

# UPDATES IN

# MMS

## HIGHLIGHTS FROM THE ECTRIMS AND ACTRIMS ANNUAL MEETINGS

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**NEUROLOGY**  
REVIEWS

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## CSF biomarker clusters correlate with MS severity

 Raturaj R.  
Masvekar, PhD


**DALLAS**—Patients with multiple sclerosis (MS) had elevated levels of specific clusters of cerebrospinal fluid (CSF) biomarkers related to astrocytes and microglia that correlated with disease severity in a blinded analysis. The researchers examined more than 1,000 proteins from the CSF of more than 400 patients with neuroimmunologic disease and healthy volunteers.

Previous studies have indicated that aberrant activation of astrocytes and microglia underlies disability progression in older patients with MS, but researchers have lacked biomarkers of these processes in living subjects. In a presentation at the 2019 annual meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), Raturaj R. Masvekar, PhD, described developing biomarkers of CNS cell-specific processes and examining how they relate to MS disability progression. Dr. Masvekar, a researcher at the National Institute of Allergy and Infectious Diseases (NIAID), and his coinvestigators used a modified DNA aptamer assay to measure proteins in the CSF of 431 patients with neuroimmunologic diseases and healthy volunteers, followed by variable cluster analysis and in vitro modeling to define 64 clusters of CSF biomarkers that relate to CNS cell types.

The study included 42 healthy donors, 20 patients with clinically isolated syndrome, 57 patients with noninflammatory neurologic disorders, 127 patients with relapsing-remitting MS, 72 patients with secondary progressive MS, and 113 patients with primary progressive MS. In a training cohort of 217 participants, the researchers assessed how

biomarkers differed between the diagnostic categories. The researchers then validated the results in an independent cohort of 214 participants.

One astrocyte-related cluster (MMP7, SERPINA3, GZMA, and CLIC1) and one microglia-related cluster (DSG2 and TNFRSF25) was significantly elevated in all MS subgroups, compared with healthy controls and patients with noninflammatory neurologic disorders. In addition, these clusters “significantly correlated with clinical measures of disability, CNS tissue destruction, and MS severity,” Dr. Masvekar said.

The microglial cluster was significantly elevated in all MS subgroups, whereas neuronal endothelial, astrocytic, and oligodendroglial biomarker clusters were elevated only in patients with progressive MS.

“Microglial activation is present in all stages of MS, while toxic astrogliosis increases with MS duration, concomitantly with neuronal and oligodendroglial degeneration,” Dr. Masvekar said. “Microglial activation and toxic astrogliosis likely partake in CNS tissue destruction and enhance MS severity.”

This study, which was recently published in *Multiple Sclerosis and Related Disorders*, was supported by the intramural research program at NIAID.

—Jake Remaly

### SUGGESTED READING

Masvekar R, Wu T, Kosa P, et al. Cerebrospinal fluid biomarkers link toxic astrogliosis and microglial activation to multiple sclerosis severity. *Mult Scler Relat Disord*. 2019;28:34-43.



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## Biologic aging is associated with MS disability progression

Kristen M. Krysko, MD



**DALLAS**—Biologic aging, as measured by leukocyte telomere length (LTL), is associated with multiple sclerosis (MS) disability progression independent of chronological age, according to a study presented at the 2019 annual meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS).

Shorter telomere length is associated with increased MS disability in cross-sectional and longitudinal analyses, said Kristen M. Krysko, MD, clinical fellow in neurology at University of California, San Francisco (UCSF). The results suggest that biologic aging may contribute to neurologic injury in MS and that “targeting aging-related mechanisms may be a potential therapeutic strategy,” said Dr. Krysko.

If validated, telomere length may be a biomarker that neurologists could use to guide decisions about MS treatment, said principal investigator Jennifer Graves, MD, PhD, also of UCSF.

“Factors leading to MS progression are not fully understood,” Dr. Krysko said. “But consistently, older chronological age has been associated with a faster time to disability milestones.” Aging may reduce remyelination capacity and alter immunologic responses. Telomere shortening, a marker of cellular aging, is “the ultimate biological clock.” It has been associated with cardiovascular disease, dementia, and autoimmune diseases, and one study found that patients with primary progressive MS have shorter telomere length, compared with controls.

To assess whether LTL is associated with clinical disability and brain volume in patients with MS, the researchers analyzed data from 516 adults with MS or clinically isolated syndrome in the EPIC cohort study at UCSF. Telomere length was measured on stored baseline DNA samples and expressed as the ratio of telomere to a single-copy gene.

The patients had an average age of 43 years, median disease duration of 6 years, and median Expanded Disability Status Scale (EDSS) score of 1.5; about 70% were women. The average telomere length was 0.97.

Older age and longer disease duration were associated with shorter LTL. For every 0.2-unit decrease in telomere length, EDSS score increased by 0.41. After adjusting for age, disease duration, and sex, every 0.2-unit decrease in telomere length was associated with a score increase of 0.27 on the EDSS. LTL also was associated with total brain volume and total white matter volume.

In addition, the investigators conducted a case-control study that included a subset of 23 patients who developed secondary progressive MS during follow-up and had DNA available at multiple time points. The researchers matched these patients with 23 patients who continued to have

**The results suggest that biologic aging may contribute to neurologic injury in MS and that “targeting aging-related mechanisms may be a potential therapeutic strategy.”**

relapsing MS. Patients were matched by age, sex, and disease duration. An adjusted analysis found that change in LTL was predictive of change in EDSS over 10 years, such that every 0.2-unit decrease in LTL was associated with a 0.34-unit increase in EDSS.

Longitudinal analyses found that baseline LTL predicted higher levels of disability over time.

The study was funded by the National Multiple Sclerosis Society.

—Jake Remaly

## Evaluations for possible MS often turn up one of its many mimics

**DALLAS**—Of 95 patients referred to two multiple sclerosis (MS) centers for a possible diagnosis of MS, 74% did not have MS, according to a study presented at the 2019 annual meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS). A majority had clinical syndromes or imaging findings that are atypical for MS, which “underscores the importance of familiarity with typical MS clinical and imaging findings in avoiding misdiagnosis,” said Marwa Kaisey, MD, and her research colleagues. Dr. Kaisey is a neurologist at Cedars-Sinai Medical Center in Los Angeles.

Physicians often refer patients to academic MS centers to determine whether patients have MS or one of its many mimics. To study the characteristics and final diagnoses of patients referred to MS centers for evaluation of possible MS, the investigators reviewed electronic medical records and MRI from all new patient evaluations at the Cedars-Sinai Medical Center and University of California, Los Angeles MS clinics between July 2016 and June 2017. The researchers excluded patients referred with a previously established diagnosis of MS.

There were 366 new patients evaluated, including 236 patients with previously established MS diagnoses and 35 patients whose evaluations were not related to MS. Of the 95 patients referred for a question of MS diagnosis, 60% had clinical syndromes that were atypical for MS, 22% had normal neurologic exams, and a third had pain or sensory changes that were not localizable to the CNS.

Sixty-seven percent had MRI that was atypical for MS, and nearly half of the patients without MS had nonspecific MRI changes. “Often, these MRI changes alone prompted referral for an MS evaluation,” Dr. Kaisey and colleagues reported. “This suggests that novel, specific imaging tools may increase diagnostic confidence in the clinical setting.”

In all, the referred patients received 28 diagnoses other than MS, most commonly migraine (10 patients), anxiety or conversion disorder (9), postinfectious or idiopathic transverse myelitis (8), compression myelopathy or spondylopathy (8), and peripheral neuropathy or radiculopathy (7).

The researchers did not have any relevant disclosures. ■

—Jake Remaly

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## What happens when patients with RRMS discontinue their DMT?

Hajime Yano, MD



**DALLAS**—Patients with relapsing-remitting multiple sclerosis (RRMS) who discontinued disease-modifying treatment (DMT) after a period of disease inactivity had a similar time to next event, compared with those who remained on treatment, results from a single-center study showed. In addition, being over the age of 45 years was associated with a better disease course after treatment discontinuation.

“Being clinically and radiologically stable for more than 2 years can be a potential milestone to regard the discontinuation of DMT as a reasonable option in a subset of patients, especially patients who are nondisabled,” lead study author Hajime Yano, MD, said in an interview at the 2019 annual meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS).

According to Dr. Yano, a research fellow at the Ann Romney Center for Neurologic Diseases and Partners Multiple Sclerosis Center in Boston, patients with RRMS without relapse for long periods on treatment may consider discontinuing DMT, but there is limited information regarding the impact of discontinuation, especially in terms of MRI activity.

In an effort to investigate the impact of DMT discontinuation on clinical and radiologic outcomes in RRMS patients, Dr. Yano and his colleagues identified 70 patients from the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women’s Hospital (CLIMB) study, which was initiated in 2000 and has enrolled more than 2,400 patients cared for at the Partners Multiple Sclerosis Center. Relapse date, symptoms, and Expanded Disability Status Scale (EDSS) were evaluated at 6-month intervals for each patient during the time of clinic visits by the treating neurologist. Additionally, brain MRIs were performed annually.

Next, the researchers matched the patients with 70 patients who remained on DMT identified by age, sex, treatment, treatment duration, disease duration, and EDSS. They used univariate and multivariable Cox proportional hazard models to test the differences between DMT discontinuation status with time to clinical relapse, MRI event,

disability progression, and any inflammatory event (either clinical relapse or MRI event).

The mean age of patients was 45 years, 87% were female, their mean disease duration was about 13 years, and they had been receiving treatment for a mean of about 6 years. In adjusted analyses, the 70 pairs of patients who discontinued DMT and patients who continued DMT had similar outcomes in time to clinical relapse (hazard ratio [HR], 0.93;  $P = .84$ ), MRI event (HR, 1.01;  $P = .98$ ), disability progression (HR, 1.33;  $P = .43$ ), and any inflammatory event (HR, 0.93;  $P = .85$ ). In a subgroup analysis, which compared the impact of DMT discontinuation between patients over the age of 45 years and those aged 45 years and younger, the researchers observed a statistically significant difference in effect of discontinuation on time to clinical relapse ( $P = .032$ ), time to MRI event ( $P = .013$ ), and time to any inflammatory event ( $P = .0005$ ), all favoring patients over the age of 45 years.

“This finding makes sense, since age has been reported as one of the factors that negatively impacts the inflammatory activity in patients with RRMS,” Dr. Yano said. “However, our study is the first study [to find] that the impact of discontinuing DMT on RRMS patient prognosis may differ based on the age at the discontinuation. In short, stopping DMT at a younger age has a statistically significant higher risk on inflammatory activities, compared to [stopping DMT at an] older age.”

He acknowledged certain limitations of the study, including its small sample size and single-center design. However, Dr. Yano said that a key strength of the analysis was the inclusion of MRI activity prior to DMT as the definition of stable state, “which is an integral piece of information when physicians and patients consider DMT discontinuation in a ‘real world’ clinical setting. We also used MRI activity as an outcome measure, which is lacking in prior discontinuation studies.”

Dr. Yano reported that he has received a research grant from Yoshida Scholarship Foundation in Japan. His coauthors reported having numerous financial ties to industry. ■

—Doug Brunk

## Just over half of patients with MS get DMD therapy



Jacqueline A.  
Nicholas, MD, MPH

**DALLAS**—In 2 years of follow-up, about 43% of U.S. patients diagnosed with multiple sclerosis (MS) had not received disease-modifying drug (DMD) therapy, a rate that is consistent with other published studies. The finding comes from a retrospective analysis of claims data presented at the 2019 annual meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS). “This rate of DMD treatment merits further exploration, given that evidence suggests the importance of early DMD treatment initiation in patients with a confirmed diagnosis of relapsing forms of MS to help optimize the benefits of treatment,” Amy L. Phillips, PharmD, a study author, said in an interview in advance of the meeting.

Little is known about current DMD treatment patterns in U.S. patients with MS following an increase in the number of available DMDs in recent years, according to Dr. Phillips, of the department of health economics and outcomes research at EMD Serono.

“Most previous studies have focused on self-injectable DMDs or self-injectable and infusion DMDs,” she said. “Information about the treatment patterns including oral DMDs is scarce, particularly in large population samples. The objective of our study was to describe treatment patterns and sequences of therapy among U.S. patients with MS newly initiating DMD treatment between Jan. 1, 2011 and June 30, 2015.”

Dr. Phillips, lead study author Jacqueline A. Nicholas, MD, MPH, of the OhioHealth Multiple Sclerosis Center, and their colleagues used data from the IQVIA RWD Adjudicated Claims database to identify patients who had at least two medical claims with an MS diagnosis and at least one DMD claim during the study period. Other eligibility criteria included continuous eligibility with commercial insurance 1 year before (baseline period) and 2 years after (follow-up period) initiation of the DMD, no evidence of DMD use during the baseline period, and being between ages 18 and 63 years.

Of 63,946 diagnostically eligible patients, 36,175 (57%) had a claim for a DMD. The researchers reported findings from 8,251 patients who met all of the eligibility criteria. Their mean age was 43 years, 76% were female, and the mean number of DMDs over 2 years among newly treated patients was 1.27.

The most common first-line DMD therapy was glatiramer acetate (GA, 38%), followed by intramuscular interferon beta (IM IFN $\beta$ -1a, 14%), subcutaneous interferon beta (SC IFN $\beta$ -1a, 14%), dimethyl fumarate (DMF, 14%), and fingolimod (9%). DMF was the most common second-line therapy (36%), followed by fingolimod (17%), GA (17%), SC IFN $\beta$ -1a (8%), and IM IFN $\beta$ -1a (7%).

“Numerous DMD treatment patterns observed in this study highlight the diverse patient and treatment needs,” Dr. Phillips said. “DMD treatment patterns in MS vary due to the heterogeneity of the disease, physician preferences, and patient needs and treatment goals. Patient-centered care and shared decision making has been shown to improve patient satisfaction and to encourage treatment adherence in MS.”

She acknowledged certain limitations of the study, including the fact that the analysis presents only the most common DMD treatment sequences observed in this patient population.

“Future analyses might examine less common DMD treatment sequences,” she said. “Also, more research is needed to understand how DMD treatment patterns and sequences change over time, and the factors that may be associated with DMD switching and treatment discontinuation.”

She also noted that the administrative claims data studied represent mostly patients with commercial health insurance, limiting the generalizability of the findings. Furthermore, ICD-9 and ICD-10 codes do not distinguish between MS types.

Funding for the study was provided by EMD Serono, the biopharmaceutical business of Merck KGaA, Darmstadt, Germany, in the United States and Canada. Dr. Phillips is an employee of the company.

—Doug Brunk

## When is the optimal time to start treatment in patients with relapsing-remitting MS?



Pietro Iaffaldano, MD

**BERLIN**—Data from the Big Multiple Sclerosis Data (BMSD) Network indicate that the optimal time to start disease-modifying therapy in patients with multiple sclerosis (MS) to prevent the long-term accumulation of disability is within six months of disease onset. This finding was presented by Pietro Iaffaldano, MD, and colleagues at the 2018 annual congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). Dr. Iaffaldano is Assistant Professor of Neurology at the University of Bari, Italy.

Many randomized clinical trials support the early start of disease-modifying therapies in MS. However, there is still an ongoing discussion on the optimal timing of treatment. For insight into this and other questions, the Danish, Italian, and Swedish national MS registries, MSBase, and the OFSEP of France pooled data for specific research projects in the BMSD Network. One question they sought

**The optimal time to start disease-modifying therapy in patients with multiple sclerosis to prevent the long-term accumulation of disability is within six months of disease onset.**

to answer with this large, real-world data set was the optimal time to start disease-modifying therapy to prevent long-term disability accumulation in MS.

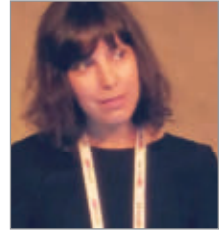
A cohort of patients with relapsing-remitting MS who had 10 or more years of follow-up, three or more years of cumulative disease-modifying therapy exposure, and three or more Expanded Disability Status Scale (EDSS) score

evaluations was selected from the pooled cohort of the BMSD Network. The researchers conducted a set of pairwise (1:1) propensity score matching analyses with 10 different cutoffs for early versus delayed treatment (> 0.5 year up to > 5.0 years, using 0.5-year intervals) to allow an unbiased comparison between groups. The logistic model to predict propensity score included the following covariates: age at onset of the disease, sex, baseline EDSS, number of relapses in the two years before disease-modifying therapy start, number of EDSS evaluations, decade of birth, and registry source. To estimate the risk of reaching 12 months-confirmed EDSS progression (EDSSpr), a set of Cox models, adjusted for disease duration and relapses after disease-modifying therapy start as time-dependent covariates, was calculated.

A cohort of 11,871 patients with relapsing-remitting MS (71.0% female) was retrieved from the pooled BMSD Network database. The median (interquartile range) age at onset was 27.7 (22.3–34.6), median follow-up was 13.2 (11.4–15.4) years, and median time to the first disease-modifying therapy start was 3.8 (1.5–8.5) years. During the follow-up, an EDSSpr was reached by 4,138 (34.9%) patients. The lowest hazard ratio (HR) with relative 95% confidence interval (CI) for the propensity score matched models was obtained by a cutoff of treatment start within six months from disease onset (n = 873 per group). Early treatment significantly reduced the risk of reaching an EDSSpr (HR, 0.72). All subsequent comparisons between early and delayed treatment were not statistically significant.

This project was supported by Biogen International (Zug, Switzerland) on the basis of a sponsored research agreement with the BMSD Network. ■

## Revamped MS criteria boost pediatric diagnoses



Georgina Arrambide, MD

**BERLIN**—The 2017 McDonald criteria boosted the rate of definitive multiple sclerosis (MS) diagnosis in children by 40%, compared with the 2010 criteria. The increased accuracy largely hinged on a positive finding of oligoclonal bands in cerebrospinal fluid—a diagnostic hallmark that was not included in the earlier criteria, Georgina Arrambide, MD, said at the 2018 annual congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

“Application to children of the new diagnostic criteria is limited,” said Dr. Arrambide, of the University Hospital Vall d’Hebron Multiple Sclerosis Centre of Catalonia, Barcelona. “There are still some uncertainties with regard to fluid biomarkers and how they predict or confirm a diagnosis of MS in children, and also their relationship to the disease evolution.”

The updated McDonald criteria are intended to boost early, definitive MS diagnosis, leading to earlier initiation of therapy. They are intended primarily for patients aged 11 years and older who present with a typical clinically isolated syndrome and high probability of MS.

Dr. Arrambide and her colleagues used the revamped criteria to reassess MS diagnoses in a prospective Spanish cohort of children who experienced an acute first demyelinating event and were diagnosed with the 2010 criteria. The Kids-METOMS-MOGBCN Study enrolled children aged younger than 18 years within 1 year of a first acute demyelinating episode. It included demographic, clinical, and imaging data, as well as data on oligoclonal bands and antibodies against aquaporin-4 and myelin oligodendrocyte glycoprotein (MoG). Of these fluid biomarkers, only oligoclonal bands are included in the new McDonald criteria.

The 55 children in Dr. Arrambide’s analysis were followed for a mean of 16 months. They included 25 (45%) girls with an overall median age of 6 years at the first acute event. Oligoclonal bands were present in 56%, and both anti-MoG and anti-aquaporin-4 antibodies in 82%.

All children had abnormal brain MRI at baseline, with about 33% having gadolinium-enhancing brain lesions. Spinal cord MRI was abnormal in 50%, with 39% having gadolinium-enhancing lesions. According to the 2010 criteria, only three had a definitive MS diagnosis at baseline. The diagnosis was

acute disseminated encephalomyelitis in 51%, clinically isolated syndrome in 31%, radiologically isolated syndrome in 2%, and nonencephalopathic disseminated encephalomyelitis in the remainder.

At baseline, three of those had a definitive MS diagnosis, displaying dissemination in both space and time, as required by both the 2010 and 2017 criteria. The addition of oligoclonal band positivity added one more patient over the 2010 criteria, and assessing the cohort with the complete 2017 criteria added three more definitive diagnoses. This was a significant increase in definitive MS diagnoses, when compared against the earlier criteria (70% vs. 30%).

Diagnoses changed in 10 other patients during follow-up. The patient with radiologically isolated syndrome was definitively diagnosed with MS. Of the 7 with clinically isolated syndrome, 6 were diagnosed with MS and 1 with a relapsing optic neuritis. Of the 28 with a nonencephalopathic encephalitis, 2 were diagnosed with optic neuritis.

The study also confirmed the benefit of adding oligoclonal bands as a diagnostic marker in children. Of those with an MS diagnosis at last follow-up, 71% were positive for the cerebrospinal fluid finding, compared with 4% of those with a non-MS diagnosis. However, none of those children had anti-MoG antibodies, compared with 58% of those with a non-MS diagnosis. None of the patients were positive for anti-aquaporin-4, regardless of diagnosis.

That finding does not necessarily mean that the absence of anti-MoG antibodies can rule out an MS diagnosis in children, Dr. Arrambide cautioned. Nevertheless, the finding is a useful clinical marker during a diagnostic workup. “The presence of oligoclonal bands and the absence of MOG-IgG are both useful biomarkers when evaluating the risk of MS in children with a first demyelinating event,” she said.

She disclosed financial relationships with several pharmaceutical companies.

—Michele G. Sullivan

### SUGGESTED READING

Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.



## Cortical damage at onset may indicate risk of secondary progressive MS



Antonio Scalfari, MD, PhD

**BERLIN**—Widespread focal cortical damage at multiple sclerosis (MS) onset identifies patients likely to have frequent early relapses and a rapid development of progressive disease, which results from worsening global cortical pathology over time, according to a study presented at the 2018 annual congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). The results provide a basis for patient stratification with the goal of therapeutic optimization. In addition, the data “highlight the importance of elucidating mechanisms involved in early cortical pathology,” according to the investigators.

Among patients with relapsing-remitting MS, a high frequency of early relapses is associated with increased risk of developing severe disability, which suggests that early biologic mechanisms influence long-term disease evolution. Antonio Scalfari, MD, PhD, a consultant neurologist at Imperial College Healthcare in London, and colleagues sought to investigate the relationship between early cortical pathology, early relapses, and the risk of converting to secondary progressive MS.

Dr. Scalfari and colleagues examined 219 patients with relapsing-remitting MS. Participants had one ( $n = 116$ ), two ( $n = 53$ ), or three or more ( $n = 50$ ) relapses during the first two years. Follow-up lasted for a mean of 7.9 years. The researchers assessed the number of cortical lesions and white matter lesions and the rate of cortical thinning using 3D double inversion recovery, 3D T1-weighted imaging, and Freesurfer analysis.

During the observation period, 59 (27%) patients converted to secondary progressive MS in a mean of 6.1 years. At disease onset, the investigators detected 674 cortical lesions in 166 (76%) patients. A larger number of cortical lesions was associated with a significantly higher risk of secondary progressive MS. The hazard ratios (HR) for secondary progressive MS were 2.16 for patients with two lesions, 4.79 for patients

with five lesions, and 12.3 for patients with seven lesions. A large number of cortical lesions also was associated with shorter latency to secondary progressive MS and a faster rate of global cortical thinning. The mean loss per year was 0.93% for patients with no lesions, 0.99% for patients with one to three lesions, 1.13% for patients with four to six lesions, and 1.33% for patients with seven or more lesions. In the group with no cortical lesions ( $n = 53$ ), no patients entered the secondary progressive phase, and four reached an Expanded Disability Status Scale score of 4.

Patients with a high number of early relapses, compared with those with low and moderate numbers, had a larger volume of white matter lesions and cortical lesions at onset. The mean volumes of cortical lesions were 181.6 mm<sup>3</sup>, 386.8 mm<sup>3</sup>,

**Patients with a high number of early relapses, compared with those with low and moderate numbers, had a larger volume of white matter lesions and cortical lesions at onset.**

and 544.0 mm<sup>3</sup> for patients with one, two, and three or more early relapses, respectively. Patients with a high number of early relapses also accrued more cortical lesions (mean cortical lesion volumes were 118.8 mm<sup>3</sup>, 138.8 mm<sup>3</sup>, and 790.5 mm<sup>3</sup> for patients with one, two, and three or more early relapses, respectively), had a faster rate of cortical atrophy (mean loss/year was 0.47%, 0.79%, and 0.94% for patients with one, two, and three or more early relapses, respectively), and entered the secondary progressive phase more rapidly.

In the multivariate model, older age at onset (HR, 1.97), a larger baseline cortical lesion (HR, 2.21) and white matter lesion (HR, 1.32) volume, early changes of global cortical thickness (HR, 1.36), and three or more early relapses (HR, 6.08) independently predicted a higher probability of secondary progressive MS. ■

## Particular lesions early after CIS predict long-term MS disability

Karen  
Chung, MBBS



**BERLIN**—The presence of infratentorial (IT) and deep white matter lesions early in the course of relapse-onset multiple sclerosis (MS) was associated with high levels of disability 30 years later in a study looking at MRI predictors.

Univariate predictors of an Expanded Disability Status Scale (EDSS) score of more than 3.5, which is indicative of impaired mobility, after 30 years were the presence of an IT lesion at baseline, with an odds ratio (OR) of 12.4 (95% confidence interval [CI], 3.35-46.0; *P* less than .001), the presence of a deep white matter (DWM) lesion 1 year after presenting with clinically isolated syndrome (CIS; OR = 10.65; 95% CI, 2.84-39.84; *P* less than .001), and the presence of an infratentorial (IT) lesion 1 year post CIS presentation (OR = 11.1; 95% CI, 3.31-37.22; *P* less than .001). At 5 years after a CIS presentation, the EDSS score, EDSS score change, and a DWM lesion score of more than 5 were indicative of worse disability after 30 years.

There was no significant association with age of onset, gender, CIS type, baseline EDSS, or disease duration, study investigator Karen Chung, MBBS, reported at the 2018

**For combinations of predictors, patients who had at least one IT and one DWM lesion within 1 year of a CIS had a higher probability (94%) of having an EDSS score of more than 3.5 at 30 years than when compared with those with neither lesion (13%) and those with one DWM but no IT lesions (49%).**

annual congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS).

“As we know, approximately 85% of people with MS initially present with a clinically isolated syndrome,” said Dr. Chung, a clinical research associate at the Queen Square Multiple Sclerosis Centre in the UCL Institute of Neurology in London. She added that the long-term prognosis after CIS is variable, with some patients developing little detectable disability over time, while others may experience considerable decline.

There have been few studies examining whether there are any MRI parameters that might help predict patients’ long-term outcomes, so the aim of the study Dr. Chung presented was to see if there were any MRI parameters that

might be predictive of clinical outcome 30 years after the onset of CIS.

Dr. Chung and her coauthors examined data on 120 of 132 individuals from the First London CIS Cohort who were prospectively recruited between 1984 and 1987 and had known outcomes. They looked at prospectively gathered MRI data and EDSS data at baseline, 5, 10, 14, 20, and 30 years. MRI data were obtained for 1 year after the CIS event, and data on the lowest EDSS score after the CIS event were retrospectively determined from patient notes or recall. The cohort was predominantly female (61%), with a mean age of 31.5 years at CIS onset. Around half (52%) presented with optic neuritis, 27% with a spinal cord syndrome, and 20% with a brainstem syndrome. The high percentage of patients presenting with optic neuritis may be due to the fact that one of the recruiting centers was a specialist eye hospital, Dr. Chung noted later during discussion.

The 2010 McDonald Criteria and death certificates were used to determine whether patients had CIS, relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), or death related to MS.

“We looked at all the MRIs available to us and quantified the T2 lesion count for whole brain as well as by location,” Dr. Chung explained. The locations considered were juxtacortical, periventricular, infratentorial, and deep white matter.

“I think it is important to remind ourselves that we have come a long way with MRI technology in the 30-year time span,” she added, noting that there was “clearly a difference in the quality.”

Clinical outcomes at 30 years were as follows: 80 patients (67%) developed MS, of whom 35 (44%) had RRMS, 26 (33%) had SPMS, 15 (20%) had died as a result of MS, and 3 (4%) had died for unknown or unrelated causes. Of the 40 patients (33%) who remained with CIS, 10 (25%) died without developing MS.

“This is a largely untreated cohort where, within the 80 people with MS, 11 (14%) were treated with a DMT [disease-modifying treatment] at some point,” Dr. Chung reported. All DMTs used were first-line injectable agents, she observed.

EDSS scores could be obtained for 107 patients. At 30 years, people with low EDSS scores were those who remained with CIS or RRMS, and as EDSS scores increased, the severity of MS increased.

“Overall, T2 lesions were better predictors of 30-year outcome than EDSS,” Dr. Chung said. For combinations of

predictors, patients who had at least one IT and one DWM lesion within 1 year of a CIS had a higher probability (94%) of having an EDSS score of more than 3.5 at 30 years than when compared with those with neither lesion (13%) and those with one DWM but no IT lesions (49%).

Looking at the best independent predictors up to 5 years, the predicted probability of an EDSS score of more than 3.5 if there were no IT lesions and fewer than five DWM lesions was 18%. But if there were no IT but more than 5 DWM lesions, the probability of disability at 30 years rose to 52%. The probabilities rose even higher to 63% if there was one or more IT and five or fewer DWM lesions and 90% if there was one or more IT and more than five DWM lesions.

“In this cohort, the presence of early infratentorial and deep white matter lesions following a CIS are associated with higher level of disability 30 years later,” Dr. Chung concluded. “Early predictive models can add information to risk-benefit stratification.”

During discussion, one delegate expressed concerns that these data were “not generalizable to the current situation.” This was a cohort of patients that largely was not treated or if they were, treatment was delayed by more than 10 years. These data were interesting “from a historical perspective,”

he argued, “but I don’t understand, how in the absence of contemporary therapies this is applicable in a way that will allow us to use this information to make prognoses for the future.”

**Looking at the best independent predictors up to 5 years, the predicted probability of an EDSS score of more than 3.5 if there were no IT lesions and fewer than five DWM lesions was 18%.**

Dr. Chung agreed, noting that this was more of a natural history study. “However, I think it is applicable in clinical practice. When you have a patient presenting with a CIS, at the time of diagnosis, especially now when we can diagnose patients earlier with the new 2017 criteria, it will be helpful for the patient and ourselves to apply some of the information I presented to help perhaps in aiding decisions regarding treatment.”

The study was funded by a grant from the MS Society of Great Britain. Dr. Chung disclosed receiving honoraria from Teva, Biogen, and Roche.

—Sara Freeman

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## Ongoing neuronal loss is greater in secondary progressive MS than primary progressive MS



Jens  
Kuhle, MD, PhD

**BERLIN**—Levels of neurofilament light chain (NfL) indicate that patients with secondary progressive multiple sclerosis (MS) have more ongoing neuronal loss than patients with primary progressive MS of comparable age, both in the presence and in absence of gadolinium enhancing lesions, according to research presented at the 2018 annual congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). In secondary progressive MS and primary progressive MS, NfL may serve as a prognostic marker of brain atrophy, said the investigators.

NfL is considered a blood biomarker for monitoring neuronal damage, disease activity, and treatment response in MS. Most studies of blood NfL have focused on patients with relapsing-remitting MS, and little is known about blood NfL levels in patients with progressive MS.

Jens Kuhle, MD, PhD, Head of the MS Center at University Hospital Basel in Switzerland, and colleagues, compared baseline blood NfL levels and assessed the prognostic potential of NfL for brain atrophy in patients with primary progressive MS and secondary progressive MS in placebo-controlled phase III trials of fingolimod (ie, INFORMS) and siponimod (ie, EXPAND).

The researchers retrospectively analyzed blood NfL levels in 1,452 patients with secondary progressive MS (mean age, 48.2; Expanded Disability Status Scale [EDSS], 5.4) and 378 patients with primary progressive MS (mean age, 48.7; EDSS, 4.6). They quantified NfL levels at baseline using single molecule array technology and grouped them into the categories of low (< 30 pg/mL), medium (30–60 pg/mL), and high (> 60 pg/mL). High and low baseline NfL categories were compared using Chi-square and Wilcoxon rank sum tests. Dr. Kuhle and

colleagues examined the association of baseline NfL levels with MRI parameters by Spearman rank correlation (gadolinium enhancing lesion count, T2 lesion volume) and the Jonckheere Terpstra test (brain volume change).

NfL levels at baseline were higher in patients with secondary progressive MS than in patients with primary progressive MS (32.1 pg/mL vs 22.0 pg/mL). A similar trend was observed when patients of the same age were compared. Patients with secondary progressive MS had higher NfL levels than those with primary progressive MS.

Similarly, patients with no gadolinium enhancing lesions at baseline had NfL levels of 29.2 pg/mL and 21.0 pg/mL in secondary progressive MS and primary progressive MS, respectively, while patients with gadolinium

**In secondary progressive MS and primary progressive MS, NfL may serve as a prognostic marker of brain atrophy.**

enhancing lesions had NfL levels of 45.0 pg/mL in secondary progressive MS and 34.0 pg/mL in primary progressive MS. The gadolinium enhancing lesion count and T2 lesion volume at baseline correlated best with baseline NfL. In secondary progressive MS and primary progressive MS, high NfL at baseline was associated with higher percentage of brain volume loss at Month 12 (high NfL vs low NfL:  $-0.8\%$  vs  $-0.2\%$  in secondary progressive MS and  $-0.8\%$  vs  $-0.4\%$  in primary progressive MS) and at Month 24 ( $-1.5\%$  vs  $-0.5\%$  in secondary progressive MS and  $-1.9\%$  vs  $-0.8\%$  in primary progressive MS).

The study was funded by Novartis Pharma. ■