Evolution of Diagnostic Criteria for Multiple Sclerosis: Implications for Clinical Trials

Clinically establishing a diagnosis of multiple sclerosis (MS) typically does not represent a difficult diagnostic challenge, notwithstanding the tendency to recall one's diagnostic errors or atypical presentations. However, the progress recently made regarding the presence of partially effective treatments and the requirement for earlier diagnosis have highlighted the need for consistent diagnostic criteria. Since the first description of the disease by Charcot in 1868, who recognised a non-specific triad of symptoms (nystagmus, intention tremor and scanning speech), knowledge about clinical presentation of MS has progressed, culminating in the first diagnostic criteria published by Allison and Muller[1] 1954, who introduced the terms "early", "possible", and "probable" MS. These criteria were quite intuitive and required extensive clinical experience. Broman[2] (1965) enhanced Allison-Muller's clinical criteria with cerebrospinal fluid (CSF) examination, which became the precursor to oligoclonal bands. For the first time, there was also a categorical statement requiring a "dissemination in space and time." The term "clinically definite" MS was first time used by Schumacher[3] in 1965 and it required objective evidence for the disease affecting two or more white matter parts of the CNS, occurring in two or more episodes lasting more than 24 hours separated by one month or more, or with progression over six months. In spite of the fact that the Schumacher criteria became a gold standard particularly for epidemiological studies, a lot of criticism was directed to age restriction of disease occurrence (10–50 years) as well as to the inability to grapple abortive and ambiguous forms of disease presentations.

Since many patients did not fit the diagnosis of definite MS, a further attempt was made to clarify 'probable' and 'possible' MS. Rose[4] (1976) defined "probable MS" as a disease with two episodes with signs at a single site, or a single episode with signs of widespread disease; whereas "possible MS" was defined as condition with two episodes with no or few signs. Apparently the entire diagnostic process was based on clinical impression. Poser[5] (1983) recognised this persistent problem with classification and highlighted the importance of CSF assessment, as well as the role of paraclinical evidence using evoked potentials, computerised brain tomography (CT), specific urological studies and further magnetic resonance imaging (MRI) to support the diagnosis of MS. Poser's diagnostic criteria aimed to incorporate all previous criteria, and therefore characterised definite and probable MS. Although Poser's criteria were widely accepted until the late 1990s, he himself stated that "in retrospect it would have probably been better not to have included a category of 'probable MS' because of its unsuitability for research and drug trials".

As a result of accumulative importance of the role of MRI in diagnosing MS, the new, so-called McDonald's criteria[6] for diagnosis of MS were introduced (2001). Although MRI was not required for diagnosis of MS, the criteria became strongly MRI-dependent, which rendered many experienced clinicians reluctant to accept it. Contrasting this, a "technology and web supporting" group of younger clinicians became uncritically oriented towards this technology-dependent criteria, frequently neglecting the clinical assessment as the most salient aspect of the diagnostic process. Despite assurances that the criteria still required 'objective clinical evidence', the strong emphasis on imaging served to undermine this statement. Nonetheless, the McDonald criteria became the gold standard for diagnosis and were incorporated in most immunotherapy clinical trials. Interestingly, the criteria also defined the structure for diagnosis of primary progressive MS which required abnormal CSF analysis. It was rapidly acknowledged that the original criteria had been interpreted by some as "mainly relying on MRI" but still insisting that a diagnosis could only be made with "careful clinical evaluation of the patient". Therefore a revised version of the McDonald criteria were published in 2005[7]. Dissemination in time could now be shown by the detection of new T2 lesions at least 30 days after the onset of the initial clinical event, and a spinal cord lesion could be considered equivalent to a brain infratentorial lesion.

Although the 2005 McDonald criteria for MS (MCMS) allowed for earlier diagnosis of definite disease, areas of ambiguity remained that could lead, and probably have led, to misinterpretation and incorrect classification. The MCMS 2005 criteria provided examples of "objective clinical evidence" or "objective findings lesions" although the word "objective" may be interpreted to signify abnormalities on physical examination, documented change in symptoms or abnormal investigations such as MRI or evoked potentials. MRI or evoked potential are certainly objective, but signs/symptoms of pallanaesthesia or statanesthesia are not. Finally 'two or more lesions' could be interpreted as a symptom, sign or abnormal special test result, and it is uncertain if all or just one of these are significant. There is further ambiguity regarding paroxysmal symptoms such as trigeminal neuralgia or the L'Hermitte symptom. The MCMS 2005 criteria disallow both of these.

The McDonald criteria were reviewed for a third time in May 2010[8] with the aim of clarifying the 2005 guidelines and incorporating more recent information from the European Magnetic Imaging in MS (MAGNIMS) research group, which made the diagnostic criteria applicable to Asian, Latin American and paediatric populations. The simpler and more sensitive criteria for dissemination in space (DIS) taken from MAGMIS were accepted. However, dissemination in time (DIT) by MCMS 2005 required MRI evidence of a new T2 lesion compared to a previous MRI at least 30 days previously. According to 2010 criteria, DIT could be confirmed in clinically isolated syndrome (CIS) on the basis of a single scan if there were asymptomatic gadolinium enhanced and non-enhanced lesions in the areas specified by the definition of DIT. Thus diagnosis of MS can be made in someone with CIS with only one MRI scan. The 2010

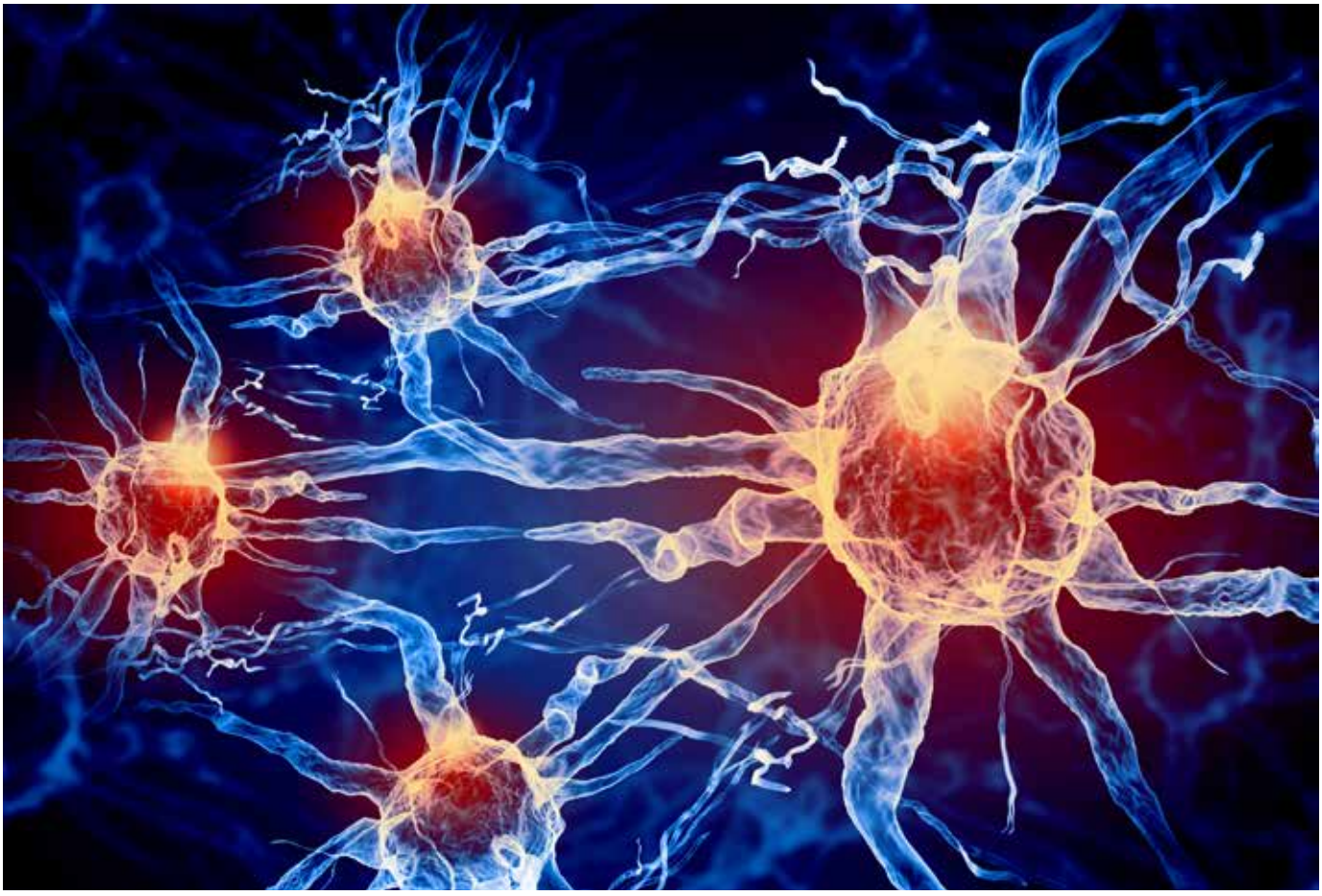
criteria clarified MRI requirements but challenges left over from the 2005 MCMS were not adequately addressed. Additional criteria to confirm diagnosis are still quite complex, but it was still possible to make a diagnosis of MS without neuroimaging. Paroxysmal symptoms were allowed in MCMS 2010 as long as they exceeded 24 hours in duration. Examples are not given but presumably trigeminal neuralgia and many other episodic disturbances could be included.

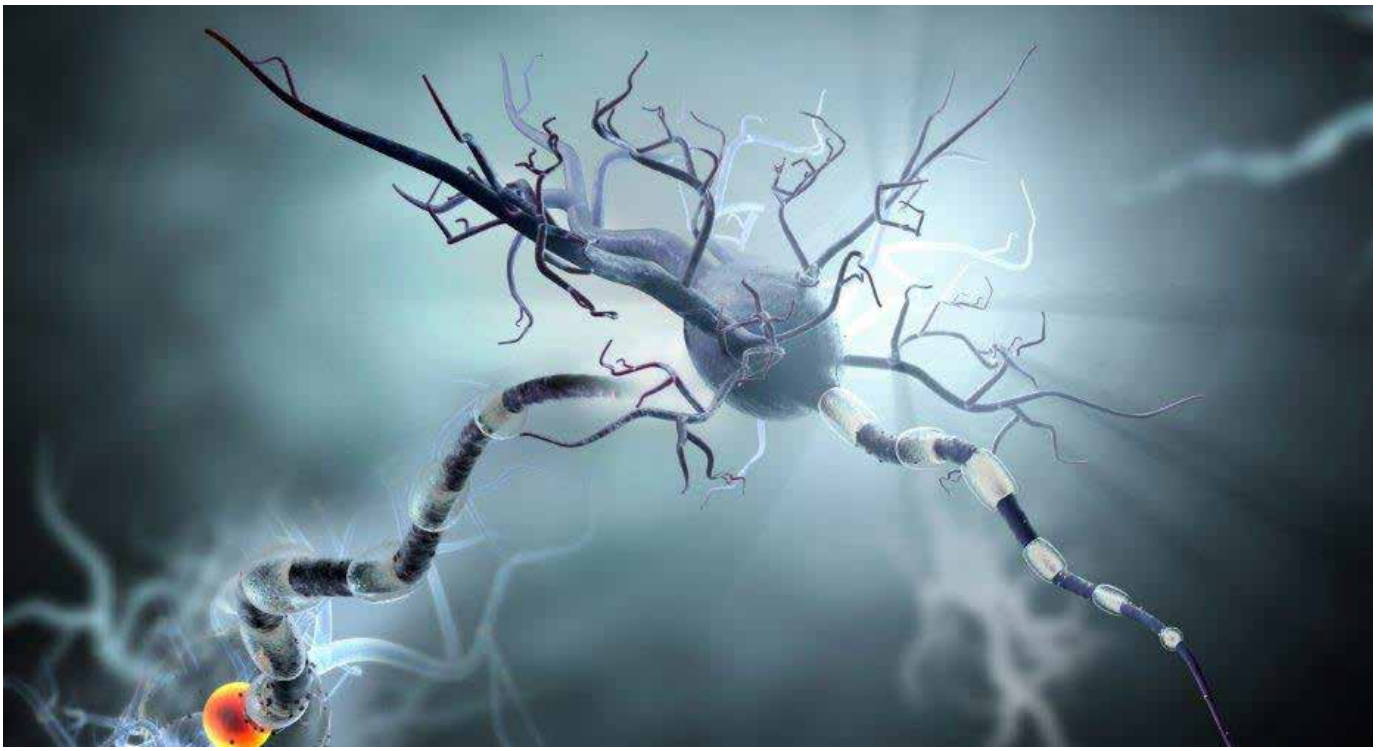
The fourth revision of the MCMS criteria was published in 2017, introducing again the value of the presence of oligoclonal bands in CSF as an evidence of DIT. In addition, MCMS 2017 accepted that both asymptomatic and now symptomatic MRI lesion could be considered in determining DIS and DIT. This does not include MRI lesions in the optic nerve in someone presenting with optic neuritis. Finally cortical lesions have been added to juxtacortical lesions for use in determining MRI criteria for DIS. MCMS 2017 suggests that MRI of brain and spinal cord should be obtained during the diagnostic procedure, whereas CSF examination of oligoclonal bands should be associated with their examination in the serum.

The advent of MCMS 2017 criteria will undoubtedly aid in the earlier diagnosis of MS, usually at the time of CIS, although there is a concern that the revised criteria may be accompanied by either higher rate of false-positive diagnosis or presence of MS with less active disease among patients participating in clinical trials, which may make it difficult to detect changes between drug and placebo groups. Regardless of progress made in diagnostic procedures, use of the terms "objective clinical evidence" and "two or more lesions" could benefit from further clarification with more supporting examples.

Additionally, in regard to clinical trials, the use of MCMS 2017 diagnosis criteria enables the researcher to identify patients and intervene in an earlier stage of disease, increasing the number of patients eligible for treatment and enlarging the pool of patients potentially available to participate in clinical trials. However, this upsurge of potential patients might vary between geographic regions as a function of the availability of the modalities of earlier diagnosis and of patient access to treatment. Moreover, several issues may be present for patients in earlier stages of MS that may have less active disease and a different clinical evolution from the patient groups that were studied in clinical trials using previous diagnosis criteria. First it should be considered whether the expected effect size on clinical or biomarker endpoints would be impacted and thus, whether the design and powering of the clinical trial remain adequate with the notion that less symptoms and more variability typically result in increased sample sizes. This may lead to reconsidering the homogeneity of the population enrolled and potentially adjusting inclusion/exclusion criteria to accommodate this as well as adding clinical and biomarker assessments.

In practice, the harmonisation of diagnosis and assessment of eligibility of patients across all investigative sites and regions based on clinical assessment presents some degree of variability depending on the local clinical practice and standard of care. Therefore the selection of experienced investigators and harmonisation of the evaluation of clinical features remains critical to ensure the consistency and reliability of assessments for diagnosis and outcome, and ultimately to maximise the likelihood of detecting treatment differences. The addition of MRI evidence criteria will certainly aid the harmonisation of diagnosis. It is recommended to further enhance this process that centralised reading be utilised to minimise the variability of assessments, as well as to monitor the quality of MRI acquisition at each site. Finally, the introduction of oligoclonal band number (OCB) in CSF may be beneficial as another objective biomarker to establish diagnosis as an aid to better characterisation of patients enrolled in MS clinical trials. However, unless it has been introduced





in the standard monitoring of the patients in a clinical setting, many patients may be hesitant to undergo this procedure as part of the clinical trial, and it is often challenging to obtain CSF samples to conduct exploratory research which limits the possibilities for specific studies. In our experience, a patient's acceptance of repeated CSF sampling is typically driven by the clinician's experience and their confidence in performing the procedure and minimising the patient's discomfort. As it is now part of diagnosis criteria in the MCMS 2017, more clinicians may be performing the CSF analysis so that it becomes more common in the patient's standard of diagnosis for MS, and more widely accepted as part of clinical research for the benefit of future explorations in developing new therapies for MS. It will be interesting to follow whether the implementation of MCMS 2017 criteria in future clinical trials will impact enrolment or, ultimately, how the inclusion of patients using these criteria will impact not just enrolment rates but also affect sizes and approval rates.

REFERENCES

1. Allison RS, Millar JH. Prevalence of disseminated sclerosis in Northern Ireland. Ulster Medical Journal 1954;23:1–27.
2. Broman T, Bergmann L, Fog T, et al. Aspects on classification methods in multiple sclerosis. Acta Neurologica Scandinavica Supplement 1965;Part 2:543–8.
3. Schumacher GA, Beebe G, Kibler RF, et al. Problems of experimental trials of therapy in multiple sclerosis: report by panel on the evaluation of experimental trials of therapy in multiple sclerosis. Annals of the New York Academy of Sciences 1965;122:552–68.
4. Rose AS, Ellison GW, Myers LW, Tourtellotte WW. Criteria for the clinical diagnosis of multiple sclerosis. Neurology 1976;26:20–2.
5. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Annals of Neurology 1983;13:227–31.
6. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Annals of Neurology 2001;50:121–7.
7. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald Criteria'. Annals of Neurology 2005;58:840–5.
8. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Annals of Neurology 2011;69: 292–302.
9. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2017.

Tomislav Babic, MD, PhD.

Tomislav is Vice President of Medical and Scientific Affairs/Neuroscience Franchise at Worldwide Clinical Trials Inc. Dr Babic is a board-certified neurologist and clinical pharmacologist, with particular interest in drug development for Alzheimer's disease, Parkinson's, and MS. He is the author of more than 60 peer-reviewed articles and books and has been integral to the development of many approved drugs for PD. His expertise has been widely noted in neurodegenerative disorders in both industry and academia for the past 25 years.

Email: tomislav.babic@worldwide.com

Anne-Claude Muratet, PharmD.

Anne-Claude is the Global Project Management, Neurology Franchise Lead at Worldwide Executive Director and has more than 20 years of clinical research experience at both CRO and pharmaceutical companies. In the past 15 years, her focus is on oversight strategy and management of global programmes. Her experience includes a variety of neurologic indications spanning the full spectrum of activities and services. She serves as the portfolio lead within a strategic partnership in multiple sclerosis, providing operational strategy for the development plan and overseeing the delivery of clinical programmes for several compounds in multiple sclerosis, as well as in other indications.

Email: anneclaude.muratet@worldwide.com