 months. A test was considered failed if the corresponding z-score was 2 standard deviation (SD) below the mean Italian normative values. The Cognitive Impairment Index (CII) as a measure of global cognitive function was calculated for each patient. Patients were propensity score (PS)-matched on a 1-to-1 basis at the time of treatment start using the following covariates: sex, age, prior treatment exposure, relapses prior the treatment, school education, and BDI score. The relapse risk during the treatment was estimated through a Poisson regression model. A generalized linear mixed model for repeated measures with an autoregressive variance-covariance structure was applied to evaluate changes in CII, the mean number of cognitive tests failed and FSS score at 1 year of treatment.

Results: the effect of treatment on cognitive functions was evaluated in 62 matched RRMS patients receiving NTZ(n=31) or FIN(n=31). The relapse incidence was not significant different between the treatments (FIN vs NTZ: Incidence rate ratio=0.71, p=0.6). The mean±SD number of cognitive tests failed was significantly reduced only in FIN treated patients (2.8±2.2 vs 1.7±1.8, p=0.0014). The CII significantly improved in both groups (NAT 18.5±6.1 vs 14.5±6.1, p=0.0075; FIN 14.0±7.3 vs 11.5±7.5, p< 0.0001), but there was not a significant interaction between group X time. The FSS was unchanged in both groups.

Conclusions: Our results indicates, for the first time, that both NAT and FIN treatments significantly ameliorate cognitive functions in RRMS. Moreover, the effect on the number of tests failed suggest that FIN could have a greater impact on cognition than NTZ. The effect on cognition of these two drugs goes in parallel with the reduction of the relapse rate. This latter finding support the hypothesis that in the short-term, NTZ and FIN, exert a positive impact on cognition likely by means of their anti-inflammatory properties.

Disclosure

Iaffaldano P. has served on scientific advisory boards for Biogen Idec, and has received funding for travel and/or speaker honoraria from Sanofi-Aventis, Biogen Idec, Teva and Novartis. Trojano M. has received honoraria for consultancy or speaking from Biogen, Sanofi-Aventis, Merck Serono and Bayer-Schering and research grants from Merck Serono, Biogen and Novartis. Viterbo RG and Lucisano G: nothing to disclose.

P1299

Gait kinematic changes after fampridine therapy in primary progressive multiple sclerosis

D. Gómez-Andrés[1,2], I. González-Suárez[3], A. Montero[1], I. Pulido Valdeolivas[1], J.A. Martín-Gonzalo[4], C. Oreja-Gevara[5], E. Rausell[1]
[1]Anatomía, Histología y Neurociencia, Universidad Autónoma de Madrid, Madrid, [2]Hospital Universitario Infanta Sofia, San Sebastian de los Reyes, [3]Neurology, Hospital Clinico San Carlos, [4]Escuela de Fisioterapia ONCE-UAM, [5]Hospital Universitario Clínico de San Carlos, Madrid, Spain

Introduction: In patients with primary progressive multiple sclerosis (PPMS), walking speed increases after the treatment with fampridine. We hypothesize that fampridine would produce changes in a number of angular joint movements during gait cycle to allow this improvement in translation capacity.

Objective: To analyse the fampridine effect on gait kinematics parameters and to define which changes in gait kinematic parameters are related with walking speed improvement.

Methods: Walking speed and 37 kinematic parameters were acquired by means of instrumented gait analysis in 10 patients with PPMS before and after 15 days of treatment with fampridine (10 mg TID). Normalization with a sample of 13 healthy subjects of each parameter was calculated by the difference of Z-score before and after treatment. Random forests were used to model influence of normalization of kinematic parameters on normalization of walking speed.

Results: The model's prediction of normalization in walking speed was acceptable (square Pearson's r: 0.251). The most important kinematic changes to predict walking speed normalization were "range of pelvic rotation in second double support",

"range of knee flexion", "time to peak knee flexion", "range of ankle dorsiflexion in stance" and "dorsiflexion at initial contact".
Conclusion: Specific kinematic changes after treatment with fampridine explain improvement in walking speed. Faster walking after fampridine is related with an increased range of knee flexion, a less retarded peak knee flexion, an increased pelvic rotation impulse in the latter support and an improved ankle dynamics in weight acceptance. Unravelling the kinematic change after fampridine in PPMS may be important to improve gait rehabilitation strategies and to enhance combinations of available therapies in the symptomatic treatment of PPMS gait disturbance.

Disclosure

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P1300

The impact of fampridine treatment on fatigue, quality of life and mood in patients with multiple sclerosis

A. Barros, J. Sequeira, S. Vaz, J. Morgado, P. Brás, D. Melancia, A. Fernandes, A. Sousa, S. Dias, C. Capela, R. Pedrosa
Centro Hospitalar de Lisboa Central, Lisboa, Portugal

Introduction: Multiple Sclerosis (MS) is the principal cause of non-traumatic disability among young adults. Fampridine prolongs action potentials through the blockage of potassium channels, thus ameliorating neurotransmission in demyelinated axons and improving motor disability in patients with MS. Several post-marketing studies suggest fampridine might be beneficial in other domains.
Objectives: The aim of this study was to assess the effects of treatment with fampridine on life quality, fatigue and mood among MS patients.
Methods: Prospective, post-marketing, single-center study, recruiting consecutive Portuguese patients eligible for treatment with fampridine, from November 2015 to March 2016. Evaluations were performed at baseline (D0) and after 14 days (D14) of treatment for gait velocity by Timed 25-Foot Walk (T25FW), quality of life through Functional Assessment of Multiple Sclerosis (FAMS), fatigue through Fatigue Severity Scale (FSS) and mood using the Hospital Anxiety and Depression Scale (HADS). Responders were defined as those having improved 20% or more in the T25FW at D14.
Results: Twenty patients were included with different types of MS, 65% females, with a median age of 53 years old and a median Expanded Disability Status Scale of 6.0. Twelve patients (60%) were responder by D14 and in this group a significant improvement was observed comparing with D0 in FSS (median 39,0 *vs* 46,0; p=0,032) and FAMS (median 125 *vs* 115; p=0,012). In non-responders there was no significant improvement of FSS (median 37,5 *vs* 40,5; p=1,000) or FAMS (median 84,5 *vs* 82,5; p=0,932) after 14 days of therapy. Responders and non-responders did not present significant differences in mood score (HADS).
Conclusions: Our results suggest a potential role of fampridine in improving not only walking speed but also other MS symptoms, namely life quality and fatigue, especially among timed walk responders. Further randomized, placebo-controlled studies will be needed to establish a definite role of fampridine in these domains.

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P1301

Phase II, placebo-controlled, double-blinded, crossover study of extended-release dalfampridine in monophasic transverse myelitis

K.M. Zackowski[1,2], K. Schwartz[3], N. Wymes[4], H. Huang[3], A. Jiang[4], D. Becker[3,5], P.A. Celnik[2], C.A. Pardo[3], M.A. Mealy[3], M. Levy[3]
[1]Motion Analysis Lab, Kennedy Krieger Institute, [2]Physical Medicine and Rehabilitation, [3]Neurology, Johns Hopkins University, [4]Kennedy Krieger Institute, Baltimore, [5]International Neurorehabilitation Institute, Lutherville, MD, United States

Background: Transverse myelitis (TM) is an inflammatory disorder of the spinal cord that leads to disabilities of gait. Dalfampridine, an extended-release potassium channel blocker that has been shown to be effective in improving gait and other neurologic functions in multiple sclerosis, has the potential to improve gait and neurologic function in patients with transverse myelitis as this rare disorder shares a similar pathogenic process with multiple sclerosis.
Methods: This is a randomized, double-blind, placebo-controlled cross-over study of dalfampridine extended-release (Ampyra®) versus placebo. Twenty-four study participants with monophasic transverse myelitis confirmed by MRI, aged 18-70, with no history of multiple sclerosis were enrolled if their baseline timed 25-foot walking speed was between 5 and 60 seconds. After a 2-week placebo lead-in, subjects were randomized to receive either 10 mg twice-daily doses of dalfampridine or placebo control for 8 weeks. Following a 2-week washout and 2-week lead-in, participants crossed over to the second arm of dalfampridine or placebo for 8 weeks. The primary outcome measure was timed 25-foot walk. Single pulse transcranial magnetic stimulation (TMS) was applied to participants at baseline and end of each arm to measure objective changes in neuronal conduction.
Results: Of 24 enrolled participants, 2 screen failed, 3 withdrew and 19 completed the trial. Among the 19 completers, 7 were women, 17 were white and the average age was 42 years. Timed 25-foot walk improved in 10 of 19 completers in the

dalfampridine arm compared to the placebo arm by an average of 22%. TMS demonstrated increased latencies in TM participants at baseline. Analyses of dalfampridine on TMS neuronal conduction as well as other secondary outcomes measures including strength, balance assessments, spasticity and Expanded Disability Status Scale (EDSS) score are underway.
Conclusions: Dalfampridine extended release improved walking speed in 53% of participants with monophasic TM by an average of 22%.

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P1302
Experience of fampridine treatment in a cohort of 167 Portuguese MS patients
J.D. Ferreira[1], J.C. de Sá[1,2]
[1]Neurosciences Department, Hospital Santa Maria, [2]University of Lisbon, Lisbon, Portugal

Fampridine (4-aminopyridine) is a potassium-channel blocker approved for symptomatic treatment of gait disturbances in Multiple Sclerosis (MS). The drug is available in Portugal since 2014, only in hospital units, because its prescription follows strict evaluation criteria. After being eligible to fampridine, patients have a baseline evaluation followed by 2, 4, 8-week and, then, every 3 months, using timed 25-foot walk scale (T25FW) and 12-item MS Walking Scale (MSWS-12). A positive response was established as an improvement of at least 20% in T25FW, although they can continue to be treated if there is a perception of benefit in MSWS-12 analysis in the appointment with assistant neurologist.

In our MS Unit, a total number of almost 650 patients are regularly followed. Until December 2015, 167 patients were enrolled for fampridine treatment, with gait impairment and EDSS between 4,0 and 7,0. This cohort has a mean age of 51,4 ± 10,7 years and 59,3% patients are female (n=99), 102 being relapsing-remitting, 36 primary progressive and 24 secondary progressive MS (in 5 patients data about disease course was not available). The mean EDSS was 5,1. From total number of patients, 123 have at least an 8-week follow-up evaluation. Among those, 52 patients (42,3%) didn't achieve 20% improvement level in T25FW, although they continued to be treated based on subjective clinical criteria: the mean MSWS-12 for these patients at 8 weeks was 35,70 points vs. 45,20 at baseline (p=0,022). Seventeen patients from total cohort stopped treatment due to side effects - seizures, repetitive urinary tract infections, pain, allergic reaction and others.

Fampridine was a useful treatment in this group of patients and well tolerated. In 42,3% of patients there was a mismatch between T25FW and MSWS-12 findings. These results reflect a subjective perception of benefits by patients regarding fampridine treatment in other MS domains beyond gait (cognition, fatigue, sexual, bladder and visual function).

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João Ferreira: nothing to disclose
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Quality of life

P1304
A survey of risk tolerance to multiple sclerosis therapies
R.J. Fox[1], C. Cosenza[2], L. Cripps[2], P. Ford[1], M. Mercer[1], S. Natarajan[1], A.R. Salter[3], T. Tyry[4], S.S. Cofield[5]
[1]Cleveland Clinic, Cleveland, OH, [2]University of Massachusetts Boston, Boston, MA, [3]Washington University School of Medicine, St. Louis, MO, [4]Dignity Health St. Joseph's Hospital and Medical Center, Phoenix, AZ, [5]University of Alabama at Birmingham, Birmingham, AL, United States

Background: Clinical trials characterize efficacy and safety of MS therapies, but patient acceptance of the risk/benefit balance is less well understood. This deficit presents challenges to regulators, who must decide if the known risks are appropriately balanced by the known benefits. We conducted a survey of people with MS to better understand risk tolerance to MS therapies among people with MS.
Methods: A series of focus groups across the United States and formal cognitive testing of the derived questions were used to design a survey for people with MS. While North American Research Committee on MS (NARCOMS) registry participants were recruited directly, the survey was also made available through an open link on the National MS Society (NMSS) website. Using a standard gamble paradigm, we identified the highest tolerated risk level for a hypothetical therapy that would reduce rate of clinical relapses by 50% and disability by 30%. Starting from a risk of 1:1000, the risk was iteratively changed to identify the highest risk tolerated, ranging from "would take regardless of the risk of death" to "no acceptable risk." Risks included skin rash or infection (both of which could require hospitalization), kidney injury (which could require life-long dialysis), thyroid injury (which could require life-long thyroid medication), liver injury (which requires blood test monitoring), and progressive multifocal leukoencephalopathy (PML, which is often fatal).
Results: 3719 people with MS completed the survey (2446 NARCOMS, 1273 NMSS): mean(SD) age 55.4(11.1) yrs, 78%

female, disease duration 16.8(9.8) yrs, median(IQR) Patient Determined Disease Steps 3-Early Gait Disability (1-Mild Disability, 5-Late Cane Use), 89% had been on a DMT with 51% reporting current use. The median (IQR) risk tolerance for each complication was (in descending order): infection 1:1000 (1:100, 1:500 000); thyroid injury 1:1000 (1:500, 1:1 000 000), skin rash 1:2000 (1:500, 1:1 000 000), liver injury 1:10 000 (1:1000, 1:1 000 000), kidney injury 1:1 000 000 (1:5000, no acceptable risk), and PML 1:1 000 000 (1:5000, no acceptable risk).

Conclusions: People with MS report different levels of tolerance to various risks. Respondents were most willing to accept infection or thyroid injury and least willing to accept kidney injury or PML. Risk tolerance data can help inform clinicians and regulatory agencies about patient preferences regarding the balance of risks and benefits.

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P1305

Development of a conceptual framework for daily life activities in patients with early stage relapsing-remitting multiple sclerosis

S.-Y. Chen[1], F. Pompilus[2], S. Strzok[3], S. Cleanthous[2], S. Cano[2], P. Marquis[2], S. Cohan[4], M.D. Goldman[5], K. Kresa-Reahl[4], J. Petrillo[1], C. Castrillo-Viguera[1], D. Cadavid[1]
[1]Biogen, Cambridge, [2]Modus Outcomes, Newton, MA, [3]Concentrated Consulting, Minneapolis, MN, [4]Providence Multiple Sclerosis Center, Portland, OR, [5]University of Virginia, Charlottesville, VA, United States

Objectives: A disease and its treatment may impact patients' lives in different ways that are only known by the patients. This study sought to identify daily life activities important to patients with early stage relapsing remitting multiple sclerosis (RRMS) that are impacted by the disease. Findings will also inform patient-reported outcomes instrument use and development.

Methods: Semi-structured interviews were conducted with RRMS patients scoring 0 or 1 (none to mild disability) on the Patient Determined Disease Steps. Interviews were audio-recorded, transcribed and analysed using an inductive and iterative line-by-line coding technique using ATLAS.TI software. A saturation analysis was conducted in order to confirm the appropriate sample size. Concepts derived from the patient interviews were inductively categorized into conceptual domains and sub-domains. Codes reflecting Impacts of early RRMS were further reviewed and inductively selected for inclusion in a conceptual framework focusing on daily life activities that were identified as relevant and important by early RRMS patients.

Results: A sample of 88 early RRMS patients were interviewed (mean age = 40 years; 74% female), 97% of whom were diagnosed within the previous two years. A rich pool of 446 unique concept codes was generated. These codes were separated into symptoms, bodily function, and impacts. A saturation analysis yielded only 3% (n=12) of the total concept codes emerging in the final eight interviews, suggesting that saturation was reached. The final conceptual framework of daily life activities comprises five sub-domains: Self-care (e.g. dressing and bathing); Domestic life (e.g. shopping, driving, and cleaning); Social and recreational (e.g. attending social events and hobbies); Sports and exercise (e.g. running), and Work and school (e.g. work attendance and productivity).

Conclusions: In order to fully understand the impact of early stage RRMS symptoms, it is vital to collect information about the extent, type and kind of issues important to this patient population. In this study, we have provided a comprehensive conceptual framework of relevant daily life activities important to early stage RRMS patients. This framework can be used as a foundation for future patient-reported outcomes instrument development and selection to quantify and capture the impact of new treatments in a clinically meaningful and individualized way.

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P1306

Well-being, health, and adjustment in early onset multiple sclerosis (MS): the role of personality

L. Strober, A. Becker
Kessler Foundation, West Orange, NY, United States

Background: Personality is known to play a role on one's health, well-being, coping, and illness management. More specifically,

neuroticism is a significant predictor of poor health and negative affect. Extraversion has consistently been shown to be related to positive well-being and conscientiousness is a known correlate of perceived health and engagement in health-related behaviors.
Objective: The purpose of the present study was to examine the role of personality on perceived physical and mental health, illness management, self-efficacy (SE), locus of control (LOC), coping, psychological well-being (PWB), quality of life (QOL), and social support/marital satisfaction in a sample of early onset MS (⩽ 5 years).
Method: 69 individuals with early onset relapsing-remitting MS (Mean = 3.06 years) were administered a comprehensive battery assessing personality, disease symptoms and management, self-efficacy, LOC, coping, PWB, QOL, and social functioning. Correlation analyses were conducted to examine the relationships among these factors.
Results: Neuroticism (N) and extraversion (E) were significantly correlated with reports of fatigue, pain, sleep difficulty, and anxiety (r's ⩾ .41). Conscientiousness (C), N, and E were related to depression (r's ⩾ .39). With regard to illness management, N was associated with greater substance use and worse medical adherence (r's ⩾ .29) while greater disease management and MS SE was related to E and C (r's ⩾ .26). General SE and LOC were both inversely related to N (r = -.46,-.74) and positively related to E (r = .38, .63) and C (r = .51, .47). In general, maladaptive coping was positively related to N (r's ⩾ .29) and inversely related to E and C (r's ⩾ -.25). Conversely, adaptive coping was positively related to C and E (r's ⩾ .32) and negatively related to N (r's ⩾ -.34). QOL and PWB were positively associated with C and E (r's ⩾ .32) and inversely related to N (r's ⩾ -.43). Perceived stress was associated with N (r=-.80), E (-.46), and C (r=-.32). Finally social support and marital satisfaction were related to N (r=-36,-.31), C (r=.39,.43) and E (r=.33,.37).
Conclusions: Consistent with the literature, personality plays a pivotal role on health and well-being in early onset MS. Consideration and assessment of personality traits at the onset of the illness appears warranted in assuring optimal outcomes. Moreover, longitudinal investigations examining the influence of premorbid personality on long-term outcomes are needed.

Disclosure

Lauren Strober: Nothing to disclose
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P1307

Longitudinal study of the effect of PR-fampridine walking and quality of life in people with severe MS-related walking impairment

R.A.L. Ewe[1], R. Farrell[2,3], H. Louissaint[3], H. Bleasdale[3], K. Bull[3], B. Beare[3], J. Allen[3]
[1]Medical School, University College London, [2]Institute of Neurology, University College Hospital, [3]University College Hospital NHS Foundation Trust, London, United Kingdom

Background: Prolonged release (PR) Fampridine improves walking speed and satisfaction with walking in people with MS (PwMS). It was licensed in the US and EU (conditional) in 2011. Longitudinal data on real-world patient experience on PR-Fampridine is invaluable in guiding the management of MS patients with walking impairment.
Objectives: To develop an MDT walking service to manage severe walking impairment in PwMS incorporating PR-Fampridine in routine clinical practice.
Methodology: People with MS and walking impairment were reviewed in a specialist MDT ambulation clinic since June 2013. Subjective and objective outcomes included: Timed 25 Foot Walk (T25FW), Multiple Sclerosis Walking Scale (MSWS-12), health-related quality of life using the EuroQol 5-dimension instrument, 5-level version (EQ-5D-5L), VAS walking and functional goals of treatment. Follow-up data was collected for existing subjects. New patients treated with PR-fampridine were evaluated for this study. Responder status was defined by ⩾20% increase T25FW velocity compared to baseline with concomitant MSWS-12 improvement.
Results: 142 subjects were included. Mean age 52.3 years [34-73 years], 93 female subjects and 49 males were trialled. Mean Expanded Disability Status Score (EDSS) 6.5 [6.0-7.0]. After 2 weeks, 72.9% walked ⩾20% faster than baseline. Median change in T25FW velocity was 68.0% [21.2 - 453 %] in responders versus -6.0% [-32.0-12.0%] in non-responders (p< 0.0001). Responders continued walking faster than baseline at 22 months (55.0%, p=0.002), 26 months (78%) and 30 months (75.9%). At 2 weeks, MSWS-12 improved more in responders (-19.0) than non-responders (-11.23) (p=0.073), EQ-5D-5L index changed by +0.166 [-0.402 - +0.740, p< 0.0001] in responders and - 0.03 [-0.909 - +0.541] in non-responders (p< 0.0001). Responders continued to have better EQ-5D-5L index scores at 4 months (+0.116), 10 months (+0.163) and 16 months (+0.087). At 10 months, 83.3% had achieved their treatment goals. At the end of the study period, T25FW responders discontinued PR-Fampridine due to treatment failure (n=32), side effects (n=5), patient choice (n=3), impaired eGFR (n=2), relapse (n=2) and inability to adhere to dosing (n=1)
Conclusio: PR-Fampridine improves walking speed, self-reported walking ability, quality of life and functional ability in an open-label longitudinal study of MS patients with severe walking impairment. Use within an MDT service optimises ability.

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P1308

Using social media to communicate with people affected by multiple sclerosis

A. Thomson[1], D. Baker[1], G. Giovannoni[1,2]
[1]Barts MS, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Whitechapel, London, [2]Barts Health NHS Trust, London, United Kingdom

Background: Public engagement in science (PeS) and public-patient involvement (PPI) are becoming increasingly important in research. PeS and PPI initiatives are used for disseminating and

interpreting research results and other information, assessing research impact, setting research priorities and for involving people with MS (pwMS) in the research process. At Barts-MS we have been running a multiple sclerosis research blog (www.ms-res.org) and a linked slideshare site, both social media platforms, for people with MS (pwMS) for approximately 7 years. The blog and slideshare sites are two-way platforms for communicating with people affected by multiple sclerosis, i.e. blog posters interact with readers via comments linked to each post.

Objectives: To present summary metrics in relation to an MS research blog usage and to describe global trends in the research blog readership.

Methods: Blog activity is described using statistics from blogger and google analytics. The overall analysis covers the period 3-Sep-2009 until 24-April-2016 with more detailed annual analysis for the period 1-April-2015 to the 31-March-2016.

Results: As of the 24th April there have been 5,879 individual MS research blog posts, 34,062 published comments, 17 published blog pages and >6.4 million page views. In the preceding 12 months there was an average of 199,552 page views per month (Std. dev. = 7,926; range = 148,393-240,982). In the preceding calendar month visitors were registered from 155 countries. The per capita readership of the top 10 countries in decreasing order of magnitude were the UK (25,419 pageviews/million population/month), Australia (14176), Ireland (12836), Switzerland (11843), Norway (11271), Denmark (8229), Canada (7622), Sweden (6067), USA (5751) and Greece (4823). The sister slideshare site has 360 shared files with >21.5 million views. Over 65% of traffic to the slideshare site is from embedded content from the research blog. Qualitative research has shown that readers value the site.

Conclusions: Social media platforms are becoming increasingly important as means to interact with people affected by MS. This study demonstrates the global reach and potential impact social media may have for researchers in the field of MS. This data suggests that the MS research community could use social media as a tool for PeS and PPI.

Disclosure

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P1309

Evaluation of e-learning tools for MS patients - mymsmagazin.com

G. Winkler, A. Raji
Center of Neurology, Hamburg, Germany

Objective: To find out and evaluate the optimal e-learning tool for MS patients with the now 1 year old multimedial internet platform.

Background: Besides the neurologists the internet has become the most important information resource for MS patients. The hypothesis is that effective learning about important MS topics supports therapy compliance and improves quality of life. We introduced mymsmagazin.com at ECTRIMS 2015. To raise the e-learning effect we compared different tools presented on mymsmagazin.com. Comparable data that adress e-learning effects from other MS internet platforms are not published yet.

Design/Methods: The study was prospective and cross-sectional. The different formats were patient's interview, reports from MS conferences or teaching lessons with different lengths of time. The different topics like new therapeutical approaches, neuropsychology, MRI, disease modifying therapies and basic knowledge were addressed using the different tools. The e-learning effects were evaluated with online questionnaires from a data base of 400 responders. The impact was defined by the percentage of users that gained knowledge.

Results: In general the video podcasts revealed a marked learning effect on an average of 75% of the responders. The different results are influenced by the variability of prelearning knowledge and the chosen podcast tool. The highest impact up to 90% was found for short (about 5min) performed teaching lessons including a few animated slides. But from the emotional point of view users reported a risk of being scared by the teaching lessons. The e-learning impact of patient's interviews was below average but the majority of users experienced a sense of safety. The reports showed an average e-learning impact. Users felt comfortable with this tool. Patients interviews and reports were most frequently requested by the users.

Conclusion: The optimal video podcast e-learning tool apears to be a combination of a 5 minute teaching lesson or report with a patient's interview to minimize the possible anxiety induced by the new information.

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P1310

Depression in multiple sclerosis, prevalence and contributing risk factors

A. Nikseresht, M. Sharifian Dorche, M. Nomovi
Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran

Introduction: Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS) which is affect young adult especially young females. In this study we tried to investigate the prevalence of depression among female patients with MS and the most important contributing risk factors.

Methods: During a cross-sectional study 1750 female patients with MS from our outpatient's clinic in Shiraz Southern Iran were involved. Depression was assessed using the Beck Depression Inventory-II (BDI-II).

Descriptive analysis and multiple logistic regressions were performed to examine the association between depression and disability, education, employment, marriage status, course and income.

Results: Overall, 647 patients (37 %) had moderate to severe depression. The mean age of participants was 38.2 years (SD = 9.57). The results obtained from logistic regression analysis showed that expanded disability status scale (EDSS), Progressive course and unemployment ($P < 0.01$) were significantly related to the severity of depression. Marriage and higher education had related to lower depression scales.
Conclusions: These findings suggest that depression in patients with MS has multiple contributing factors and patients with higher social supports and lesser disability have lower rates of depression. Physiotherapy , regular employment and family supports may help to reduce depression.

Disclosure

there is no conflict of interest.

P1311

Nutrition is of great concern for people newly diagnosed with multiple sclerosis

G. von Geldern[1], A. Wundes[1], K.N. Alschuler[2]
[1]Department of Neurology, [2]Department of Rehablitation Medicine, University of Washington, Seattle, WA, United States

Background: Dietary factors have been discussed to influence risk or disease course of multiple sclerosis (MS). While there is no conclusive evidence on the best dietary interventions for MS, multiple specific diets and dietary supplements are used among people with MS. However, nutrition is an often overlooked topic for physicians and how much people newly diagnosed with MS are concerned about the impact of nutrition has not been studied.
Objective: To assess whether nutrition is a concern for individuals recently diagnosed with multiple sclerosis.
Design/Methods: A cohort of 100 individuals with MS is followed in our center longitudinally starting at the time of diagnosis. Questionnaires assessing different psychological domains were administered at 1, 2, 3, 6, 9, and 12 months following the diagnosis of MS. We assessed their dietary practices including use of supplements and their attitudes towards nutrition with a questionnaire with open and closed ended items.
Results: In our cohort which consisted of predominately patients with relapsing-remitting disease, 83% of individuals queried reported having started a new supplement since receiving the diagnosis of MS, in particular Vitamin D supplementation. The type of supplements used changed somewhat throughout the course of the study and included supplements like turmeric, magnesium, and biotin at later time points. A large percentage expressed an interest in changing their diet throughout the time points studied. The most common diets followed were paleo diet, gluten-free diet and sugar free diet. A significant proportion of participants expressed interest in discussing their nutrition further and indicated planning to talk to a provider about their diet. Naturopathic doctors were most often mentioned as the providers patients sought advice from.
Conclusions: Nutrition is of great concern for individuals with multiple sclerosis even early in their disease. The evidence for individual dietary interventions is very limited and more studies assessing the effect of diet and supplements on the course of MS as well as quality of life and MS symptoms is needed. When treating patients with MS, addressing nutrition and supplements is important even early on in the disease.

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P1312

Comparison of quality of life in autoimmune diseases of the spinal cord

M.A. Mealy[1], A. Simpson[2], M. Levy[1]
[1]Neurology, Johns Hopkins University, [2]University of Maryland School of Medicine, Baltimore, MD, United States

Objective: To compare the burdens of neuromyelitis optica, idiopathic transverse myelitis and multiple sclerosis on a patient's psychological mindset and quality of life.
Background: Multiple sclerosis (MS), neuromyelitis optica (NMO), and idiopathic transverse myelitis (TM) are the most common autoimmune inflammatory disorders that target spinal cord producing varying levels of neurological disability. A decade of studies in MS provide strong evidence that MS patients are on average, more disabled, fatigued, depressed, and pain-ridden than healthy populations. Although NMO and TM are diseases that relatively spare the brain, there is emerging data that these rarer patient populations are impacted by psychological burdens as well.
Design/**Methods:** We compared the extent of disability and prevalence of depression, fatigue, and pain across three cohorts of MS, TM and NMO patients. We recruited 23 patients with MS, 14 with TM and 38 with NMO and collected data by online surveys for pain using the Brief Pain Inventory, fatigue using the fatigue severity scale, depression using the Beck Depression Inventory and disability using the patient-administered Expanded Disability Status Score (pEDSS). Using MS as a comparator group, we assessed correlations between disability and depression, fatigue, and pain.
Results: NMO patients as a group were more disabled than patients in the MS and TM cohort and scored higher on the brief pain inventory. Despite greater disability and more pain, NMO patients were less depressed and fatigue compared to TM and NMO patients, especially when controlled for level of neurological disability. We found that MS patients were more likely be depressed and fatigued with higher levels of disability.
Conclusions: Autoimmune diseases of the spinal cord lead to pain, fatigue and depression. Compared to MS, NMO patients have a lower rate of depression and fatigue despite greater levels of disability and pain.

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P1313

Benefits of a mindfulness- based intervention compared to psychoeducation among multiple sclerosis patients

I. Gonzalez-Suarez[1], A. Muñoz-San José[2], S. Cebolla Lorenzo[3], L. Carrillo Notario[4], V. López de Velasco[1], A. Orviz García[1], C. Bayón Pérez[4], B. Rodriguez Vega[4], C. Oreja-Guevara[1]
[1]Neurología, Hospital Clínico San Carlos, [2]Centro de Salud Mental Alcobendas, [3]Centro de Salud Mental Tetuan, [4]Hospital Universitario La Paz, Madrid, Spain

Introduction: Stress management, including mindfulness, might improve quality of life and produce significant reductions in depression, anxiety and fatigue among multiple sclerosis (MS) patients.
Objective: To study if mindfulness based intervention can improve quality of life and fatigue in MS patients.
Material and methods: A randomized clinical trial was designed to study and compare the effect of an inspired mindfulness- based intervention to a psychoeducative program with relaxation techniques on quality of life (measured by SF-36 questionnaire), fatigue (measured by visual analogic scale), anxiety and depression (measured by the Hospital Anxiety and Depression Scale,HADS), at the beginning of the study (pre-intervention) and at the end of the intervention (post-intervention, 8 weeks). Both are group interventions over 8 weekly 1.5 hour sessions. The sample is comprised of 58 patients with RRMS, 31 of them randomized to mindfulness intervention and the other 27 to educative program. No differences in sociodemographical characteristics have been found between the groups.
Results: Mindfulness patients show significative increase of puntuactions in subescales of mental health ($Z=-4.65$; $p< 0.05$)and vitality ($Z=-6.18$; $p< 0.05$) in SF-36 in relation to psichoeducative group; subescales of physical functioning, social functioning, bodily pain, general health, role-physical and role-emotional have not showed differences between groups. Both interventions have been produced significative decreased of levels of fatigue at 8 week ($Z=5.04$; $p< 0.05$) but no differences have been showed between interventions in fatigue reduction. Patients randomized to mindfulness intervention also show significative decreased scores in HADS-A ($Z=4.68$, $p< 0.05$), HADS-D ($Z=5.89$, $p< 0.05$) and HADS-T ($Z=5.89$, $p< 0.05$) than patients randomized to psychoeducative program.
Conclusions: Our data support the beneficial effects in some aspects of quality of life of a mindfulness-based interventions compared to a psychoeducative program. Both interventions have showed benefits in terms of fatigue reduction.

Disclosure

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Enhancing CNS plasticity

P1314

Brain activations during the kinetic scenes perception and their changes after physiotherapy in patients with multiple sclerosis

M. Prochazkova[1], J. Tintera[2], S. Spanhelova[3], T. Prokopiusova[1], G. Angelova[1], N. Hruskova[1], D. Vavrova[1], J. Rydlo[2], I. Stetkarova[4], M. Grunerova Lippertova[1], K. Rasova[1]
[1]Department of Rehabilitation Medicine, Third Medical Faculty and Faculty Hospital Kralovske Vinohrady, Charles University, [2]Department of Diagnostic and Interventional Radiology, Institute for Clinical and Experimental Medicine, [3]Department of Rehabilitation and Sports Medicine, Faculty Hospital in Motol and Second Faculty of Medicine, Charles University, [4]Department of Neurology, Third Medical Faculty and Faculty Hospital Kralovske Vinohrady, Charles University, Prague, Czech Republic

Background: Imaging methods (especially functional magnetic resonance imaging - fMRI) are widely used for mapping of neuroplasticity in patients with multiple sclerosis (MS). They can contribute to better understanding and describing of pathological and repair processes in the brain as well as they can be used for objectification and evaluation of physiotherapy effect.
Aims: To contribute to the better understanding of the brain pathological processes in MS patients by analysing fMRI data (captured during watching kinetic video scenes). To compare these records with records of healthy controls and demonstrate the effect of facilitation physiotherapy by evaluating fMRI records (brain activation) and clinical features.
Methods: 39 patients with MS (mean age 46.7±12.3, Expanded Disability Status Scale - EDSS 4.3±1.7, disease duration 12.1±7.2 years) and 42 healthy volunteers (mean age 43.7±14.8 years) participated in the study. People with MS underwent a two-month program of facilitation physiotherapy (2x a week,1 hour). The clinical examination (evaluation of fine motor skills, balance, walk and cognitive functions) and fMRI examination while watching alternating kinetic and static video scenes were performed at the beginning and at the end of the program. FMRI data were analysed in software SPM8 (Statistical Parametric Mapping).
Results: The healthy controls had stronger activation in secondary visual cortex and cerebellum than MS patients while watching kinetic video ($p=0.01$). Statistically significant differences remain unchanged after physiotherapy. In healthy controls, there was found significant activation in the posterior areas of insula while watching static scenes. The pattern of activation after physiotherapy transforms - after therapy it is generally smaller. It has been shown that the activation while watching kinetic videos increases with the disease severity (rising EDDS), especially in the areas of middle frontal gyrus, angular gyrus, insula and precentral gyrus. In clinical trials, there was an improvement, most in the walk and cognitive tests.
Conclusions: Perception of kinetic events evokes lower brain activation in MS patients compared to healthy controls - especially in areas where information is processed. These differences are unchanged after two months of the physiotherapy. People with MS reduce the extent of activation patterns after physiotherapy. Clinical status of the patients slightly improved after physiotherapy.

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Multi-disciplinary rehabilitation

P1315
Integrated assessment of handwriting movement in people with multiple sclerosis

L. Pedullà[1,2], A. Bisio[1], L. Bonzano[1], A. Tacchino[2], G. Brichetto[2], M. Bove[1]
[1]University of Genoa, [2]Italian Multiple Sclerosis Foundation (FISM), Genoa, Italy

Writing is a mean of communication which requires complex motor, perceptual and cognitive skills. Although handwriting deficits are common in people with Multiple Sclerosis (PwMS), there are only few studies on this matter in the literature. To date there is not a standardized method to assess adults´ handwriting and it is still unclear what impairment mostly affects writing ability in PwMS.

The present study is a part of a project granted by the Italian Multiple Sclerosis Foundation (grant N° 2014/R/5) and aims at investigating the relation between clinical evaluation of different domains (e.g., strength, fatigue, cognition) and handwriting parameters in PwMS.

At present, 13 PwMS (9 females, mean age±SD: 46±11 years, mean EDSS±SD: 3.1±1.5) participated in the study and were evaluated with: dynamometer evaluation for pinch strength, Nine Hole Peg Test (NHPT), Visual Analog Scale (VAS) for self-perception of upper limb disability, Modified Fatigue Impact Scale (MFIS) and Symbol Digit Modalities Test. Moreover, PwMS were tested by means of the DGM-P test to assess grapho-motor impairments during writing. They were required to write a sentence twice, as accurate and as fast as possible. As outcome parameters time to write the sentence, inaccuracy of the tract (dysmetria), distance from the line (fluctuation), ascending/descending tracts disproportion and variability in letters height were measured. Analysis included Pearson´s or Spearman´s correlation coefficient between clinical tests and writing parameters, depending on data distribution.

Results showed a significant correlation between dysmetria and MFIS ($R= -0.67$, $p< 0.05$), fluctuation and pinch strength ($R= -0.59$, $p=0.003$), fluctuation and NHPT ($R= 0.58$, $p< 0.05$), tracts disproportion and pinch strength ($R= -0.62$, $p< 0.05$), tracts disproportion and VAS on perceived weakness ($R= 0.85$, $p< 0.05$), and variability and NHPT($R= 0.68$, $p< 0.05$).

We can conclude that upper limb weakness plays a crucial role in writing dysfunction, since pinch deficit and VAS higher values were related to increased handwriting fluctuation and tracts disproportion. Moreover, patients reporting higher fatigue showed decreased handwriting dysmetria. This apparent paradox was previously reported in the literature, and can be an index of a greater effort (causing fatigue) needed to reach higher performance. Finally, tests evaluating manual dexterity, such as NHPT, seem to be reliable tools to assess handwriting in PwMS.

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P1316
Kinematic evaluation of handwriting movement in people with multiple sclerosis

A. Bisio[1], L. Pedullà[1,2], L. Bonzano[1], P. Ruggeri[1], G. Brichetto[2], M. Bove[1]
[1]University of Genoa, [2]Italian Multiple Sclerosis Foundation (FISM), Genoa, Italy

Writing is a mean of communication which requires complex motor, perceptual and cognitive skills. If one of these abilities gets lost handwriting could deteriorate, as in the case of people with multiple sclerosis (PwMS). This deficit considerably interferes with daily life activities inducing a sense of frustration. Nonetheless, until now the scientific community did not examine in depth this aspect of MS disability, and the international literature dealing with this matter is limited to few studies. In Italy occupational therapy administered by Italian Multiple Sclerosis Society Rehabilitation Centers proposes, as part of rehabilitation programs, the recovery of writing. However, due to the low sample of scientific work at disposal, reliable quantitative data on the efficacy at behavioral level of this kind of interventions are lacking, as also it is not clear what are their effects on brain networks.

The present study is a part of a project granted by the Italian Multiple Sclerosis Foundation (grant N° 2014/R/5) and aims at defining an evaluation methodology that allows to quantitatively characterize the kinematics of handwriting movements and to evaluate their neural correlates. At present 15 PwMS (11 females, mean age±SD=44±10, mean EDSS±SD=3.37±1.59, 12 RR and 3 SP MS course) and 17 healthy age-matches controls (12 females, mean age±SD=38±12) participated in the study. PwMS underwent clinical evaluations and the evaluation of kinematics of the writing movements by means of a magnetic resonance imaging (MRI) compatible tablet (E.M.S., S.r.l., Bologna). The participant was seated at a table and was required to write the Italian sentence "Il sole scalda" over the tablet. The duration, length and height of the sentence were considered as outcome parameters.

Results showed a significant increase of PwMS's movement duration with respect to the controls. Movement duration negatively correlated with the Simbol Digit Modality Test and positively correlated with the Visual Analog Scale for self-perception of weakness. Sentence height increased significantly with the increasing

of the grip and pinch force. These results suggested that both motor and cognitive deficits affected the writing performance. The next step of the project will evaluate the brain activity of handwriting during a functional MRI examination, which will provide insight concerning the motor and cognitive brain areas involved in the task.

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P1317

Both anticipatory and compensatory postural adjustments are altered during external perturbations in multiple sclerosis individuals with a previous fall history

S. Tajali[1,2], M. Rouhani[3], M. Mehravar[2], H. Negahban[4], M.A. Eteraf-Oskouei[3]
[1]Student research committee, Ahvaz Jundishapur University of Medical Sciences, [2]Musculoskeletal Rehabilitation Research Center, Ahvaz, [3]Tabriz University of Medical Sciences, Tabriz, [4]Mashhad University of Medical Sciences, mashhad, Islamic Republic of Iran

Impaired balance is one of the most common and disabling multiple sclerosis (MS) symptoms. Anticipatory (APAs) and compensatory (CPAs) postural adjustments are two main postural mechanisms to maintain and restore balance during expected and unexpected perturbations. The main purpose of this study was an update to previous literatures and to investigate the relationship between APAs and CPAs and falls in MS subjects. Seventeen MS fallers, 11 MS non-fallers and 11 age-and-gender matched healthy controls were exposed to backward external pull perturbations. Subjects received pull perturbations through a cable attached to an axillary belt. The perturbations were either predictable or unpredictable as subjects were informed through verbal auditory feedback. Electrical activity of 12 leg and trunk muscles were recorded and quantified within the time intervals typical of APAs and CPAs. The results revealed that MS subjects with previous fall history had significant delay in the both anticipatory and compensatory onsets of muscle activity ($p< 0.0.5$ for bilateral erector spinae, Left biceps femoris and left rectus femoris muscles) in comparison to non-faller and healthy control subjects. In addition, MS subjects with previous fall history exhibited smaller activity levels in the most studied muscles in the both anticipatory and compensatory phase of perturbations. The results revealed apparent deficits in the APAs during expected perturbations in MS subjects with a previous fall history. The reduced APAs were not accompanied by greater and earlier compensatory muscle activity. This inability to maintain and restore balance in response to external perturbations may explain high incidence of falls in these individuals. Future rehabilitation programs should focus on perturbation training protocols in order to improve both anticipatory and compensatory responses to daily perturbations.

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"Shirin Tajali: nothing to disclose"

P1318

Effects of core stability on functional capacity in patients with multiple sclerosis

A. Guclu-Gunduz[1], C. Ozkul[1], T. Ozkan[1], Y. Aydın[1], K. Cekim[1], C. İrkeç[2]
[1]Gazi University / Faculty of Health Sciences, [2]Gazi University Medical Faculty, Ankara, Turkey

Background: People with Multiple Sclerosis (MS) experience disabling walking and ability impairments. Although core stability is an important component of walking, evidence on the relationship between core stability and functional capacity in patients with MS is insufficient.
Objectives: To investigate the relationship between core stability and functional capacity in patients with MS.
Methods: Thirty seven ambulatory patients with MS (Age:37.38±8.42 years, EDSS: 1.49±0.99) participated in the study. Core stability was assessed in two parts; core endurance and core power. Core endurance as assessed using the McGill protocol (trunk flexion test, a modified Biering-Sorensen trunk extension test, right-left bridge tests and prone breach test). McGill' tests were scored by the duration the individuals could maintain these isometric postures. Core power was assessed by maximum number of sit-ups and modified push-ups. The number of successful repetitions in 30 second was recorded. Functional capacity was assessed with six minute walking test (6MWT) and walking distance was recorded as meter. Pearson correlation analysis were used to determine relationships between core stability and functional capacity. To determine the most powerfull predictors of functional capacity, multiple regression analysis was used.
Results: 6MWT was associated with core endurance and core power tests (r=between 0.259 to 0.538 $p< 0.05$, except for the modified Biering-Sorensen trunk extension and sit up tests) in patients with MS. Regression analysis revealed that the most powerfull predictor of functional capacity is trunk flexion test, right-left bridge test, prone breach test and modified push-ups test ($R^2 = 0.735$ $p< 0.05$).
Conclusion: This results show that core muscles' endurance and power related and predicted to functional capacity in patients with MS. Therefore, we think that core stability based training such as Pilates which is becoming increasingly popular today could improve functional capacity in patients with MS.

Disclosure

There is no financial support for this study

P1319

Physiotherapy and steroids in the management of motor relapses in multiple sclerosis: a combined therapy

S. Sánchez, I. Galán, À. Vidal-Jordana, G. Loyola, D. Fàbregas, C. Santoyo, M. Janer, X. Sibera, J. Castilló, J. Río, G. Arrambide, L. Midaglia, B. Rodríguez-Acevedo, M. Zuluaga, P. Mulero, C. Oriol, R. Horno, M. Tintoré, J. Sastre-Garriga, X. Montalban

Multiple Sclerosis Centre of Catalonia/Neuroimmunology Dept & Epidemiology Dept, Vall d'Hebron University Hospital, Barcelona, Spain

Background: Studies conducted on rehabilitation have shown physiotherapy to be of benefit in MS patients; however, the current therapy of MS relapse is based on steroids.
Objective: To study the potential benefits of physiotherapy as add-on therapy to steroids in the treatment of MS relapses.
Method: A prospectively and consecutively cohort of PwMS experiencing a motor relapse, described as 1-point increase in the EDSS pyramidal function, was recruited. Patients were treated either with steroids alone (control group-CG) or with steroids plus 12 individual physiotherapy sessions (experimental group-EG). The following outcome measures were assessed: EDSS at baseline and month1 (M1); Motor Index (MI), Timed 25-Feet Walking Test (T25FWT) and 2-Minute Walking Test (2MWT) at baseline, M1 and M3. A VAS on the degree of achievement of a lost functional goal (VASFG) due to the relapse was fulfilled at M1. Non-parametric tests were used to compare baseline characteristics and change in outcome measures. A logistic regression analysis was performed to predict EDSS improvement at M1.
Results: 39 out of 41 patients completed the full protocol; median age was 41 (range 26-73), median disease duration was 14 years (range 3-45), median EDSS was 4.0 (range 1.0-8.0), median 2MWT, T25FWT and MI were 93, 8.5 and 90 respectively. Baseline EDSS was higher in the EG, but differences were not significant (median 5.0 vs 3.5, p=0.346). At M1, a higher proportion of patients showed EDSS improvement in the EG compared to the CG (56% vs 14.3%, p=0.017). In logistic regression analysis, and controlling for baseline EDSS, receiving combined therapy was associated with a higher probability of EDSS improvement at M1 (OR 7.7, 95% CI 1.2-50.8, p=0.034). Accordingly, the mean VASFG was higher in the EG (7.43 vs 4.72, p=0.031). At M1, the 2MWT, T25FWT and MI scores significantly improved in both groups, and this effect was maintained at M3. Although a higher proportion of patients improved the T25FWT in the EG compared with the CG, this difference was not significant (65.2% vs 41.7%, p=0.181 at M1, and 59.1% vs 50%, p=0.391 at M3). The magnitude of change for T25FWT, 2MWT, and MI scores was not different between both groups at M1 and M3.
Conclusions: Our findings suggest that combined therapy improves both objective (EDSS) and subjective (VASFG) measures. Walking measures and motor index improved similarly in both groups. Future studies with larger sample are needed to confirm these results.

Disclosure

The authors have nothing to disclose

P1320

The effect of vibrotactile biofeedback of trunk sway on balance control in multiple sclerosis

H.M. Rust[1], R.P. van der Logt[1], O. Findling[2], L. Kappos[1], Ö. Yaldizli[1], J.H.J. Allum[1]
[1]University Hospital Basel, Basel, [2]Kantonsspital Aarau, Aarau, Switzerland

Background: Patients with multiple sclerosis(MS) suffer from diminished balance control due to slowed sensory conduction and possibly delayed central processing. Vibrotactile biofeedback of trunk sway has been shown to improve balance control in patients with peripheral and central vestibular disorders.
Objective: To measure the effects of vibrotactile feedback training on trunk sway in MS during different stance and gait tasks.
Methods: In total, 10 MS patients(6 relapsing-remitting, 2 secondary-progressive and 2 primary-progressive MS, mean age 46.8 ± 7.7 years, 40% male, median EDSS 4.0[range 2.5 - 6.0]) with complaints of balance impairment participated in a randomized controlled crossover study in which 7 different stance and gait tasks were trained with and without sway angular feedback for stance and sway angular velocity feedback for gait tasks. Dizziness Handicap Inventory(DHI) questionnaires were used to measure the subjective balance deficits. The 12-item MS walking scale(MSWS-12) was used to measure the impact of MS on subject's walking ability. An assessment sequence of 12 stance and gait tasks was performed once before and twice after the training sequence including standing one or two legs with eyes open and closed on a firm or foam surface, tandem stance eyes open and closed, walking 8 tandem steps eyes open and closed, walking over barriers, walking 8 m eyes open and 3m eyes closed. Trunk sway was measured with body-worn gyroscopes mounted near the body's centre of mass, in the centre of the lower back at vertebral level L3-L5. Head mounted vibrotactile biofeedback of lower trunk sway was provided during one crossover training arm and the following second but not the third assessment sequence.
Results: Mean DHI and MSWS-12 scores were 30.0±15.9 and 28.9±12.8, respectively. In most tasks, biofeedback led to a marginal decrease in sway and increase in sway angular velocities for stance tasks and vice versa for gait tasks when compared to training without biofeedback. For example, walking eyes open resulted in a decreased sway angular velocity. The greatest changes during gait were found in the pitch direction of trunk sway (-13.87±6.03 degree/sec, p=0.02). Effects diminished after biofeedback was removed.
Conclusions: Vibrotactile biofeedback of trunk sway may beneficially effect stance and provide improvement in gait compared to training without biofeedback in MS. Trials with intensive vibrotactile feedback training may enhance this effect.

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Neurobiology & rehabilitation

P1321

Prolonged-release fampridine and active motor training in MS patients: a Phase IV, double-blind, placebo-controlled

F.H. Jacques[1], A. Nativ[2], A.J. Schembri[3], C. Paquette[1], P. Kalinowski[3]
[1]Clinique Neuro-Outaouais, [2]Clinique Neuro-Gym, Gatineau, QC, Canada, [3]CogState, Melbourne, VIC, Australia

Introduction: Prolonged-release fampridine (PRF) has been shown in multiple sclerosis (MS) patients to improve walking capabilities by more than 20% in approximately 34% of subjects. Active motor training in MS patients is both feasible and beneficial. Studies have shown it to improve walking ability, fatigue, depressive symptoms and cognition. The objective of our study is to test the hypothesis that active motor training when combined with PRF in patients with MS will produce a larger and more sustained measurable clinical benefit than with active motor training alone.
Methods: Phase 4, single center, double-blind placebo-controlled 14 week study. Patients were randomized to receive PRF 10 mg or placebo BID. All patients underwent active motor training as per the NeuroGym method consisting of 3, I hour session, per week for a period of 6 weeks (total of 18 sessions).Patients were evaluated at times -4, 0, 6, and 14 weeks using the timed 8 meter walk (T8MW), the six minute walk (6MW) and the Five-Times-Sit-to-Stand (FTSST).A responder was defined as a patient who improved more than 20% from baseline in a specific task and time point. Mean percent improvement was measured for the whole group (PRF or placebo) for a task and time point.
Results: 37 patients completed the study. There were no statistical difference between the two groups at baseline. A measurable benefit was noted from the training in both groups which was sustained at week 14. The greatest improvement in both groups was noted in the sit to stand measure with an OR of 2.7 (p=0.13) of being a responder in the PRF treated group. The incidence of responders was higher in the PRF treated group and ranged from 22 to 66% (p =0.1 or more) The PRF treated group showed a higher mean percent improvement in all three measurements at both time points but this did not reach statistical significance. (p values ranging from 0.07 to 0.4)
Conclusions: MS patients can obtain a sustained benefit from strength training. PRF appears to increase the degree of improvement at both the individual and the group level. The latter will need to be confirmed in a larger trial.

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P1322

Predicting multiple sclerosis disease course with patient centred outcomes (PCOs): a machine learning approach

G. Brichetto[1], S. Fiorini[2], M. Ponzio[1], A. Barla[1], A. Verri[2], A. Tacchino[1]
[1]Scientific Research Area, Italian Multiple Sclerosis Foundation (FISM), [2]DIBRIS, Univesity of Genoa, Genova, Italy

Background: Achieving an accurate clinical course description in Multiple Sclerosis (MS) is a very hard task even for clinical experts, but it is crucial for communication, prognosis, treatment decision-making, design and recruitment of clinical trials. In this context, meaningful data being "hidden" into Patient Centered Outcomes (PCOs), could provide, through Advanced Machine learning (ML) approaches, a new perspective in predicting MS disease course.
Aims: This work aims at using PRO, CS and anthropometric measures to build a statistical model for the detection of MS courses by means of machine learning techniques. The analysis has been conducted on the dataset of the ongoing Italian MS Foundation (FISM) initiative "A New Functional Profile to Monitor the Progression Of Disability In Multiple Sclerosis - PROMOPRO-MS".
Methods: The dataset is composed of 778 patients with MS, that were enrolled in the study without any inclusion/exclusion criteria unless MS diagnosis. The variables identified in the study were based on functions sufficient to encompass the patient's disability and to represent whole-person behaviours. The set of PCOs selected were related mainly to mobility, fatigue, cognitive performances, emotional status, bladder continence, quality of life. Both unsupervised and supervised machine learning methods were taken into account. The first goal was to assess whether the collected features could discriminate any of the different disease courses by using unsupervised learning techniques looking for a meaningful data structure, then to apply a supervised approach, inferred in the previous step, in order to learn a classifier based only on a subset of the available features.
Results: The applied machine learning techniques showed that patients with MS (PwMS) diagnosed as relapsing-remitting (RR) could be isolated from other clinical courses (ALL). In particular, nine "top" questions were selected by the 'Features Selection' supervised (FS) algorithm: three questions from Life Satisfaction Index, three items from Functional Independence Measure; two from Modified Fatigue Impact Scale and one from Hospital Anxiety and Depression Scale.
Conclusions: To the very best of our knowledge this is the first study which predicted MS course taking only into account a small subset of anthropometric and questionnaires variables, which could be proposed as a novel questionnaire, tailored for RR detection.

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P1323

Adaptive conflict resolution: Structural variability in regions that trigger adaptation is related to cognitive performance

S.A. Holmes[1,2], J. Zhong[1,3,4], J.C. Nantes[1,2], L. Koski[1,3,5]
[1]Neurology and Neurosurgery, McGill University, [2]Integrated Program in Neuroscience, [3]Research Institute of the McGill

University Health Centre, Montreal, QC, [4]Toronto Western Hospital, Toronto, ON, [5]Psychology, McGill University, Montreal, QC, Canada

Background: Multiple sclerosis (MS) is a disease of the central nervous system (CNS) characterized by damage to neurons and their myelin coating that can lead to a myriad of behavioral disabilities. The relationship between disease-related pathology and disability has recently been shown to be sensitive to how the CNS triggers the integration of adaptive resources (Holmes et al., 2016). Cortical regions responsible for this event are contained within the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) and may overlap with those predisposed to disease-related pathology (Lansley et al., 2013). The current study evaluates the presence and impact of structural variance in regions implicated in triggering adaptation.
Objectives: The first objective of this study was to evaluate if disease-related pathology could be observed in regions within the ACC and DLPFC responsible for triggering adaptation. The second objective was to evaluate in a group of healthy controls (HC) and participants with MS the extent to which structural variability in these regions of interest was related to general cognitive ability.
Methods: Participants with MS (n=41) were compared with a group of HC (n=21) using independent sample t-tests to evaluate disease-related pathology in regions of interest (ROI) using magnetization transfer ratio (MTR) imaging. Linear regression analysis was performed to determine if general cognitive ability on the Symbol Digit Modality Test (SDMT) could be predicted from MTR within regions of interest.
Results: The MS group had lower MTR values in the right ACC ($p = 0.03$) and in the right DLPFC ($p = 0.002$) when compared with the HC group. MTR in the right hemisphere ROIs significantly predicted performance on the SDMT in both the HC ($p = 0.03$) and MS ($p = 0.04$) groups. MTR in the left-hemisphere ROIs were comparable in the two groups and did not predict performance on the SDMT.
Conclusions: Findings from the current study demonstrate how regions involved in functional adaptation to disease burden may become compromised by MS pathology. Together, results suggest that individual differences in adaptation to neurological injury may be determined in part by the health of brain structures that trigger the recruitment of alternate functional neural pathways.

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Neuropsychology and fatigue management

P1324

Are coping strategies related to negative work events in multiple sclerosis patients?

K. van der Hiele[1,2,3], D.A.M. van Gorp[1,2,4], R.H.B. Benedict[5], P.J. Jongen[6,7], E.P.J. Arnoldus[3], E.A.C. Beenakker[8], H.M. Bos[9], J.J.J. van Eijk[10], J. Fermont[11], S.T.F.M. Frequin[12], B.M. van Geel[13], G.J.D. Hengstman[14], E. Hoitsma[15], R.M.M. Hupperts[16], J.W.B. Moll[17], J.P. Mostert[18], P.H.M. Pop[19], W.I.M. Verhagen[20], G.A.M. Verheul[21], D. Zemel[22], S.E. Frndak[23], M.A.P. Heerings[1], H.A.M. Middelkoop[2,24], L.H. Visser[3,4]
[1]National Multiple Sclerosis Foundation, Rotterdam, [2]Psychology, Section Health, Medical and Neuropsychology, Leiden University, Leiden, [3]Neurology, Elisabeth-TweeSteden Hospital, Tilburg, [4]University of Humanistic Studies, Utrecht, The Netherlands, [5]Neurology, Buffalo General Hospital, Buffalo, NY, United States, [6]MS4 Research Institute, Nijmegen, [7]Community & Occupational Medicine, University Medical Center Groningen, Groningen, [8]Neurology, Medical Center Leeuwarden, Leeuwarden, [9]Neurology, St. Anna Hospital, Geldrop, [10]Neurology, Jeroen Bosch Hospital, 's-Hertogenbosch, [11]Neurology, Amphia Hospital, Breda, [12]Neurology, St. Antonius Hospital, Nieuwegein, [13]Neurology, Medical Center Alkmaar, Alkmaar, [14]Neurology, Catharina Hospital, Eindhoven, [15]Neurology, Alrijne Hospital Leiden, Leiden, [16]Neurology, Zuyderland Medical Center, Sittard, [17]Neurology, Maasstad Hospital, Rotterdam, [18]Neurology, Rijnstate Hospital, Arnhem, [19]Neurology, VieCuri Medical Center, Venlo, [20]Neurology, Canisius Wilhelmina Hospital, Nijmegen, [21]Neurology, Groene Hart Hospital, Gouda, [22]Neurology, Albert Schweitzer Hospital, Dordrecht, The Netherlands, [23]University at Buffalo, State University of New York, Buffalo, NY, United States, [24]Neurology, Leiden University Medical Center, Leiden, The Netherlands

Background: Many MS patients leave their jobs prematurely, which is known to negatively influence their quality of life. In order to examine risk factors of job loss it is important to focus on the process of job loss. This process may include productivity losses, occurrence of negative work events and an increased use of accommodations. Recent studies support the influence of coping strategies in job loss. Disabled MS patients were found to use more dysfunctional coping strategies than employed MS patients. In order to provide more insight in the process of job loss and related coping strategies, the current study examines the prevalence of negative work events and accommodations in employees with MS, and their associations with coping strategies.
Methods: 97 MS patients with a paid job (77% females; 21-59 years old) completed questionnaires about their work situation, work productivity, coping strategies, demographic characteristics, physical and cognitive functioning, depression, anxiety and fatigue in the context of the MS@Work study. Forward binary logistic regression analyses were conducted to examine predictors of reported negative work events (i.e. reporting/ not reporting negative work events) and reported accommodations (i.e. reporting/not reporting accommodations).
Results: 17% of the MS patients reported one or more negative work events (in particular verbal criticism for errors) and 73% used one or more accommodations at work (in particular flexible scheduling and physical changes to the workplace). The presence of negative work events was associated with a higher use of emotion-focused coping ($p=0.01$; B(SE)= 0.12(0.04)) and more absenteeism ($p=0.07$; B(SE)=0.39(0.21)). The use of work accommodations was related to a higher educational level ($p=0.04$; B(SE)= 0.34(0.17)) and more presenteeism ($p=0.02$; B(SE)=0.54(0.22)). MS patients reporting physical changes to the workplace employed more emotion-focused coping and MS

patients reporting flexible scheduling used a more task-oriented coping style.
Conclusion: Emotion-oriented and task-oriented coping strategies were associated with negative work events and the use of accommodations. Although no causal inferences can be made, this study provides additional evidence for the beneficial effect of a more problem-oriented and less emotion-oriented coping style. It may be useful to incorporate (internet-based) interventions aimed at enhancing adequate coping styles in employees with MS.

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P1325

Patient education for people with multiple sclerosis-associated fatigue: a systematic review

M.J. Wendebourg[1], C. Heesen[1], M. Finlayson[2], B. Meyer[3], J. Pöttgen[1], S. Köpke[4]
[1]University Medical Center Hamburg-Eppendorf (UKE), Center for Molecular Neurobiology (ZMNH), Hamburg, Germany, [2]School of Rehabilitation Therapy, Queen's University, Kingston, ON, Canada, [3]GAIA AG, Hamburg, [4]Nursing Research Unit, Institute of Social Medicine and Epidemiology, University of Lübeck, Lübeck, Germany

Background: Fatigue is a common and disabling symptom related to multiple sclerosis (MS), often causing decreased quality of life, social withdrawal and unemployment. Studies examining the effect of pharmacological interventions demonstrated only minor effects, whereas non-pharmacological interventions as e.g. patient education programs have shown more promising results.
Methods: We performed a systematic review and meta-analysis including randomized controlled trials (RCTs) that evaluated patient education programs for MS-related fatigue. Two authors independently assessed studies for inclusion and performed data extraction. We assessed risk of bias using the Cochrane tool and evidence quality using GRADE. Meta-analyses were performed using generic inverse variance methods in RevMan.
Results: Of 856 citations, 10 RCTs with n=1021 participants met the inclusion criteria. Educational interventions differed in terms of extend, content and method of information provision. Overall positive intervention effects on fatigue severity (weighted mean difference (WMD) -0.43; 95% confidence interval (CI) -0.74 to -0.11; high quality evidence) and fatigue impact (-0.48; -0.82 to -0.15; high quality evidence), but not for depression (-0.35; -0.75 to 0.05) were shown. Four interventions were based on cognitive-behavioral therapy (CBT) approaches. Analysing CBT studies only (n=4) the pooled WMD for fatigue severity was -0.60 (95% CI; -1.08 to -0.11) compared to non-CBT approaches (n=6) (-0.20; 95% CI; -0.60 to -0.19). Furthermore, interventions employing an individual approach seem to reduce fatigue more effectively than group-based approaches (pooled WMD for fatigue severity in face-to-face approaches: -0.80 (95% CI; -1.13 to -0.47) compared to group-based studies with -0.17 (95% CI; -0.39 to 0.05). Follow-up was generally short, with longest follow-up data available for 12 months.
Conclusion: Overall, included studies demonstrated that educational programs and especially CBT-based approaches seem to have a positive effect on reducing fatigue. Since fatigue is thought to be a multidimensional symptom, it should be treated with multidimensional approaches targeting patients' behavior as well as their emotional and mental attitude towards fatigue. However, clinical relevance of treatment effects and long-term effects remain unclear and warrant further work.

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P1326

Is empathy related to work participation, work role functioning and productivity in multiple sclerosis patients?

D.A.M. van Gorp[1,2,3], K. van der Hiele[1,3], M.A.P. Heerings[1], P.J. Jongen[4,5], I. van Lieshout[6], M.F. Reneman[7], J.J.L. van der Klink[8], E.P.J. Arnoldus[9], E.A.C. Beenakker[10], H.M. Bos[11], J.J.J. van Eijk[12], J. Fermont[13], S.T.F.M. Frequin[14], B.M. van Geel[15], G.J.D. Hengstman[16], E. Hoitsma[17], R.M.M. Hupperts[18], J.W.B. Moll[19], J.P. Mostert[20], P.H.M. Pop[21], W.I.M. Verhagen[22], G.A.M. Verheul[23], D. Zemel[24], H.A.M. Middelkoop[3,25], L.H. Visser[2,9]
[1]National Multiple Sclerosis Foundation, Rotterdam, [2]University of Humanistic Studies, Utrecht, [3]Psychology, Section Health,

Medical and Neuropsychology, Leiden University, Leiden, [4]MS4 Research Institute, Nijmegen, [5]Community & Occupational Medicine, University Medical Center Groningen, Groningen, [6]Van Lieshout Arbo Advies, Uden, [7]University Medical Center Groningen, Groningen, [8]Tilburg University, [9]Neurology, Elisabeth-TweeSteden Hospital, Tilburg, [10]Neurology, Medical Center Leeuwarden, Leeuwarden, [11]Neurology, St. Anna Hospital, Geldrop, [12]Neurology, Jeroen Bosch Hospital, 's-Hertogenbosch, [13]Neurology, Amphia Hospital, Breda, [14]Neurology, St. Antonius Hospital, Nieuwegein, [15]Neurology, Medical Center Alkmaar, Alkmaar, [16]Neurology, Catharina Hospital, Eindhoven, [17]Neurology, Alrijne Hospital Leiden, Leiden, [18]Neurology, Zuyderland Medical Center, Sittard, [19]Neurology, Maasstad Hospital, Rotterdam, [20]Neurology, Rijnstate Hospital, Arnhem, [21]Neurology, VieCuri Medical Center, Venlo, [22]Neurology, Canisius Wilhelmina Hospital, Nijmegen, [23]Neurology, Groene Hart Hospital, Gouda, [24]Neurology, Albert Schweitzer Hospital, Dordrecht, [25]Neurology, Leiden University Medical Center, Leiden, The Netherlands

Background: Empathy refers to the ability to understand other persons intentions, predict their behaviour and experience an emotion triggered by their emotion. It allows us to interact with the social world and has been associated with improved labor climate and teamwork. Empathy has a down side as well, considering its associations with Neuroticism and fatigue in professionals caring for suffering people. A few studies have reported reduced degrees of empathy, empathic concern and fantasy in multiple sclerosis (MS) patients. The current study examines relations between empathy and work participation, work role functioning , productivity and other clinical and personal variables in employed relapsing-remitting MS patients.
Methods: In the context of the MS@Work study, 19 unemployed and 148 employed patients with relapsing-remitting MS completed the Baron-Cohen's Empathy Quotient and questionnaires on demographics, work role functioning and productivity, physical and cognitive functioning, fatigue, depression, anxiety, personality and coping. Mann-Whitney U-tests were used to examine group differences in empathy. Correlation analyses and stepwise linear regression analysis were used to examine relations between empathy and work role functioning, productivity, demographic, clinical and personal variables in employed MS patients. The significance level was set at 0.05. We used p< =0.001 for the correlations.
Results: Empathy was, although not statistically significant, lower in unemployed as compared with employed MS patients (U=1059.50, p=.081, r=.14). Empathy was higher in females (U=1409.50, p=.002,) and in patients with a higher educational level (H(7)=17,99, p=.012). We found significant relations between empathy and the personality traits Agreeableness (r_s=.560, p < .001), Conscientiousness (r_s=.287, p< .001) and Extraversion (r_s=.263, p=.001). Empathy did not correlate with work role functioning and productivity. In a stepwise linear regression, controlling for gender and education, the personality trait Agreeableness (β=.50, t(147) = 7.21, p< .001) was positively associated with empathy (R^2=.41, p< .001).
Conclusions: Empathy did not differ significantly between employed and unemployed MS patients. Empathy was not associated with work role functioning and productivity in employed MS patients, but was associated with the personality trait Agreeableness. Longitudinal studies are needed to examine further relations between empathy and employment.

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P1327

Randomized, blinded, controlled study to assess the efficacy of a cognitive training program in patients with multiple sclerosis (MS)

M.Y. Pérez Martín[1], M. González Platas[1], P. Eguía del Río[2], A. Jiménez Sosa[3]
[1]Service of Neurology, Complejo Hospitalario Universitario de Canarias, La Laguna, [2]Service of Neurology, Hospital Doctor José Molina Orosa, Arrecife, [3]Unit of Research, Complejo Hospitalario Universitario de Canarias, La Laguna, Spain

Background: Cognitive impairment is a common symptom in MS and can have a substantial impact on quality of life. The evidence on the effectiveness of neuropsychological rehabilitation is still limited, but current data suggest that computer-assisted cognitive training can improve cognitive performance.
Objectives: Evaluate the effectiveness of a computer-aided cognitive training with autonomous work at home to improve cognitive performance in patients with MS.
Method: 62 patients with MS and mild cognitive impairment (41 women; age: 43 (sd: 9.34); disease duration and 10.51 (sd: 7.71) and EDSS 2.0 (median)) were randomized to intervention (n = 30) or no (Control n = 32) group. Neuropsychological assessment

pre and post treatment with the Brief Battery of Neuropsychological Test (BRB-N). Multidomain Rehabilitation (memory, attention / processing speed and executive functions) was performed in 12 sessions (1 / week) for 1 hour and working paper / pencil at home.
Results: Controlling for age, schooling and baseline performance, the treatment group showed significant improvement in verbal memory variables (LTS: $F = 10,418$; $p = 0.002$), F = CLTR and SRT_LP: $F = 20,514$ and $F = 17.002$; $p < 0.001$), processing speed (SDMT: $F = 4.886$; $p = 0.032$), working memory (PASAT: $F = 19.154$, $p < 0.001$) and phonetic fluency (COWAT: $F = 4.339$; $p = 0.042$). The control group showed no improvement in any of the neuropsychological functions evaluated.
Discussion: The computer-assisted cognitive training and combined with reinforcement work at home is effective in promoting neuropsychological functions most commonly affected in MS patients.

Disclosure

Nothing to disclose

P1328

Facilitating the use of an alternative pointing system for patients with Multiple Sclerosis with motor and cognitive impairments through procedural learning

N. Moyano[1], G. Delrue[2], E. Gester[3], D. Guillaume[1], V. Delvaux[2], P. Maquet[4]
[1]CNRF, Fraiture-en-Condroz, [2]MS Group - Neurology, CHU de Liège, [3]Université de Liège, [4]Neurology, CHU de Liège, Liège, Belgium

Multiple Sclerosis (MS) is a disease with multiple symptoms. The motor symptoms can become disabling and severely restrict patients autonomy. New technologies can therefore become a window to the outside world. But this access can be hindered by the presence of motor/sensory disorders of the upper limbs making use of a mouse difficult. Different tools have been developed to overcome these difficulties, but that doesn't solve the problem of how to use these devices, especially for patients with cognitive impairments. The aim of this study is to improve the quality of life of MS patients (with motor/sensory disorders of the upper limb with or without cognitive impairments) by the evaluation of the applicability of using an alternative pointing system based on the detection of head movements via webcam (eViacam) with theoretically based learning techniques. We applied a procedural learning technique on a "constant mode" (the learning modalities does not vary between sessions, resulting in less transferability to other activities but with a possible learning for people with major cognitive impairments). 17 patients were recruited and, after a neuropsychological evaluation, they had to perform a task on a computerized battery (Batterie d'Attention William-Lennox (BAWL)) and write a sentence using the alternative pointing system. Two learning conditions were proposed: "the tracking task" where patients had to move a pointer to squares on the screen (experimental condition: constant mode) or working on the software "paint"© without specific instructions (control condition) for 4 weeks (for each condition). The results showed that there was a significant learning effect on median reaction times (0.008) of the BAWL test and on the time needed to write a sentence (0.025) regardless of the learning condition. Then we used the Symbol Digit Modality Test to evaluate the degree of cognitive impairments. Non parametrical tests showed that there was a significant learning effect on median reaction times of the BAWL test for patients with cognitive impairments but only for those who were in the experimental condition. There was also significant effect on the time needed to write a sentence no matter the condition. However, note that it has been impossible for some patients with major cognitive impairments to use "paint"©. These results should encourage therapists to teach their patients to use these systems as adjunct to the use of conventional computer tools.

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Exercise

P1329

Attenuated salivary cortisol and cardiovascular-autonomic response to aerobic exercise in people with multiple sclerosis

M.S. Pedersen[1], U. Dalgas[2], J.S. Kesselring[3], J. Bansi[4]
[1]Sports Science, Aarhus University, Århus C, [2]Sports Science, Aarhus University, Aarhus C, Denmark, [3]Neurology, [4]Sports Therapy, Rehabilitation Centre Valens, Valens, Switzerland

Purpose: To compare salivary cortisol, blood lactate levels and cardiovascular function in the acute recovery phase following different exercise modalities in persons with multiple sclerosis (MS) to healthy matched controls (CON).
Methods: 15 persons with MS and 17 CON were enrolled and matched for age, weight and BMI. All participants performed three different cycling exercise modalities, on separate days. The supervised exercise bouts consisted of; a) Cardio-pulmonary exercise test (CPET) to voluntary exhaustion; b) 30 min continuous cycling at 70-75% of peak heart rate (HR peak) and c) High Intensity Interval (HIT) session including 4*5 min at > 80% of HRpeak with 2 min between the intervals. Oxygen consumption (VO2), heart rate recovery (HRR), lactate and salivary cortisol levels were determined prior to each exercise bout, and were continuously assessed for 10 min after each bout. Lactate and Salivary samples were additionally collected 30 and 60 min post exercise.
Results: Resting HR, VO2 and lactate levels were significantly higher in the MS group (75bpm; 5.2+-1.13ml/kg/min; 2.2+-0.54mmol/l) compared to CON (62bpm; 4.1+-1.17ml/kg/min; 1.4+-0.44mmol/l ($p< 0.05$). CPET showed that VO2peak and peak lactate were significantly lower in MS (MS: 1877+-591.0ml/min; 7.1+-3.4mmol/l vs CON: 2657+-773.0ml/min, 9.7+-1.8mmol/l ; $p< 0.05$)VO2 and HR recovery was slowed in MS 60s, 120s and 5min post exercise ($p< 0.05$). Finally, there was a significant group x time interaction in the cortisol response to exercise showing attenuated post exercise cortisol response in MS

to all timepoints ($p < 0.05$), but with no difference in resting cortisol levels.
Conclusion: Persons with MS have higher resting HR, VO2 and lactate levels than healthy age matched controls. In addition, persons with MS have prolonged VO2 and heart rate recovery after different aerobic exercise modalities as well as an attenuated cortisol response.

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P1330

Exercise: finding the good in inflammation using models of MS

B.T. Lund, A.M. Levy, G. Agadjanyan, E.E. Kelland
Neurology, University of Southern California, Los Angeles, CA, United States

Background: Recent studies have shown that the brain is capable of recovering from injury and that this recovery can be enhanced with exercise and environmental stimuli which are new to the individual. Exercise has multiple biological effects in the brain and on the peripheral immune system, both of which are involved in the disease processes that we see in MS. Exercise is associated with neurogenesis and synaptogenesis, and can inhibit inflammatory processes. We assessed the mechanisms of exercise intervention in the early stages of demyelinating disease using the experimental allergic encephalomyelitis (EAE) model of MS. Assessing the effect of exercise in models of MS allowed us to remove the confounds of concomitant medications and lifestyles.
Methods: Our experimental approach evaluated the effects of exercise on clinical course, pathological hallmarks of disease, and adaptive and innate immune responses. We assessed the effect of exercise intervention, in the form of daily treadmill running, in a relapsing-remitting model (PLP-EAE: PLP inoculation in SJL/J mice) and a more chronic progressive model (MOG-EAE: MOG inoculation in C57BL6/J mice). Exercise was started only after recovery from the acute phase in PLP-EAE or after mice showed accrued disability (>1.0) in MOG-EAE. Clinical effects were compared to control EAE littermates subjected to the same environmental stimuli but which did not undergo an exercise regimen.
Results: Exercise was associated with almost complete attenuation of clinical disease in the PLP-EAE model. In MOG-EAE, exercise was associated with a dramatic reduction in clinical disease, though these mice still accrued mild disability. Analyses of spinal cord tissue showed that there was a significant reduction in disease pathology in exercised mice: reduced lesion number, lesion volume and inflammatory infiltrate. Exercise was also associated with significant changes in the immune response: reduced antigen-specific (PLP or MOG) proliferative responses, increased secretion of anti-inflammatory cytokines, reduction in typical pro-inflammatory cytokines, and changes in the mononuclear cells recruited to the CNS both at early and late stages of exercise intervention.
Conclusions: Exercise is associated with a beneficial, neuroprotective, anti-inflammatory response in animal models of demyelinating disease. These data suggest that appropriate exercise intervention may be a useful approach to the treatment of early stages MS.

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P1331

Objectively measured physical activity and sedentary behaviour profiles of people moderately affected by Multiple Sclerosis

E.H. Coulter[1], J. Freeman[2], L. Miller[3], B. Weller[4], A. Mcconnachie[1], P.G. Mattiosn[3], O. Wu[1], L. Paul[1]
[1]University of Glasgow, Glasgow, [2]Plymouth University, Plymouth, [3]NHS Ayrshire & Arran, Irvine, [4]University of Edinburgh, Edinburgh, United Kingdom

Introduction: Remaining physically active is important to maintain functional ability, independence, quality of life and reducing the incidence of co-morbid disease. People with Multiple Sclerosis (MS) may find it difficult to engage in Physical Activity (PA). Previous research in MS has focussed on PA in MS however sedentary behaviour (SB) is associated with increased cardiovascular risk in healthy and other clinical populations.
Objective: To assess the PA and SB profiles of people moderately affected by MS with respect to disability level.
Methods: Data is reported for eighty-three people with MS who were taking part in a study on web-based physiotherapy (mean age 55.7±9.9 years, 63 female). They were included if they were over 18 years old, diagnosed with MS, EDSS 4.0-6.5, not currently exercising $\geqslant$ 30 minutes, twice per week. Participants were excluded if they had poor cognitive function (Mini Mental State Examination score < 24); had a relapse within the last three months; had a significant co-morbidity for which PA/exercise is contra-indicated. PA was measured using the activPAL3 activity monitor (PAL Technologies, Glasgow, Scotland), attached to the strongest or dominant leg using a waterproof dressing and worn continuously for one week.
Results: Overall participants accumulated 4,444±2,597 [67-13,920] steps/day, 54±15 [21-94] Sit-to-Stand (STS) transitions, were upright for 5.1±2.2 hours/day [standing = 4.0±1.9, stepping 1.1±0.6 hours/day] and sedentary for 18.9±2.2 hours/day. Due to the small number of participants with EDSS 4-5.5 statistical analysis was not possible however between EDSS levels 6.0 (n=46) and 6.5 (n=18) there were significant differences in steps taken (4,884±2,496 and 1,769±1,640 steps/day respectively; $p \leqslant 0.001$), upright time (5.5±2.3 and 3.5±1.9 hours/day; $p=0.002$), standing time (4.3±2.0 and 2.9±1.6 hours/day; $p=0.014$), walking time (1.2±0.6 and 0.6±0.5 hours/day; $p \leqslant 0.001$) and sedentary time (18.5±2.3 and 20.5±1.9 hours/day; $p=0.002$).
Conclusion: The significantly lower PA, and higher SB in those with EDSS 6.5 compared to 6.0 suggests that this is a transition point for people with MS. Sedentary time in those with EDSS

6.5 was similar to our previous work in stroke survivors (20.4 ± 2.7 h; Paul et al (2015). Further research is required to determine the effectiveness of rehabilitation strategies to improve/maintain PA and reduce SB in those with MS.

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P1332

Changes in resting-state functional connectivity of the caudate following resistance exercise training in persons with MS: A preliminary report

N. Akbar, B.M. Sandroff, L.B. Strober, G.R. Wylie, J. Deluca, H. Genova
Neuropsychology and Neuroscience Laboratory, Kessler Foundation, West Orange, NJ, United States

Background: A striatal-thalamic-frontal network involving the caudate, in particular, has been implicated as a possible neural basis of cognitive fatigue in persons with MS. Furthermore, exercise training has been identified as a rehabilitative approach for mitigating MS-related fatigue. However, the effects of exercise training on neural networks underlying cognitive fatigue in MS are unknown.
Objective: To determine the influence of resistance exercise training on changes in resting-state functional connectivity (FC) of the caudate.
Methods: Ten highly-fatigued persons with MS (n=7 RRMS, mean disease duration= 14.7 years, mean age=48, 10 female) were randomly assigned to either a 4-month home-based resistance exercise training (n=6) or active control (n=4) condition. The resistance exercise training condition involved progressive strength training of the upper and lower extremities, and the control condition involved stretching activities. Fatigue was evaluated using the Modified Fatigue Impact Scale (MFIS), physical activity levels were quantified using the Godin Leisure-Time Exercise Questionnaire (GLTEQ), and FC was measured using resting-state functional MRI seed-based correlations using the caudate as the seed region.
Results: A main effect of time, independent of group, was demonstrated with respect to post-training reduction on the MFIS cognitive fatigue subscale ($F=13.02$, $p=.007$), and increase in physical activity level ($F=8.34$, $p=.023$). The resistance exercise training group demonstrated higher FC of the caudate with the left secondary somatosensory cortex (group×time interaction: $F=71.97$, $p< .001$), and lower FC of the caudate with the bilateral primary visual cortex ($F=22.84$, $p=.002$) and left premotor cortex ($F=35.26$, $p=.001$) post-training compared to the stretching group. There was a statistically significant correlation between increased FC of the caudate with the left secondary somatosensory cortex and increased physical activity level ($r_s=.617$, $p=.039$).
Conclusions: These preliminary results suggest a generalized effect of physical activity on fatigue. However, resistance exercise training might selectively affect changes in FC in regions important for MS-related fatigue. Such preliminary data are exciting in that they provide first time evidence of a possible neural mechanism underlying the beneficial effects of exercise on fatigue in MS. Importantly, larger sample sizes will be required in order to better understand this relationship.

Disclosure

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A six-week intensive treadmill training improves walking ability in MS patients with moderate disability

M.A. Biancu[1], A. Peruzzi[2,3], R. Piredda[4], I.R. Zarbo[4], A. Cereatti[2,3], A. Mirelman[5], U. Della Croce[2,3]
[1]Department of Clinical and Experimental Medicine, Sassari, [2]POLCOMING Department, [3]Interuniversity Centre of Bioengineering of the Human Neuromusculoskeletal System, [4]Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy, [5]Department of Neurology, Laboratory for Gait Analysis & Neurodynamics, Movement Disorders Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background: Multiple sclerosis (MS) is a chronic disease affecting young adults and leading to progressive disability. Motor rehabilitation strategies in MS patients are heterogeneous and the optimal duration and intensity of physical treatment are not standardized.
Rationale and aims: Abnormalities in gait biomechanics and endurance are common in MS patients; this study has been designed to test the effect of a six-week treadmill training in modifying gait parameters and improving patients' walking speed and endurance.
Methods: 44 subjects diagnosed with MS having an EDSS score between 3 and 5.5 have been enrolled. Treadmill training was provided in 18 sessions (three times perweek for six weeks), each lasting 45 minutes. In the first session, the treadmill speed was set at 80% of the participant's overground gait speed, obtained from the baseline result of the ten-meter walk test (10mwt). Each week the treadmill speed was increased by 10%. Before and after the intervention, participants were evaluated with: neurological examination, gait analysis, functional motor tests (10mwt, six-minutes walk test, timed-up-and-go test, four-square step test), self-assessed measurement of fatigue (fatigue severity scale) and health-related quality of life (MSQoL-54).
Results: ; six participants did not complete the study protocol. Statistical analysis performed on the remaining 38 participants (25 females, 13 males)demonstrated a significant improvement ($p< 0.05$) of the gait spatial-temporal parameters (gait speed, cadence, stride time, stride length) and motor tests. A significant improvement was also observed in self-perception of health

status, assessed with MSQoL-54 ($p < 0.01$ for both physical and mental health component). Perception of fatigue did not change significantly.
Conclusions: Our study demonstrates that a six-week rehabilitation protocol is effective in improving walking abilities in MS patients with moderate disability. Further studies are needed for determining the duration of the described beneficial effect over time.
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P1334

The effect of Mediterranean diet and exercise as a complementary therapy in fatigue of patients with relapsing remitting MS (RRMS)

M. Abolhasani[1], S. Razeghi Jahromi[2], M.A. Sahraian[1]
[1]Tehran University of Medical Sciences, MS Research Center, Neuroscience Institute, [2]Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran

Background: Multiple sclerosis(MS) is an immune-mediated disease of the central nervous system that characterised by disabling symptoms of which excessive fatigue is the most frequent. Fatigue is reported as the
most invalidating symptom in MS. Various mechanisms directly and indirectly related to the disease and physical inactivity
have been reported to contribute to the fatigue. Exercise therapy and change in a regular diet can induce physiological and psychological effects that
may counter these mechanisms and reduce fatigue in MS.
Methods: 70RRMS patients (age:26-41 years) with Expanded Disability Status Scale (EDSS) less than 5.5 were enrolled. Control group (n= 35) received isocaloric Mediterranean diet and intervention group received isocaloric Mediterranean dietary plus an exercise program consist of a stretching exercise program every days and 3 days strengthening program for large muscle groups in upper and lower limbs. The patients visited every three months throughout the study. The usual dietary intake and physical activity was assessed using 3-day food recall and International Physical Activity Questionnaire (IPAQ) respectively. FSS(fatigue severity scale) was evaluated at the first and the end of 6 months after beginning of the study. The adherence to Mediterranean diet and exercise was assessed using Mediterranean dietary score based on FFQ and a log book respectively.
The scores of two groups were then compared using statistical tests such as repeated measures ANOVA test.
Results: The results indicated significant changes in the intervention group in comparison to the control group in FSS: -6.9, P-value = 0.02,
Conclusion: Mediterranean diet plus exercise might have beneficial effects as a complementary therapy in reduction of fatigue in RRMS patients with EDSS< 5.5.

Disclosure

The authors declare that they have no competing interests.

P1335

Use of pedometer based internet mediated intervention for adults with multiple sclerosis to increase physical activity level

K. Novotna, R. Větrovská
Neurological Department, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic

Background: There is evidence that people with multiple sclerosis have decreased physical activity level comparing to healthy peers. With worsening of multiple sclerosis symptoms the level of physical aktivity further decrease. In this study we examined the feasibility and effectivity of a motivation program that combines a pedometer with a website to increase walking.
Methods: 42 persons with stable multiple sclerosis (MS) wore a pedometer and used website for 100 days. They uploaded step-count data to the server using their home computer. The website provided step step-count feedback, education and motivation kontent. Subjects were assessed with clinical used walking tests (Timed 25 foot walk test, 2 and 6 minute walk test, Multiple Sclerosis Walking Scale-MSWS12) at baseline and after completed 100 days in study. Level of physical activity and fatigue were measured by International Physical Activity Questionnaire-short version, Godin Physical Activity Questionnaire, Fatigue Severity Scale and MFIS.
Results: Most participanst were female 80% (n=34), mean age 39 years (SD 11 years), median EDSS 2,5 (range 0-5), mean disasese duration 10,8 years (SD 8,47 years), 38% (n=16) reported some gait impairment. 50% of participants (n=21) have high level of physical activity at baseline, 36% (n=15) reported minimal physical activity level at baseline and 14% (n=6) were inactive at baseline. One third of participants 33,3% (n=14) were able to increase thein physical activity level during this program. Mean day step count was 12 930 steps (SD 7124).71% reported no problem using the pedometer and website, 87% participants enjoyed this motivation tool to increase physical activity.
Conclusions: The use of website and pedometer was feasible and all participants enjoyed this way to monitor thein physical activity level. Some of participants were able with increase their daily walking. In sum, our findings indicie that a facilitated intervention that uses a pedometer and the internet may help to increase physical activity level among some MS patients, at least in the short term.

Disclosure

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