During more than 5 decades, a variety of criteria to enable the diagnosis of multiple sclerosis (MS) have been proposed and often widely utilized in clinical practice. Early criteria, such as those of Schumacher, were purely clinical. The Poser criteria, which were often used and cited in the 1980s and 1990s, began to incorporate “paraclinical” testing, including imaging, evoked potentials, and CSF into a complex scheme of varying diagnostic certainty. Then, beginning with the first iteration of the McDonald criteria in 2001, MRI came to occupy a central role in the diagnostic process.

Throughout most of the 20th century, the pressure for early diagnosis was dampened because of the lack of disease-modifying therapy (DMT). The attitude of neurologists who encountered people with MS was epitomized by Labe Scheinberg, generally recognized as the father of comprehensive care in MS. He described clinicians’ behavior as “diagnose and adios,” followed in the era of readily available MRI, as “MRI and goodbye.” However, a mandate for early diagnosis began to emerge with the introduction of DMT, first with interferon β-1b in 1993. The urgency to diagnose MS quickly, but accurately, has accelerated with the introduction of many additional agents and the increasing belief that early treatment offers greater likelihood that people with MS will not accrue progressive disability. As a result, the MRI requirements for the demonstration of dissemination in space (DIS) along with dissemination in time, the cornerstones of MS diagnosis, have become less stringent.

The original recommendations of an international panel convened by the National MS Society and the International Federation of MS Societies, and subsequently called the McDonald criteria in honor of Prof. Ian McDonald, the late chairman of that group, adopted the Barkhof criteria, which required at least 3 of the following 4 features: (1) at least 9 T2 hyperintense lesions or at least one gadolinium-enhancing lesion; (2) a juxtacortical lesion; (3) an infratentorial lesion; and (4) 3 or more periventricular lesions. The first revision of the McDonald criteria, published in 2005, incorporated spinal cord lesions into the scheme in a limited manner. A substantial loosening of the criteria came with the 2010 revision, which now requires only one lesion in each of 2 characteristic locations: periventricular, juxtacortical, infratentorial, or spinal cord. However, a major caveat was the insistence that a lesion not be counted toward fulfillment of the DIS requirement if it was in the region responsible for the clinical symptomatology. In this issue of Neurology®, Brownlee et al. now argue that this requirement should be abolished and lesions in the symptomatic region should be counted as contributing to the DIS requirement. Studying 30 patients with clinically isolated syndrome, the authors found that the sensitivity, specificity, and accuracy of the McDonald 2010 criteria were respectively 73%, 73%, and 73%; 80%, 73%, 77% when asymptomatic lesions in the symptomatic region were included; and 87%, 73%, 80% when any visible lesion in the symptomatic region was included for DIS. Thus, including lesions in the symptomatic region increased sensitivity without sacrificing specificity or accuracy. It must be emphasized, however, that while the use of the 2010 McDonald criteria or either of the Brownlee modifications for DIS all substantially reduce the time to MS diagnosis compared to clinically definite MS criteria, the Brownlee modifications reduce the mean time to diagnosis compared to the 2010 McDonald criteria by just 4 months (McDonald 2010: 8.9 months; DIS including only asymptomatic lesions in the symptomatic region: 6.7 months; and DIS including any lesion: 4.8 months).

Making a diagnosis of MS earlier is advantageous, but being correct is critical. In that regard, it is important to note that Brownlee et al. emphasized that their data apply only to patients presenting with clinically isolated syndrome manifest by acute spinal cord or brainstem/cerebellar syndromes and that “care should be taken to exclude conditions that mimic MS.” Furthermore, their cohort included only patients between the ages of 16 and 50, thereby excluding most patients who might have vascular lesions that could satisfy the criteria for dissemination in space.
Indeed, Filippi et al., writing on behalf of the MAGNIMS Study Group (a European collaborative research network that studies MRI in MS) recently further acknowledged the problem of alternative diagnosis with their conclusion that "a single lesion was deemed not sufficiently specific to determine whether involvement of the periventricular region is due to a demyelinating lesion." The MAGNIMS Group has now recommended that 3 or more lesions be required to define the involvement of the periventricular region to establish DIS. They point out that periventricular lesions can occur in healthy individuals and are present in up to 30% of people with migraine.

Based on a survey of MS subspecialists, Solomon et al. reported that 95.1% of the 122 respondents stated that in the past year they had encountered patients diagnosed with MS for longer than a year whom they strongly believed did not have MS. In addition, nearly two-thirds of the respondents estimated that more than a quarter of those patients were receiving DMT. The most frequently cited alternative diagnoses were nonspecific white matter abnormalities, small vessel ischemic disease, migraine, and psychiatric disorder, suggesting "over-reliance on MRI findings in patients with syndromes for which established MS diagnostic imaging criteria have not been validated." Particular caution in assessing spinal cord MRI might be advisable for clinicians assessing patients with purely sensory symptoms in view of the susceptibility of a variety of imaging artifacts and the frequency of suboptimal studies in the community.

The International Advisory Committee on Clinical Trials, jointly sponsored by the National MS Society and ECTRIMS (European Committee for Treatment and Research in MS), is expected to convene again this coming fall to revisit the McDonald criteria. Undoubtedly, participants in that workshop will consider the Brownlee observations (although replication from larger studies would be reassuring), as well as the MAGNIMS recommendations, as they deliberate making changes that may hasten diagnosis, without increasing risk of misdiagnosis. In the meantime, clinicians are urged to heed the final caveat of all diagnostic criteria, to assure that the symptoms are clearly attributable to the CNS and consistent with demyelination (such as onset and duration of symptoms); to determine that there are no better explanations for the clinical findings; to give close attention to clinical and imaging red flags; and to scrutinize MRI studies carefully, always being cognizant of conditions that may potentially mimic MS and produce similar MRI abnormalities.

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**REFERENCES**