ECTRIMS 2022

Congress Report | Imaging and non-imaging biomarkers

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

26 – 28 October 2022
Amsterdam, The Netherlands

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Day 1

Imaging and non-imaging biomarkers Session 1
Hot Topic 3: Novel body fluid biomarkers

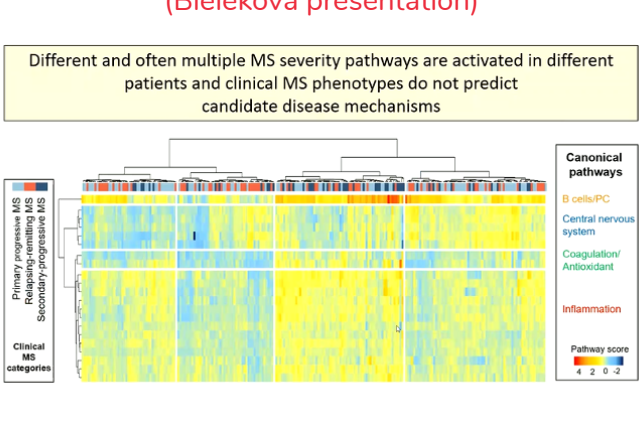
Wednesday, 26th October 10:00 – 11:00 CEST
Speakers: Bibiana Bielekova, Chalotte Teunissen and Nicolas Fissolo
Chairs: Claire Bridel and Tanuja Chitnis

Conclusion: Compartmentalised inflammation associated with MS requires the development of anti-inflammatory drugs that penetrate the central nervous system. As clinical MS types do not predict disease mechanisms, there is a need for drug development guided by cerebrospinal fluid (CSF) biomarkers. Proteomics technologies can identify novel biomarkers for MS treatment response and disease progression in blood. Some CSF biomarkers are associated with progressive forms of MS, and could help predict long-term disability progression. However, for most biomarkers, future validation studies are needed.

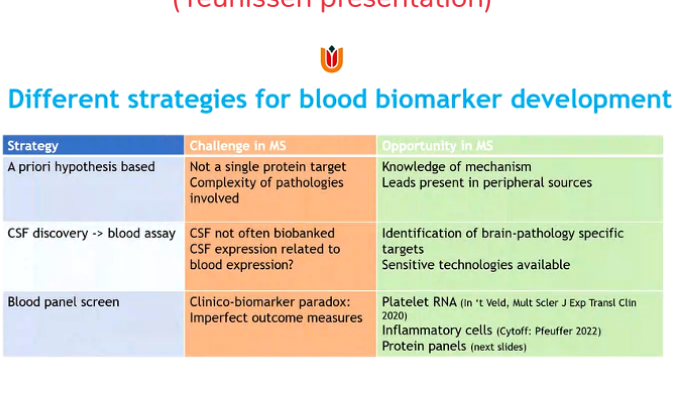
What's New: Current MS treatments have inadequate efficacy for most patients with MS because they do not sufficiently inhibit non-lesional MS activity (also called progression-independent of relapse activity, or PIRA). CSF biomarkers show that inflammation and fibrosis-related pathways increase in longitudinal samples from untreated MS patients (derived from the placebo arms of progressive MS trials). Different and often multiple MS severity pathways are activated in different patients and clinical MS phenotypes do not predict disease mechanisms. A study found that the sVCAM-1 biomarker decreases upon treatment with natalizumab. A proteomics analysis found that, after treatment with natalizumab, 56 proteins were upregulated and 227 proteins downregulated in serum. Fifty proteins were differentially expressed overtime. Some candidate fluid biomarkers for progressive forms of MS have been identified, including serine protease inhibitor family A member 3 (SERPINA3), chitinase 3-like 1 and 2 (CHI3L1 and CHI3L2) and neurofilament light chain (NfL). SERPINA3 levels are increased in CSF in patients with progressive MS. CSF SERPINA 3 levels correlate with CSF NfL levels in patients with progressive MS. CHI3L1 levels in CSF are higher in progressive MS than in relapsing-remitting MS (RRMS). CHI3L2 in CSF could potentially discriminate between high and low disability progression in progressive MS patients after long-term follow-up. Serum NfL levels predict long-term disability progression in patients with progressive MS.

Background: Biomarkers are essential to understand disease progression and treatment response. They can provide critical insights on the biology of the disease. In MS there are some biomarkers that can help stratify patients in trials. Although there are promising biomarkers of disease activity and treatment response for RRMS, there is a lack of sensitive biomarkers for progressive forms of MS. Biomarker discovery can be hypothesis-driven, based on proteomics of CSF or blood, or based on blood panel screens, among other strategies.

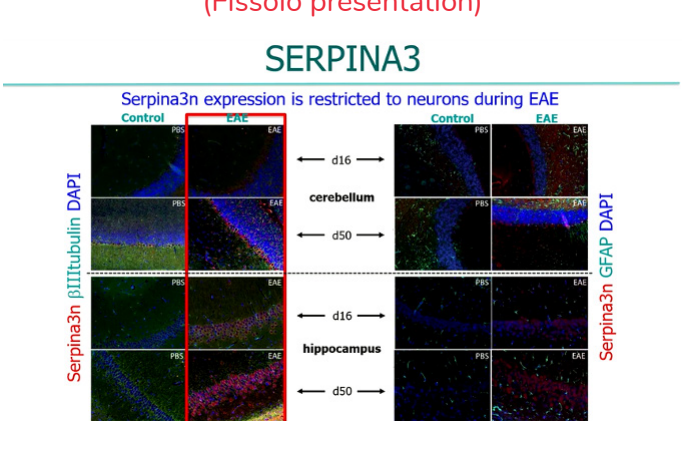
(Bielekova presentation)



(Teunissen presentation)



(Fissolo presentation)



Imaging and non-imaging biomarkers Session 2
Free Communications 1: Neurobiology of MS

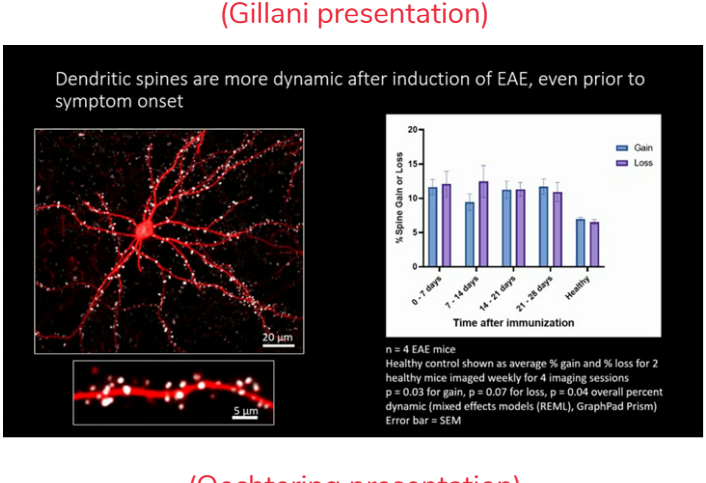
Wednesday, 26th October 10:00 – 11:00 CEST
Speakers: Rebecca Gillani, Sophia Schwarz, Johanna Oechtering, Michael Dietrich, and Christopher Hemond
Chairs: Marcin Mycko and Luisa María Villar

Conclusion: Excitatory synapses maintain the ability to form structurally normal synapses in encephalomyelitis (EAE). In another study, a large-scale atlas of optic neuritis in MS has helped decipher cell type- and lesion area-specific patterns underlying white matter demyelination, opening new strategies to address progressive white matter demyelination. MS progression beyond the currently known markers (e.g. GFAP) could be evaluated by novel biochemical serum analysis. A study showed that flecainide and safinamide attenuate EAE and degeneration of inner retinal layers, showing a protective effect in chronic and secondary progressive EAE models. The Epstein–Barr Virus (EBV)-specific CD8 T-cell responses are associated with greater MS disability and brain tissue loss, independent of age, suggesting that the immune response involving EBV reactivation may be clinically relevant in MS.

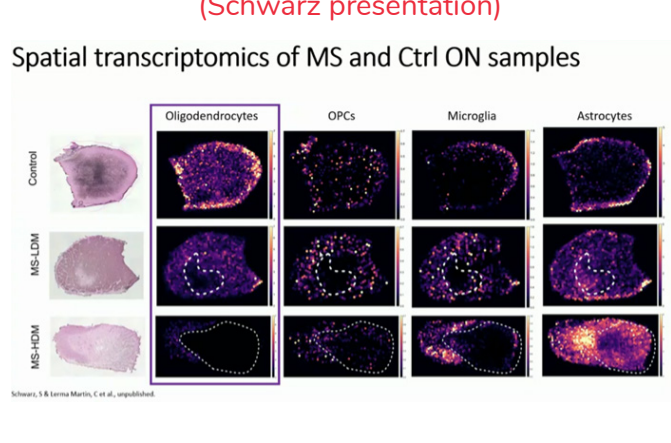
What's New: A study evaluated the dynamics of excitatory synapsis in an experimental autoimmune EAE mouse model. The results showed that dendritic spines are more dynamic (increased turnover) after induction of EAE, even prior to symptom onset. The study also found that structurally normal excitatory synapses are maintained in EAE. Another study analysed optic nerve tissue in MS with single nucleus RNA sequencing, spatial transcriptomics and histological assessment. That study found that there were cell type- and lesion area-specific patterns of inflammatory demyelination, with specific subtypes of astrocytes in the lesion rim, suggesting a more complex function for astrocytes than just forming a sclerotic scar. Also, there was tissue preconditioning by enrichment of complement factors. In addition to events occurring locally at the lesion, the study also detected preferential loss of axonal subsets leading to distant retinal ganglion cell pathology. A proteomics analysis of serum biomarkers reflecting MS disease progression detected several novel proteins (e.g. AFF, NfL, GFAP, VCAN and CXCL13) that could serve this purpose. An animal model study of experimental autoimmune EAE investigated the sodium channel blocker safinamide and flecainide and the MAO-B inhibitor rasagiline to distinguish whether the beneficial effects of blockade of Na+ channels are due to channel blocking or MAO-B inhibition. The results showed that safinamide and flecainide improved the clinical outcomes, reduced retinal tissue degeneration and improved visual function, and that these effects were due to NA+ channel blocking. Rasagiline had no beneficial effects. A prospective, cross-sectional observational study showed that the CD8+-mediated EBV lytic response is dysregulated in MS.

Background: Neurodegeneration drives disability progression in MS, and its characteristic feature is widespread excitatory synapse loss. Neurodegeneration and demyelination along the anterior visual pathway are key features of chronic MS, and optic neuritis is a common early symptom of the disease (a presenting symptom in 25% of patients). Disease progression in MS is mostly described quantitatively, and biochemical signs in serum could be relevant to assess patient care and drug development. Although EBV is a necessary but insufficient environmental factor in MS pathogenesis, as EBV infection always precedes MS, the mechanisms involved remain unclear.

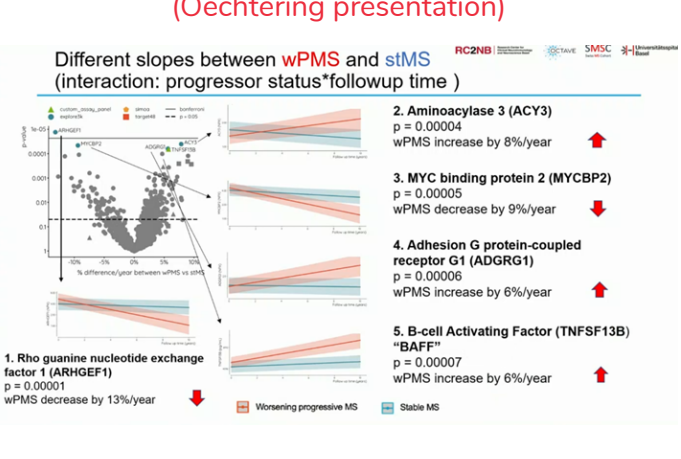
(Gillani presentation)



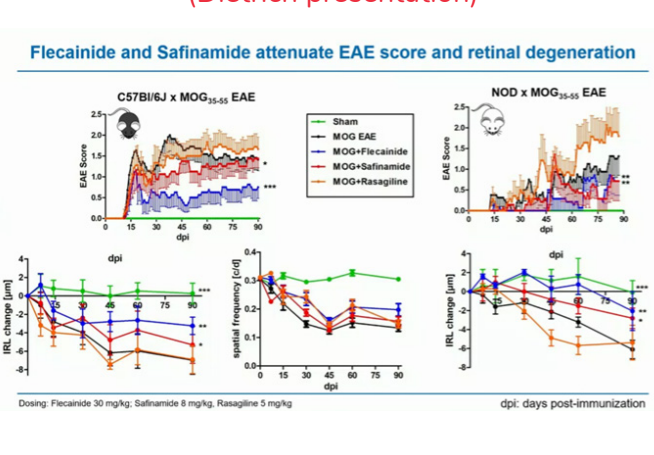
(Schwarz presentation)



(Oechtering presentation)



(Dietrich presentation)



Imaging and non-imaging biomarkers Session 3
Scientific Session 2: A network disease

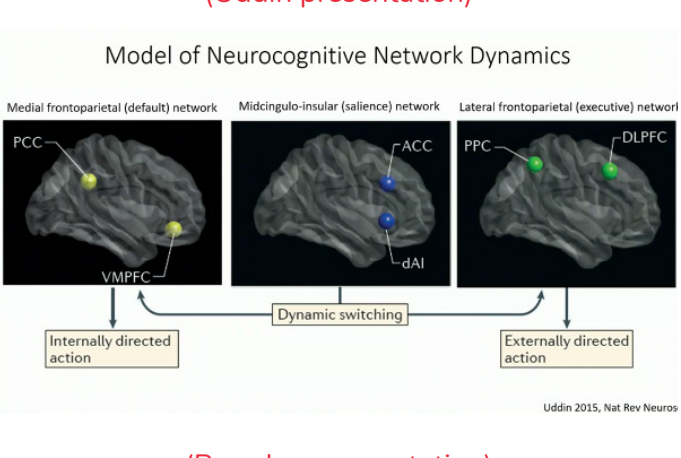
Wednesday, 26th October 14:30 – 16:00 CEST
Speakers: Lucina Uddin, Menno Schoonheim, Giuseppe Pontillo, Carmen Tur, Tommy Broeders, Elisa Colato
Chairs: Aurelie Ruet, Declan Chard

Conclusion: Dynamic functional connectivity studies show the relationship between brain dynamics and flexible cognition. These approaches show atypical patterns of brain dynamics in neurodevelopmental disorders characterised by cognitive inflexibility, such as autism. In MS, network collapse leads to clinical impairment but there is uncertainty as to why some networks collapse sooner than others, and if this can be predicted and treated. Multilayer modelling integrating different magnetic resonance imaging (MRI) modalities can reveal altered brain connectivity in MS. Models based on MRI and convolutional neural networks (CNNs) can be used to predict disability level in MS patients. Also novel models based on longitudinal network measurements can be used to predict disability and treatment effects.

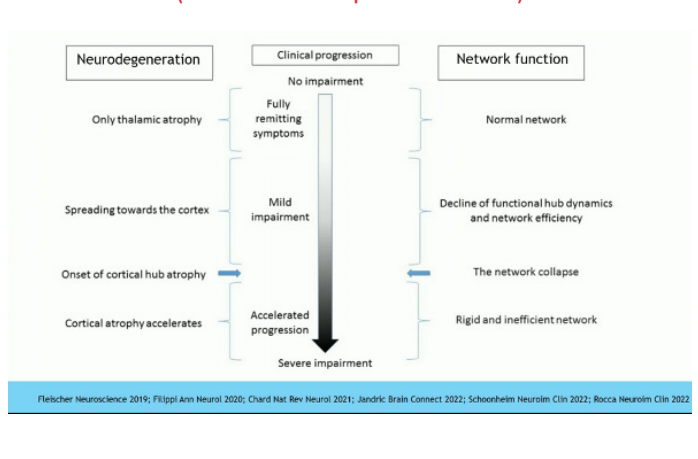
What's New: There is a great variability in brain regions involved in the networks allowing flexible behaviour. The frequency of activation patterns in networks change across the lifespan, and brain state transitions support cognitive flexibility in different ways at different ages. Connectivity models show that active brain regions are also highly variable among individuals. Greater cognitive flexibility is associated with the propensity to occupy more frequently occurring brain states. Neurodegeneration in MS starts in the thalamus and progresses towards the cortex. In early stages, initial thalamic atrophy can be compensated by network re-routing, and clinical impairment is low. In later stages of MS, network efficiency is lost, there is hub overload and re-routing is no longer viable, leading to network collapse and MS progression. When looking at multilayer networks with multimodal MRI, disruption of core-periphery network structures could be a potential new biomarker for MS-related cognitive changes. An artificial intelligence model was developed to predict patient prognosis in MS through the combination of MRI and CNNs. The model showed excellent discrimination of MS patients according to disability level. The study found that the key regions of the brain to discriminate between low and moderate disability were the frontal cortex and the cerebellum. In MS the dynamic switching between connectivity states decreases, and this could lead to a higher energy requirement to change network organisation. Imaging data from clinical trials was used to develop a predictive model for grey matter structural network changes. These network changes were shown to differ between MS phenotypes and to be associated with disability and treatment effects.

Background: Network neuroscience studies can help us understand brain responses to complex cognitive tasks. Network neuroscience has shown that cognitive flexibility involves coordination among brain regions supporting executive function. Sliding window analysis can show how the brain traverses through different brain states. This approach allows the calculation of the frequency of different brain states. MS is a network disorder in which lesions accumulate in the brain causing disconnection of various regions in the brain. Brain networks in MS have been measured using structural, diffusion or resting-state functional MRI. Dysfunctional networks leading to cognitive impairment in MS could be caused by more energetic costly re-wiring of the network. Longitudinal MRI measures can be used to study network progression and neurodegeneration in MS.

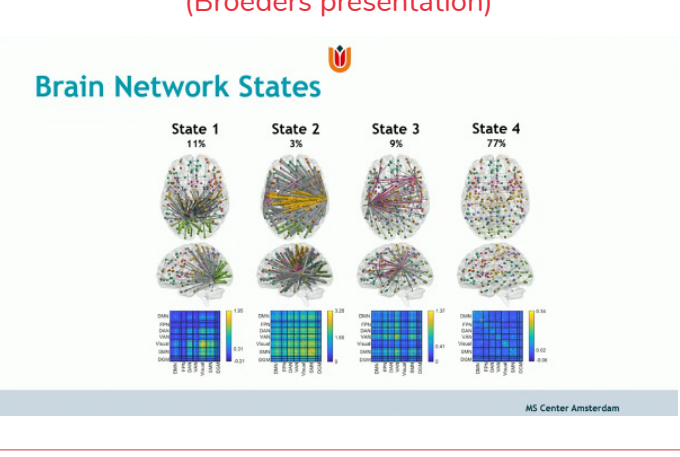
(Uddin presentation)



(Schoonheim presentation)



(Broeders presentation)



Imaging and non-imaging biomarkers Session 4
Scientific Session 4: Novel modelling approaches

Wednesday, 26th October 14:30 – 16:00 CEST
Speakers: Claudia Chien, Arman Eshaghi, Hajer Karoui, Lars Lande Skattebøl, Samantha Noteboom, Rosa Cortese
Chairs: Marco Battaglini, Douglas L Arnold

Conclusion: Machine learning (ML) and deep learning (DL) models using large data sets can be applied in MS research; however, more investigations are required into possible bias and interpretation, and should be approached by multidisciplinary teams. A challenge for the future is to use artificial intelligence (AI) to predict which patients will recover best. Prognostic modelling is still in its infancy, and there is a lengthy path to clinical use. Randomized controlled trials are needed to apply AI into clinical practice. DL models can be ideal tools to process complex imaging data and to assess cortical lesions in clinical care and research. An integration of multimodal data extraction, and data from raw images and the AI models, will be necessary to address future relevant research questions.

What's New: MS subtypes have been identified using a combination of ML and magnetic resonance imaging (MRI) data, which can then be used to predict clinical outcomes. Partitioning features used in ML models can be necessary when using multimodal data. Current research focuses on the use of deep learning algorithms to predict disease activity.

The application of an AI model to the progression of MS independent of relapses has provided insights on the role of cortical atrophy. A model used for data-driven reclassification of patients into subtypes using MRI measures found that staging was not associated with disease length. Also, the model found that immunological features were associated with NAWM-led and cortex-led subtypes.

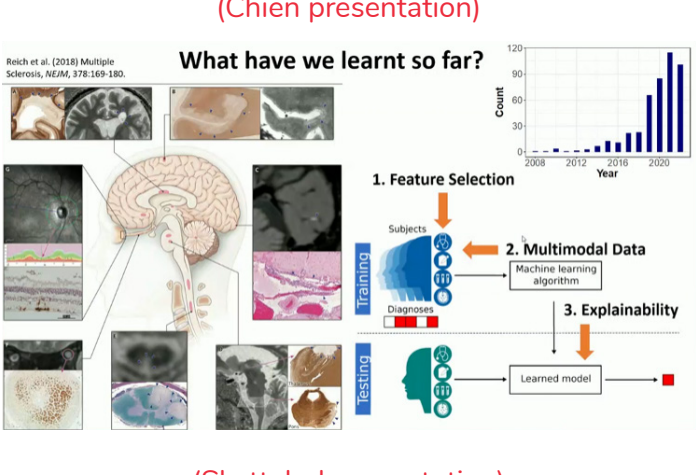
ML and DL models were developed in a study modelling brain age in MS. Both ML and DL models showed significant associations for increased brain age with higher Expanded Disabilities Status Scale (EDSS) and disease duration.

ML models were used in a study to evaluate cortical lesion detection by MRI, especially the double inversion recovery and phase-sensitive inversion recovery types. ML generated reliable results even in a multi-centre setting and good results between-reader and between-centre interpretative agreement.

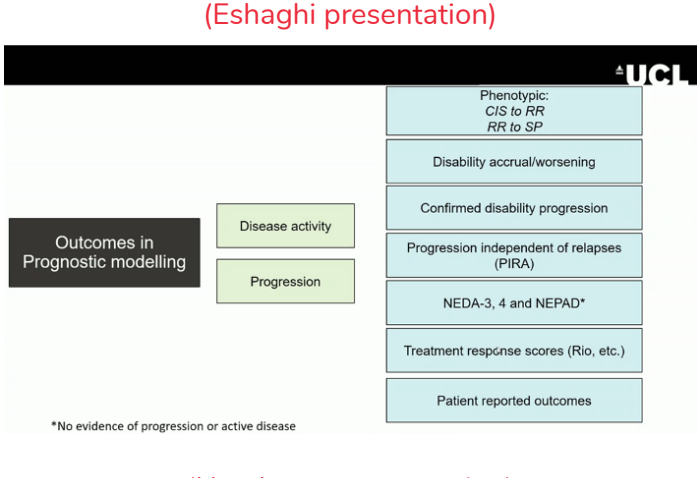
The patterns of grey matter atrophy in a cohort of MS, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) and aquaporin-4 antibody neuromyelitis optical spectrum disorder (AQP4+NMOSD), and their relationship with white matter lesions, was investigated. The research found no association between white matter lesions and grey matter atrophy in AQP4+NMOSD. However, patterns of grey matter atrophy in the temporal and occipital cortex seemed prominent in MOGAD and AQP4+NMOSD, respectively. A relationship between regional atrophy and white matter lesions was observed in MOGAD and relapsing–remitting MS.

Background: ML applied to MS has greatly expanded in recent years to predict disease states or phenotypes of disability. However, the choice of features and models can be challenging. Models can help in understanding and monitoring the disease, and in diagnosis and prognosis. However, clinical MS subtypes often overlap, leading to poor models and poor treatment assignments. Brain age, which is a calculated estimate from time-dependent morphological changes based on structural MRI data, can be altered in MS. Cortical lesions are a pathological hallmark of MS and is related to disability and cognition decline, but their visualisation by MRI is challenging. Recently, ML has been introduced to assess lesion assessment in multi-centre studies.

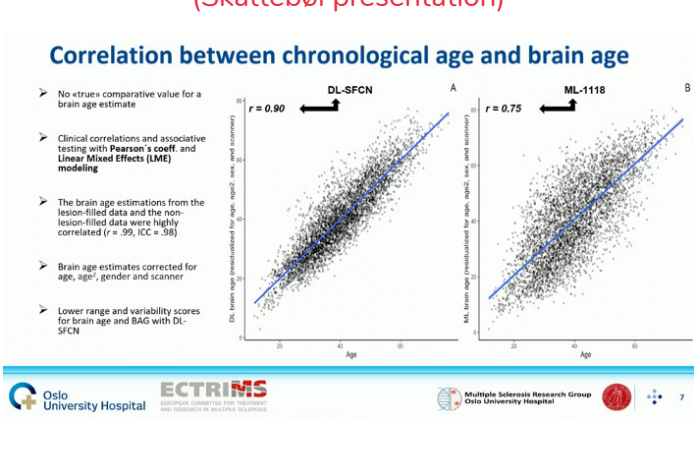
(Chien presentation)



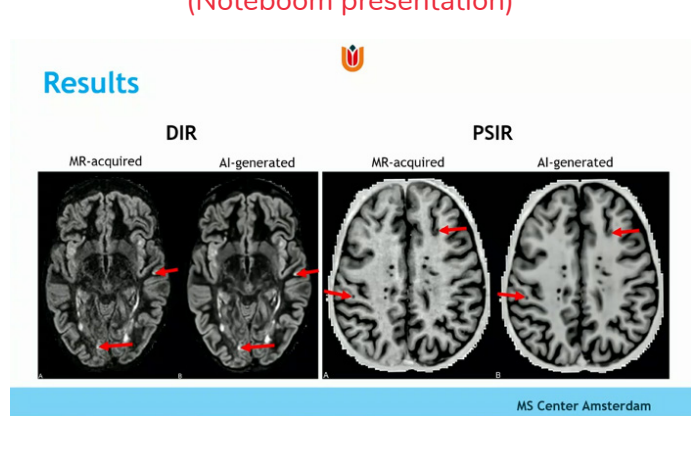
(Eshaghi presentation)



(Skattebøl presentation)



(Noteboom presentation)



Day 2

Imaging and non-imaging biomarkers Session 1
Hot Topic 6: Inclusion of optic nerve lesions in McDonald criteria

Thursday, 27 October 10.00 – 11.00 CEST
Speakers: Frederik Barkhof, Angela Vidal-Jordana, Laura Balcer
Chairs: Olivier Outteryck, Wallace Brownlee

Conclusion: Emerging evidence supports the inclusion of optic nerve lesions in the McDonald criteria for the diagnosis of MS as a fifth element for dissemination in space (DIS).

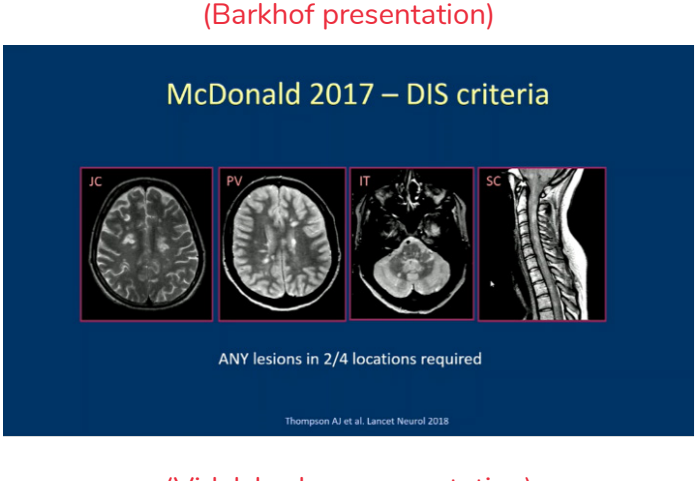
What's New: The McDonald diagnostic criteria for MS have undergone several revisions over recent years, with a progressive focus on confirmation/imaging of the affected lesion such that magnetic resonance imaging (MRI) findings can serve as surrogates for DIS or dissemination in time (DIT). Notably, optic neuritis (ON), which is often the first and most common presentation in MS, is not currently recognised by McDonald criteria as DIS. The MAGNIMS group have proposed the inclusion of at least two of five regions, including ON, symptomatic or not, in the diagnostic criteria for MS. MRI shows high sensitivity and specificity for imaging of ON; however, good resolution and fat saturation is required to contrast bright signals. Differential diagnosis findings also should be considered, especially neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody disease (MOGAD). Although ON did not feature in the 2017 McDonald criteria, the next revision is in preparation, and it is hoped that ON will then be included in these gold standard criteria for the diagnosis of MS.

A key issue with inclusion of ON in McDonald criteria is its frequent over-diagnosis. Clinical characteristics can help to establish the mechanism of optic neuropathies, and additional tests can provide diagnostic support and exclude mimics. MRI findings are also valuable for optic nerve evaluation. Evidence supporting the addition of the optic nerve into DIS criteria has recently emerged, although there are caveats. In patients presenting with a clinically isolated syndrome (CIS), the addition of the optic nerve as a fifth region to the McDonald 2017 DIS criteria improved the diagnostic criteria performance, particularly in patients presenting with an ON. A longitudinal, prospective, multicentre study within the MAGNIMS network has also provided evidence to support the addition of the optic nerve into DIS criteria. In the clinical setting, once the diagnosis of ON (inflammatory cause of an optic neuropathy) with typical characteristics of MS is confirmed (high likelihood event), optic nerve topography should be incorporated into the diagnostic process.

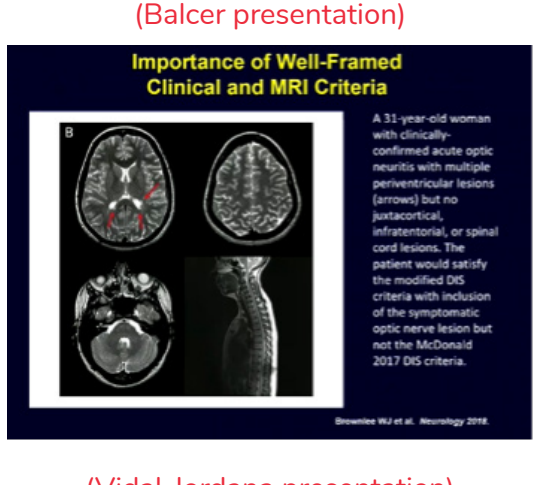
ON is a fundamental feature of MS and the first clinical demyelinating event in 25% of patients, yet other lesion sites continue to take precedence in current MS diagnostic criteria. Various imaging modalities can now identify optic nerve lesions in MS, including optical coherence tomography (OCT), visual evoked potentials (VEP) and advanced MRI. Machine learning and artificial intelligence may have a role in the analysis of OCT image files and help to provide further evidence supporting the addition of the optic nerve to existing diagnostic criteria. The importance of a clinical diagnosis of acute demyelinating ON is also paramount. A recent study, which utilised a Delphi process to attain consensus among neuro-ophthalmic and MS experts, underscored the importance of history, clinical examination, and paraclinical testing and imaging in diagnosis. Clinical diagnosis of ON and identification of optic neuropathies is also critical in establishing dissemination in space and time. Taken together, these results suggest the optic nerve should be a 'first ingredient' in MS diagnostic criteria.

Background: ON is seen at presentation in one-third of patients with CIS and in up to three-quarters of patients with MS, yet optic nerve lesions are currently under-represented in MS diagnostic criteria. According to anatomical pathological studies, ON involvement is constant or almost constant in MS. However, until recently, clinicians have had few reliable tools to detect ON.

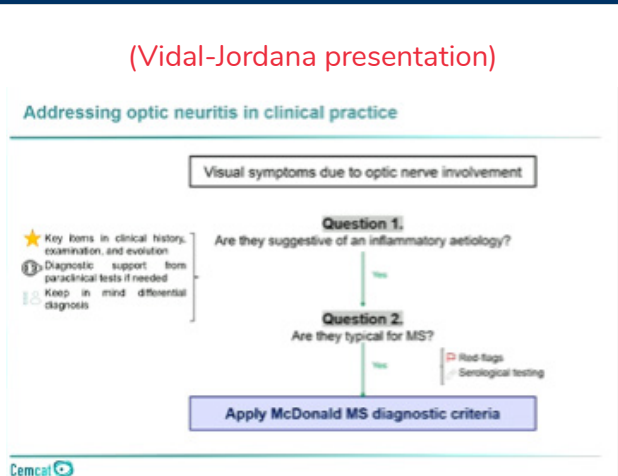
(Barkhof presentation)



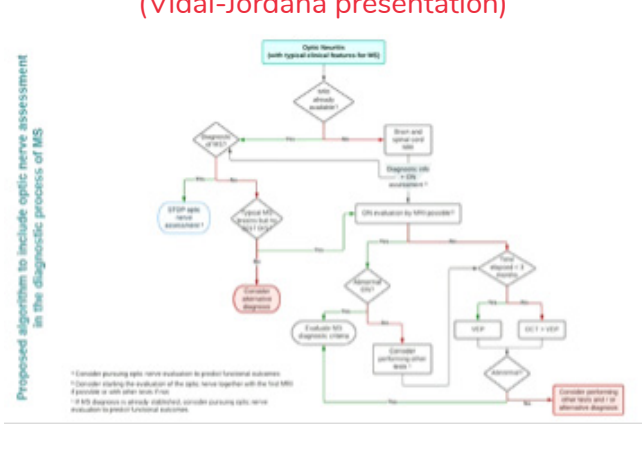
(Balcer presentation)



(Vidal-Jordana presentation)



(Vidal-Jordana presentation)



Imaging and non-imaging biomarkers Session 2
Young Scientific Investigators' Session 2: Long-term outcomes and safety

Thursday, 27 October 11.30 – 12.30 CEST
Speakers: Amjad Altokhis, Gabriel Bsteh, Francesca Bridge, Marco Mancuso, Jason Blau
Chairs: Carmen Tur, Christian Kamm

Conclusion: New and reliable imaging and non-imaging biomarkers for assessment in MS that may add to established biomarkers with potential clinical and therapeutic applications are in development. The presence and number of perilesional iron rims at a baseline scan showed utility as a prognostic imaging biomarker for long-term disability in MS. Additionally, retinal layer thickness was identified to predict disability accumulation in newly diagnosed relapsing MS. Importantly, the risk of cervical abnormalities was revealed to be more than three-fold higher in women following exposure to high-efficacy disease-modifying therapies (DMTs) than low-efficacy DMTs, highlighting clinical implications. Neurophysiology and non-invasive brain stimulation may have utility as biomarkers of brain network dysfunction in MS.

Using such tools, natalizumab was shown to improve motor fatigue in patients with MS through a central mechanism. The long-term efficacy and safety of DMT after natalizumab-associated progressive multifocal leukoencephalopathy (PML) was demonstrated and may address the challenges faced when selecting immunotherapy in the post PML phase.

What's New: Iron rims (IR) surrounding white matter lesions (WML) in MS are associated with earlier disability and severe disease progression. Retrospective analysis of 7T magnetic resonance imaging scans from a longitudinal study of 91 patients with MS or clinically isolated syndrome detected IRLs in 46% of patients, 1–3 (30%) and ≥4 (16%). Importantly, the presence and number of IRLs were shown to hold prognostic value for long-term disability. Correlation between baseline IRL count (particularly ≥4) and disability assessment scores, Expanded Disability Status Scale (EDSS)/Age Related MS Severity (ARMSS), confirmed that a greater number of IRL was a significant predictor of disability at the 12-year follow up ($p<0.05$). Notably, the influence of IRL on disability was greater than T2 WML numbers/volume, an established biomarker. These findings support the use of perilesional IR as a prognostic imaging biomarker for disease severity and worse prognosis in MS.

Thinning of the retinal layers, peripapillary retinal nerve fibre layer (pRNFL) and macular ganglion-cell-and-inner-plexiform-layer (GCIPL), is a biomarker of neuroaxonal damage in relapsing MS (RMS); however, the prognostic value in disability accumulation in newly diagnosed RMS has not been investigated. In an observational, prospective cohort of 231 patients with newly diagnosed RMS, time to disability accumulation (EDSS ≥3) was reached by 12.1% of patients. In a multivariate analysis with a known baseline demographic, and clinical and radiological risk factors, significant predictors of EDSS ≥3 were lower baseline GCIPL and pRNFL thickness ($p<0.001$). Higher age, incomplete remission of first relapse symptoms, and ≥10T2 lesions were also significantly associated with increased risk of disability accumulation ($p<0.001$), while highly effective DMT was protective ($p<0.001$). Retinal layer thickness adds to the biomarkers of disability accumulation in newly diagnosed RMS, potentially informing treatment strategy.

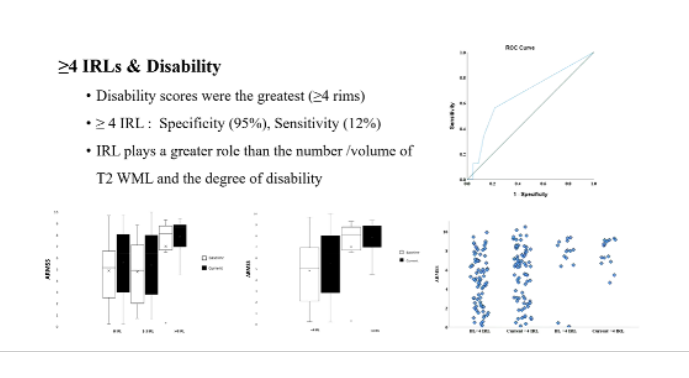
Risk assessment of prolonged exposure to DMTs on human papillomavirus (HPV) persistence and cervical cancer risk is important for the health and safety of women with MS. Retrospective analysis of registry data of 248 women with MS confirmed a 3.79-fold increased risk of developing a cervical abnormality following high-efficacy DMT (fingolimod, cladribine, dimethyl fumarate, natalizumab, ocrelizumab, rituximab, alemtuzumab) compared with low efficacy DMT (interferon beta, glatiramer acetate, teriflunomide) ($p\leq0.001$). The risk was shown to be independent of vaccination status, smoking, hormonal use and socioeconomic status. These findings may impact DMT selection strategies, cervical cancer screening frequency and HPV vaccination.

Neuroinflammation may play a role in the pathogenesis of motor fatigue, commonly seen in MS. The DMT, natalizumab, reduces neuroinflammation and may improve symptoms of fatigue. Preliminary evidence suggests that motor fatigue in MS may be due to an abnormal fatigue-related increase in the connectivity of brain networks and sensorimotor network activation. In a study of 24 patients with relapsing–remitting MS tested 1 week before and 2 weeks after natalizumab infusion – as assessed by clinical scales and central fatigue indices – natalizumab was shown to improve central motor fatigue by modulating cortical network dynamics. Natalizumab normalised fatigue-induced modulation of brain connectivity efficiency and sensorimotor network activation.

PML is a rare, life-threatening, rapidly progressive disease of the central nervous system associated with natalizumab therapy, especially 24 months of therapy. In a retrospective analysis of 32 patients with natalizumab-associated PML and long-term follow-up, clinical and radiological MS activity reoccurred in most patients (2/3) with a substantial delay since the last natalizumab dose, within 1 year for the majority. No PML reactivation occurred following re-administration of injectable and moderate-to-highly active DMT, even in patients who started DMT despite low JC virus persistence. Further data are needed to confirm the safety and efficacy of DMT in post-PML MS.

Background: The disease course in MS is highly variable in terms of future risk of disability. Reliable imaging and non-imaging biomarkers are essential to facilitate treatment decisions and impact long-term outcomes and safety in MS.

(Altokhis presentation)



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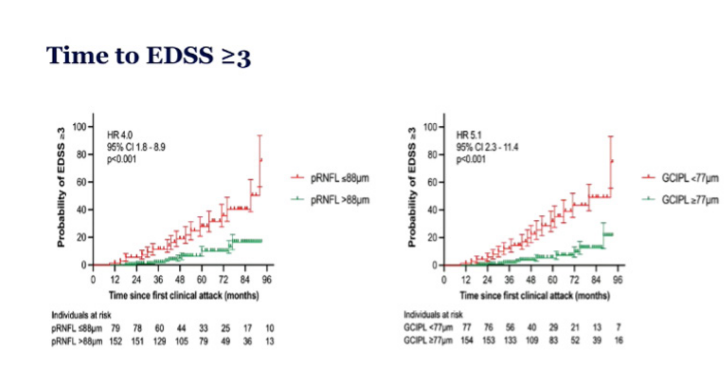

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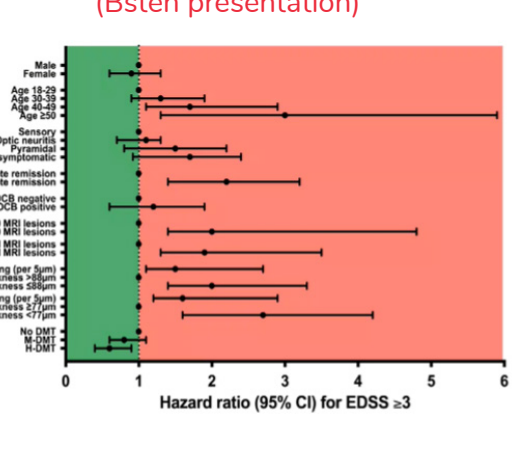
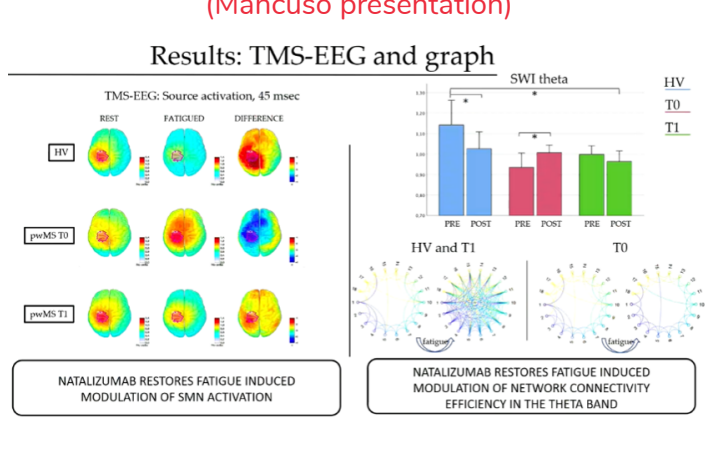


(Mancuso presentation)



Imaging and non-imaging biomarkers Session 3
Scientific Session 9 MRI: Updated MAGNIMS-NAIMS-CMSC guidelines

Thursday, 27 October 15:00 – 16:30 CEST
Speakers: Alex Rovira Canellas, David Li, Timothy Reynold Lim, Mariem Hamzaoui, Alessandro Cagol, Laura Cacciaguerra
Chairs: Daniel Ontaneda, Maria Assunta Rocca

Conclusion: There are an increasing number of factors that can help with diagnosis and prognosis in patients with MS and other related conditions. In patients with radiologically isolated syndrome (RIS), the baseline paramagnetic rim lesion (PRL) count may be predictive of the development of clinical MS over time. A high proportion of homogeneously active (HA) lesions may predict neurodegeneration and disability progression in MS over 2 years. The presence of cortical lesions (CLs) and the central vein sign (CVS) are useful prognostic factors to differentiate MS from MS mimics.

Using such tools, natalizumab was shown to improve motor fatigue in patients with MS through a central mechanism. The long-term efficacy and safety of DMT after natalizumab-associated progressive multifocal leukoencephalopathy (PML) was demonstrated and may address the challenges faced when selecting immunotherapy in the post PML phase.

What's New: Undated international consensus 2021 guidelines on magnetic resonance imaging (MRI) in MS from MAGNIMS, CMSC and NAIMS were presented. Adding spinal cord to brain MRI in the monitoring of clinically stable relapsing remitting MS (RRMS) could reveal a significant proportion of disease activity otherwise undetected. The researchers wanted the guidelines to be universal, useful, useable and used. In the past, compliance with the international MS Brain MRI protocol has been poor at around 50% at best. To improve compliance, there is a need for advocacy (promoting the protocol) and dissemination (providing the details), particularly at the local level.

In a study of 36 individuals with RIS, clinical MS developed in 9 (25%) patients within 5 years. The baseline PRL count was the most predictive measure for the development of MS over time in patients with RIS. This suggests that the accrual of chronic active inflammatory lesions increases the risk for developing MS, and that PRLs may have prognostic utility in RIS.

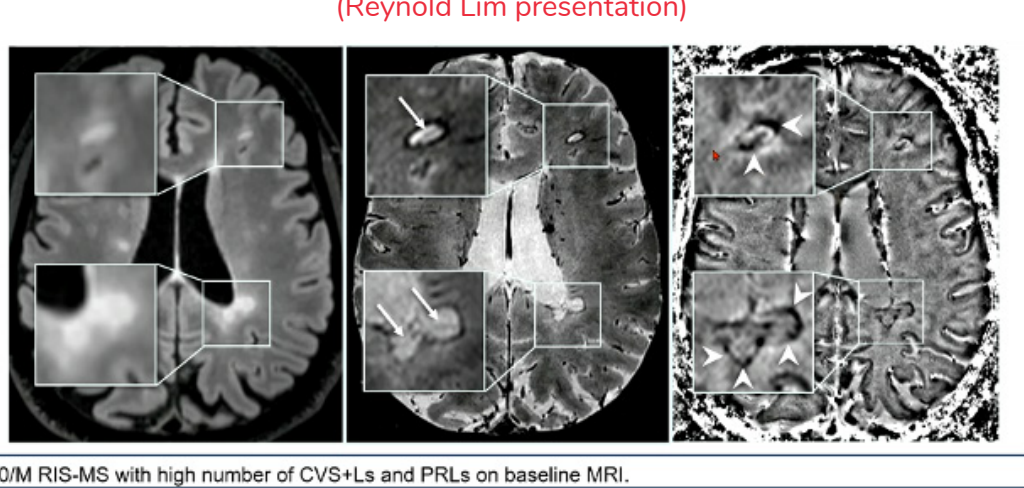
Using DPA-PET, 36 patients with MS and 19 healthy controls were examined; 60% of MS lesions were shown to have a chronic inflammatory component, including homogeneously active lesions and rim-active lesions. Homogeneously active lesions were more frequent in patients with pathological cortical atrophy over 2 years, and the number of homogeneously active lesions was shown to correlate with disability change over 2 years.

Patients with MS or clinically isolated syndrome have a higher number of cortical lesions than those with MS-mimicking conditions. Combining the presence of cortical lesions and central vein sign positivity gives high diagnostic performance, which is not reduced in patients with short disease duration (<2 years).

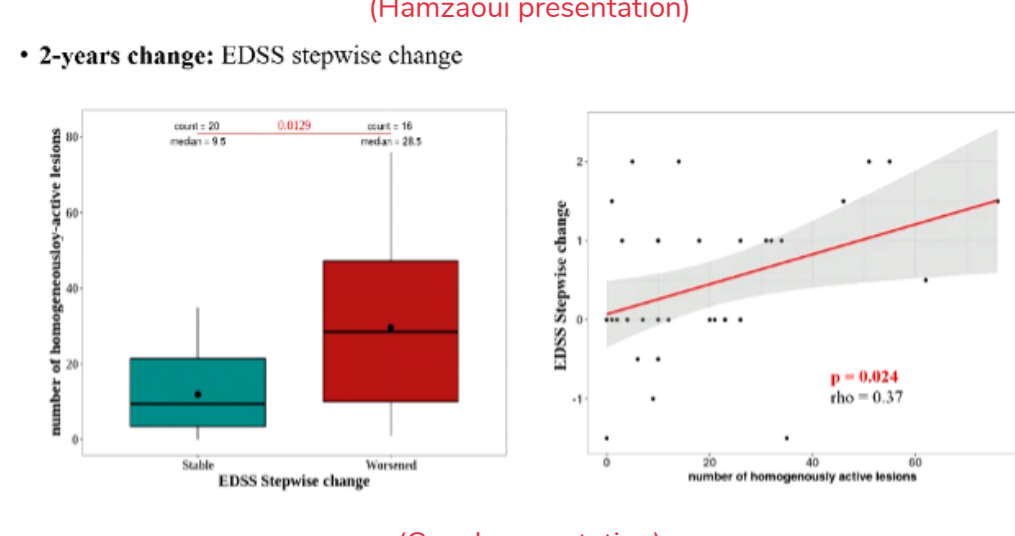
Tumefactive lesions are common in patients with myelin-oligodendrocyte-glycoprotein-IgG-associated disease (MOGAD) and are not associated with higher risk of adverse outcomes. Resolution of these lesions occurs frequently in patients with MOGAD, but not in patients with MS or aquaporin-4-IgGpositive-neuromyelitis-optica-spectrum-disorder (AQP4+NMOSD).

Background: People with RIS have an increased risk of eventually developing MS – central vein sign (CVS) is emerging as a useful diagnostic marker of MS. Paramagnetic rim lesions are another marker, associated with progressive disease phenotypes and disability in MS. CLs, CVS and tumefactive brain lesions can also have value in differentiating MS from non-MS conditions.

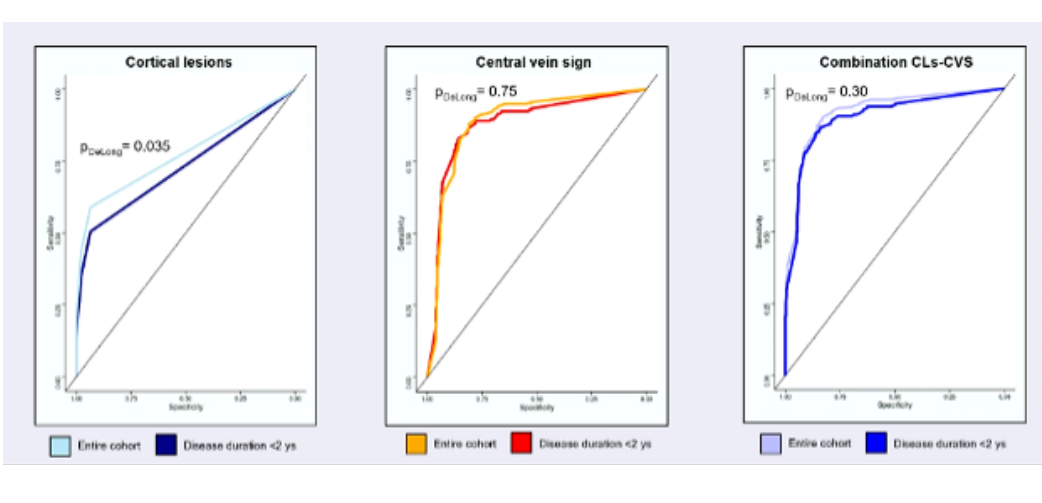
(Reynold Lim presentation)


50/M RIS-MS with high number of CVS+Ls and PRLs on baseline MRI.

(Hamzaoui presentation)



(Cagol presentation)



Day 3

Imaging and non-imaging biomarkers Session 1
Scientific Session 17: Blood-based biomarkers – when to implement?

Friday, 28 October 12:00 – 13:30 CEST
Speakers: Michael Khalil, Robert Fox, Stephanie Meier, Mark Wessels, Elias Sotirchos, Ahmed Abdelhak
Chairs: Fredrik Piehl, Charlotte Teunissen

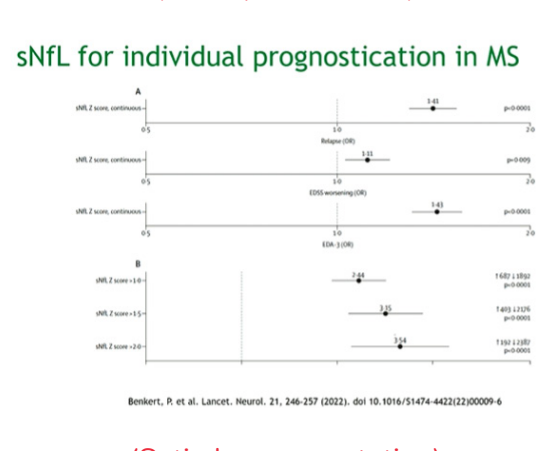
Conclusion: Both neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) are important blood-based biomarkers in MS. Recent studies have shown that NfL is strongly associated with acute inflammatory activity and has a relationship with both brain atrophy and white matter volume loss. GPAP is complementary to NfL and has shown promise as a prognostic biomarker reflecting MS disease progression. For application in clinical trials, NfL is a particularly attractive tool that can be used as both a prognostic maker, helping to enrich trials for higher-risk patients, and a dynamic marker of treatment response.

What's New: Recent approaches have shown promise in using blood NfL levels for prognostication at an individual patient level in MS. Z scores were calculated based on a large reference database accounting for factors such as age and body mass index that may influence blood NfL levels. In other NfL-centric research, a single baseline measurement of NfL was found to be associated with accelerated short-term brain atrophy in the MS PATH cohort – a large multicentre MS network. Similarly, findings from the EPIC cohort of over 800 patients followed-up for over 12 years revealed a link between longitudinal blood NfL levels and the pattern and timing of progression in MS.

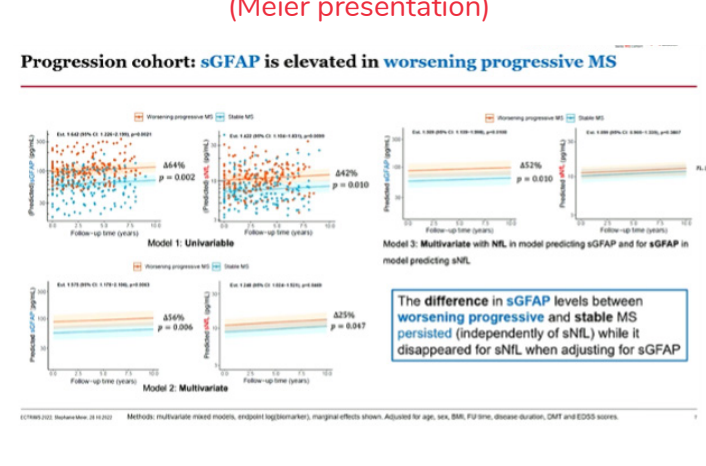
GFAP was directly compared to NfL in a study by presented by Dr Meier, which looked at the role of these counterpart biomarkers in MS disease progression. The design of the study involved two cohorts with 'extreme' MS phenotypes – worsening progression and relapse free. Serum NfL was strongly associated with acute inflammatory activity and baseline levels prognosticated white matter volume loss. In contrast, serum GFAP showed potential as a prognostic marker for disease worsening, including progression independent of relapse activity, and baseline levels were prognostic for grey matter volume loss. Another study in a cohort of natalizumab-treated patients found that GFAP and inflammation were associated, and GFAP decreased significantly after starting high efficacy treatment.

Background: NfL is a specific structural protein of neurones and a cross-disease biomarker of axonal damage. Increased levels reflect neurodegeneration and disease activity in MS. GFAP is a marker for astrogliosis and astrocytic damage. GFAP levels are increased in the serum and cerebrospinal fluid in progressive MS in some, but not all, studies.

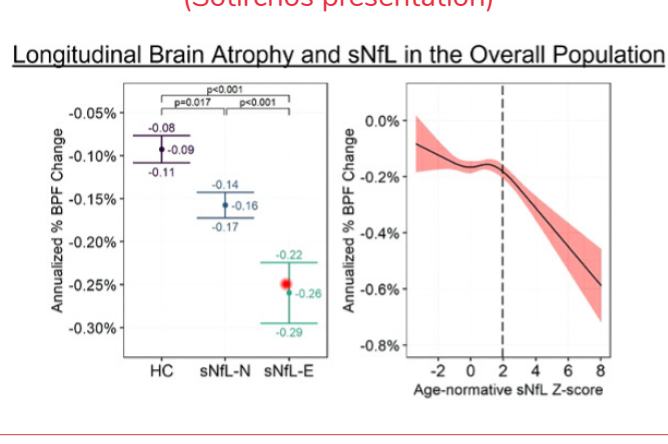
(Khalil presentation)



(Meier presentation)



(Sotirchos presentation)



Imaging and non-imaging biomarkers Session 2
Free Communications 6: Imaging

Friday, 28 October 10:00 – 11:00 CEST
Speakers: Nevin John, Paul Elsbernd, Eduardo Caverzasi, Alberto Calvi, Eero Polvinen
Chairs: Nicola De Stefano, Jiwon Oh

Conclusion: Imaging findings such as gadolinium (Gd) enhancements, brain atrophy patterns and lesion phenotype afford important insights into the underlying neurological pathology and can act as predictive biomarkers of disease progression in MS. Moving forward, it may prove possible to utilise imaging metrics of chronic disease activity in clinical practice to predict both disability outcomes and treatment response in patients with MS.

What's New: Several free communications presented during this session highlighted important new research being undertaken in the field of imaging in MS.

The presence of vascular comorbidities was associated with decreased cortical grey matter volumes at baseline, and high body mass index was strongly associated with grey matter atrophy in cross-sectional, post-hoc analysis of patients with secondary progressive MS in the MS-SmART study. No associations of vascular comorbidities with white matter volumes were noted.

A study presented by Dr Elsbernd looked at brain magnetic resonance imaging enhancement patterns in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) as compared to aquarporin-4 (AQP4)+ neuromyelitis optica spectrum disorder (NMOSD) and MS. Gd enhancement occurred in 73% of MOGAD cerebral attacks. Leptomeningeal enhancement in MOGAD was common, seen in 46% of cases, and strongly favoured it over both AQP4+ NMOSD and MS. By contrast, ring enhancement favoured MS, while linear-ependymal favoured AQP4+ NMOSD. Enhancement persisting for more than 3 months was rare across all three neurological conditions.

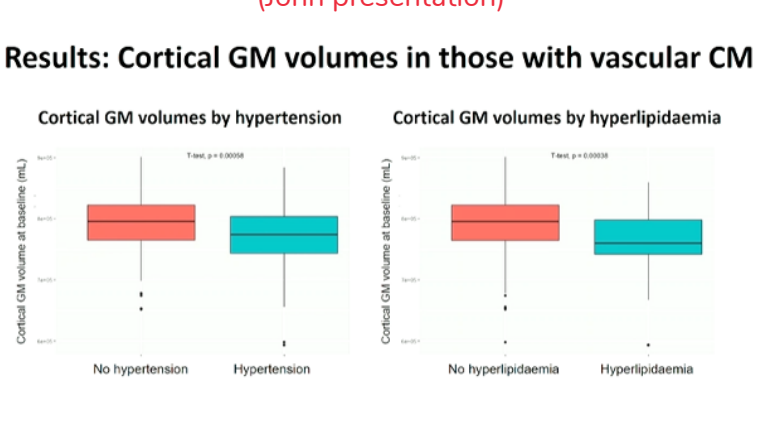
Source-based morphometry was shown to be more sensitive in detecting MRI prognostic biomarkers compared to voxel-based morphometry in a study of 107 patients. Thalamus atrophy was the main univariate difference between early MS patients and controls, while cerebellar atrophy patterns were the main biomarker and predictor of disability.

An analysis of imaging data from recently diagnosed MS patients demonstrated that nearly all had one or more slowly expanding lesion (SEL) and more than half had one or more paramagnetic rim lesion (PRLs). Patients who were both SEL+ and PRL+ had a higher lesion load and a higher rate of progression on the Expanded Disability Status Scale (EDSS) than those who were SEL+ but PRL–.

Chronic lesion phenotyping may also provide a strong predictor for disease progression in MS, according to findings presented by Dr Polvinen. In this study of 82 MS patients, a high rim-active and a low inactive proportion of lesions was strongly associated with EDSS progression (odds ratio 26.8). The ensuing model was able to predict disease progression with 57% sensitivity and 97% specificity.

Background: Imaging has an important role both in MS (differential) diagnosis and ongoing disease activity monitoring and can be used to assess atrophy patterns and brain lesions. Acute lesions in MS are characterised by hypercellularity, intense macrophage infiltration and ongoing demyelination. In contrast, chronic lesions – the dominant lesion type in progressive MS – consist of an active centre surrounded by a rim of activated proinflammatory microglia and macrophages. Brain atrophy occurs even in the earliest stages of MS and is a reliable predictor of future physical and cognitive disability.

(John presentation)



(Elsbernd presentation)

RESULTS / COMPARISON OF ENHANCEMENT PATTERNS

	MOG (n=59)	AQP4 (n=14)	p value	MS (n=26)	p value
Median age [years]	25 (10-41)	47 (42-54)	0.002[a]	37 (31-47)	0.004[a]
Females	35 (59%)	13 (93%)	0.02[b]	21 (81%)	0.06[b]
Enhancement - Baseline					
Cloud-like	5 (9%)	0 (0%)	0.58	0 (0%)	0.32
Punctate	16 (27%)	0 (0%)	0.03	7 (27%)	>0.99[b]
Ring	4 (7%)	2 (14%)	0.32	8 (31%)	0.006
Leptomeningeal	27 (46%)	1 (7%)	0.01	1 (4%)	<0.001
Linear	16 (27%)	0 (0%)	0.03	7 (27%)	>0.99[b]
Linear - ependymal	0 (0.0%)	2 (14%)	0.04	0 (0%)	>0.99
Heterogeneous/ Patchy	33 (56%)	9 (64%)	0.57[b]	16 (62%)	0.59[b]
Nodular	19 (32%)	6 (43%)	0.45[b]	12 (46%)	0.22[b]

Unless otherwise specified p values refer to Fisher's exact test
[a]Mann-Whitney U-test; [b]Pearson's Chi-square test

(Polvinen presentation)

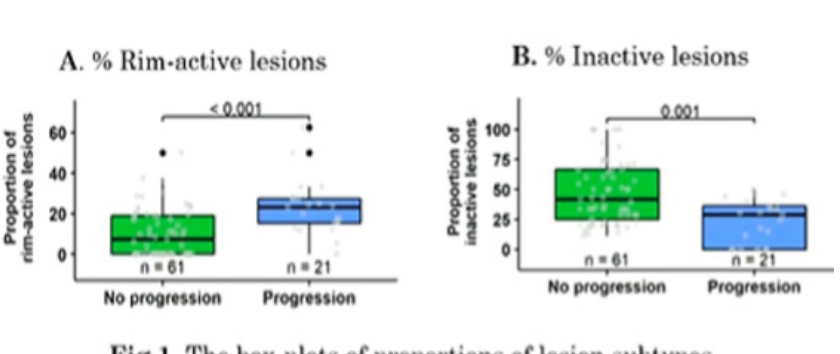


Fig 1. The box-plots of proportions of lesion subtypes.