The New McDonald Criteria: Faster and Improved Diagnosis of Multiple Sclerosis

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THE 2024 REVISED McDonald Criteria for multiple sclerosis (MS) diagnosis were explained in detail during a joint session between the European Academy of Neurology (EAN) and the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), chaired by Bruno Stankoff, Professor of Neurology at Université Pierre et Marie Curie (UPMC), Paris, France; and Celia Oreja-Guevara, Vice Chair of Neurology and Head of Multiple Sclerosis Center at the University Hospital San Carlos, Madrid, Spain. The session highlighted significant updates to these diagnostic criteria, as well as expert insights on their potential clinical applications.

THE 2024 REVISED CRITERIA

Xavier Montalban, Chair of the Department of Neurology-Neuroimmunology and Director of the Multiple Sclerosis Centre of Catalonia at Vall d'Hebron University Hospital in Barcelona, Spain, shed light on the history of MS diagnostics, revealing that the first diagnostic criteria for MS were established in 1954 and have been revised multiple times since. Notably, major updates occurred with the introduction of the McDonald Criteria in 2001, followed by further refinements in 2005, 2010, and 2017. Now, the most recent 2024 McDonald Criteria have been announced, with further changes in line with new research findings. In this session, experts delved deeper into the new revisions.

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The 2024 revised criteria, and all previous versions, were developed by the International Advisory Committee on Clinical Trials in Multiple Sclerosis (IACCTMS), and are sponsored by the National MS Society (USA) and ECTRIMS. In total, 55 international experts with backgrounds spanning clinical management, radiology, methodology, epidemiology, and patient perspectives, from 16 different countries, contributed to the 2024 revised criteria.

Significant Updates

Historically, MS diagnostic criteria have been based on the following four pillars: the presence of symptoms suggestive of MS, demonstration of dissemination in time (DIT) and dissemination in space (DIS), exclusion of other diagnoses, and the idea that diagnosis can be based on clinical assessment alone. Montalban, however, emphasised that in light of new research, the 2024 revisions challenge these statements.

He highlighted some of the most significant revisions, including the reclassification of radiologically isolated syndrome (RIS) as MS under specific conditions, the removal of the requirement for demonstration of DIT, and the recognition of the optic nerve as a fifth topography for evidence of DIS. According to Montalban, the redefinition of RIS as MS in selected cases represents the most

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consequential update, reflecting a shift toward a more biologically-based approach to MS diagnosis. Other noteworthy changes include updated DIS criteria, the introduction of the central vein sign (CVS) and paramagnetic rim lesions (PRL) as optional diagnostic tools, and the use of the same diagnostic criteria for primary progressive MS and relapsing MS.

DISSEMINATION IN TIME IS NOT NECESSARY FOR DIAGNOSIS

Montalban then focused on one significant change to the criteria: with advancements in MRI and cerebrospinal fluid (CSF) markers, DIT is no longer a necessary criterion for diagnosis, if there are lesions in four or five different topologies.

He honed in on the contradictory nature of using DIT as a diagnostic criterion whilst also wanting to treat patients early to improve long-term prognosis, as fulfilment of the DIT criterion requires observing new lesions or relapses over time, which can mean waiting months before a formal diagnosis. He stressed this point with the results of his research, which examined the impact of using different diagnostic criteria on prognosis.[1] The results demonstrated that when using the earlier criteria, the probability of reaching an Expanded Disability Status Scale (EDSS) score of ≥3 by the age of 40 years was 0.86. In contrast, with the 2017 McDonald criteria, this probability decreased to 0.20, demonstrating the benefit of using a diagnostic criterion that prioritises earlier diagnosis.

In the 2017 McDonald Criteria, the presence of oligoclonal bands (OCB) in CSF was introduced as an alternative to DIT for individuals presenting with clinically isolated syndrome. This modification was heavily influenced by a pivotal study,[2] which demonstrated that patients with clinically

isolated syndrome who had both DIS and positive CSF OCBs had a high hazard ratio for conversion to MS. Consequently, this combination was adopted in the revised criteria. The key takeaway from this study is that the most critical factor for diagnosing MS is the demonstration of DIS, specifically with lesions in typical anatomical locations. Moreover, the presence of OCBs further increases diagnostic confidence; however, DIT is not a necessary criterion.

IMPACT ON TREATMENT AND CLINICAL PRACTICE

In the next part of the session, Marcello Moccia, Department of Neuroscience, University of Naples Federico II, Italy, addressed the practical implications of these new criteria for treatment and clinical practice. Moccia emphasised an important point made by Montalban, that whilst the primary aim of diagnostic criteria is to make correct diagnoses, they are profoundly related to treatment and prognosis. This means that the criteria must enable early and precise diagnosis, which then informs timely initiation of disease-modifying therapies, which is crucial for long-term prognosis.

Moccia then explained how new diagnostic tools, such as the CVS, PRL, optical coherence tomography, and kappa free light chains (kFLC), are being integrated into routine evaluations under the revised criteria, and the impact this can have on patient outcomes.

Kappa Free Light Chain Index

With the new 2024 criteria, individuals with suspected MS are evaluated for DIS based on the presence of lesions in up to five characteristic CNS regions: periventricular, cortical/juxtacortical, infratentorial, spinal cord, and the optic nerve.

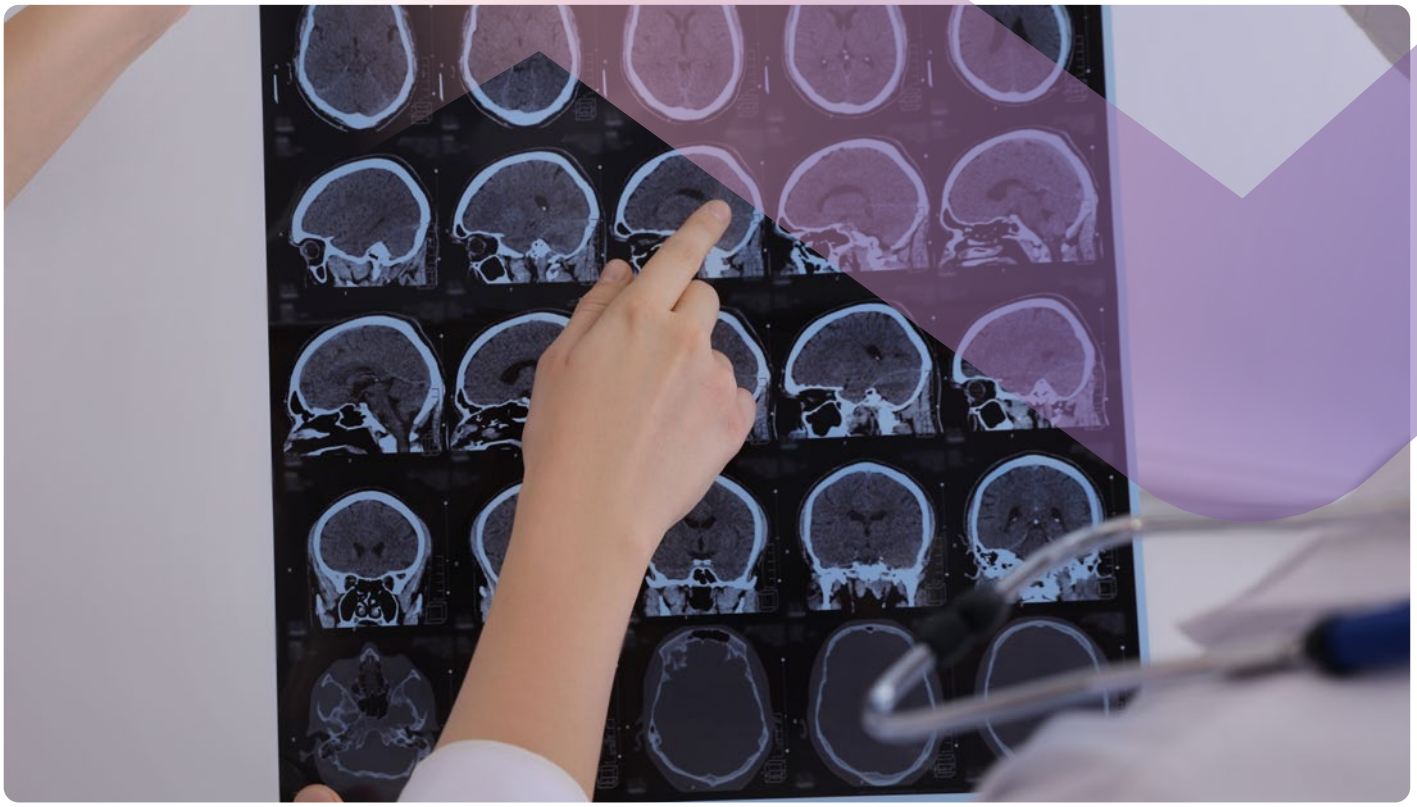
If typical lesions are identified in at least two of these regions, an MS diagnosis can be established. However, if there is only one lesion in a single region, additional criteria must be met. Among these additional criteria, Moccia explained, is a newly refined definition of CSF positivity. Traditionally, positive CSF has been defined by the presence of OCBs, specifically patterns 2 or 3. The revised criteria now include an alternative biomarker: a kFLC index >6.1. A key advantage of the kFLC index is that it is a fully automated, quantitative laboratory test, unlike OCB detection, which requires specialised technical expertise and subjective interpretation. Use of the KFLC index not only streamlines diagnosis but also enables prognostic assessment at the time of disease presentation, as kFLC measurements reflect increased immunoglobulin synthesis in MS. Globally, the ease of using the kFL index means it can be widely implemented, with the potential to improve diagnostic possibilities worldwide.

Central Vein Sign and Paramagnetic Rim Lesions

Other new markers introduced in the 2024 McDonald criteria include the CVS and PRLs, which require the use of iron-sensitive, susceptibility-based MRI sequences, such as T2-star or Fluid Attenuated Inversion Recovery (FLAIR). Both CVS and PRLs demonstrate very high specificity for MS, although their sensitivity is not very high; however, when present, these findings strongly indicate an MS diagnosis.

CVS is particularly valuable for distinguishing MS from other inflammatory and non-inflammatory central nervous system disorders, and it is unaffected by age or vascular comorbidities. Notably, CVS demonstrates even greater specificity than CSF OCBs, although it does not hold prognostic value. However, Moccia explained that it can help distinguish new MS lesions from other non-MS lesions during follow-up.

PRLs, on the other hand, can provide unique insights into the underlying pathophysiology of MS, as well as prognostic stratification. The detection of a single PRL is highly specific for MS, and, while PRLs are not a requisite for diagnosis, their presence strongly supports it. Moreover, PRLs are of particular interest because patients



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with these lesions are at higher risk of subsequent disease progression, independent of relapse frequency. Interestingly, Moccia revealed that sometimes PRLs can disappear, and when they do, this may be indicative of clinical improvements or stability; however, this remains a subject of ongoing research.

The inclusion of both CVS and PRLs in the revised criteria reflects the fact that, for the first time, we have moved beyond just counting MS lesions to now classifying lesions. This advance not only improves diagnostic confidence but also holds potential to refine prognostication, long-term management, and the development of precision medicine (particularly for therapies that target PRLs). From a technical perspective, the integration of susceptibility-weighted imaging protocols in routine MRI will facilitate the identification of these new markers, without significantly impacting diagnostic workflows.

CONCLUDING REMARKS

Moccia expressed confidence that the new 2024 McDonald Criteria will greatly enhance the accuracy and timeliness of MS diagnosis. Moving beyond the traditional requirements of DIT and DIS, the revised criteria introduce highly specific diagnostic tools that will aid earlier and more reliable diagnoses. He spotlighted one notable advancement, which is the inclusion of the optic nerve as a recognised region for lesion assessment, as this may enable the reclassification of cases previously considered RIS as definite MS.

Additionally, Moccia emphasised the shift toward a more mechanism-based approach to diagnosis. Whilst the increased complexity of the revised criteria presents new challenges, this complexity is justified by the goal of improving early recognition and reducing the risk of misdiagnosis. Furthermore, Moccia argued that to

counteract the increased complexity, we need to improve imaging protocols. Most importantly, by incorporating susceptibility-weighted imaging sequences and ensuring thorough assessment of the optic nerve through modalities such as visual evoked potentials, optical coherence tomography, or MRI. Additionally, routine CSF analysis should now include the kFLC index. He also argued for a cultural change. In the past, MS diagnosis relied on relatively straightforward criteria, but now, neurologists need to combine multiple diagnostic tools. Not every person suspected of having MS will require the full complement of assessments, but it is up to clinicians to tailor assessments for each individual with suspected MS.

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