The field of multiple sclerosis (MS) stands out from other areas of clinical neurology not only by the large number of therapeutic options, but also the availability of diagnostic tests that allow for an early and accurate diagnosis.[1] Magnetic resonance imaging (MRI) readily detects asymptomatic brain and spinal cord lesions in over 90% of people with MS at the time of presentation, and more than 80% have cerebrospinal fluid (CSF)-specific IgG oligoclonal bands.[2]

Observational studies in patients with clinically isolated syndrome (CIS) have established the prognostic value of conventional MRI (and CSF) findings in predicting a second clinical attack (i.e. clinically-definite MS) in this group of patients. This work formed the basis for modern diagnostic criteria for MS (the McDonald criteria), first proposed in 2001. The McDonald criteria provide guidance on the use of MRI and CSF examination in the diagnostic process, while preserving the key requirements from earlier MS diagnostic criteria. These include: the need for a clinical syndrome compatible with MS; objective evidence of lesions disseminated in space and time; and importantly no better explanation for the patient's symptoms, an essential step in diagnosing MS in the absence of a pathognomonic clinical or para-clinical test that differentiates MS from other conditions.

The original McDonald criteria were revised (tweaked) in 2005, 2010 and 2017 with simplification of the MRI criteria for dissemination in space and time on the basis of new evidence from prospective observational studies in CIS patients. The most recent modifications to the McDonald criteria in 2017 include the integration of symptomatic and cortical grey matter lesions into MRI criteria for dissemination in space and time, and allowing CSF-specific IgG oligoclonal bands to be used as a substitute for MRI (or clinical) evidence of dissemination in time.[3] This latest set of changes has the potential to stream-line the diagnostic process in people with suspected MS, increasing the number of patients diagnosed at the time

of disease onset rather than requiring follow-up MRI scans, or a second clinical attack.[4] However, nearly half of people with MS are unable be diagnosed at the time of presentation, even when applying the most up-to-date revisions to the McDonald criteria.[4] It seems likely that there will be further changes to the diagnostic criteria for MS in the future as new evidence becomes available. For example, a recent study found that including optic nerve lesions (detected clinically and/or with visual evoked potential testing) in patients with optic neuritis in dissemination space criteria improved the performance of MS diagnostic criteria.[5]

The aim of the McDonald criteria is to diagnose MS. The criteria have not been developed or validated as a tool for differentiating MS from other neurological disorders, or to rule-out MS in patients presenting with non-specific symptoms like dizziness or parasthesia.[3] MRI and CSF examination are highly sensitive diagnostic tests in patients with suspected MS, but the specificity is only moderate. For example, brain white matter lesions (potentially compatible with demyelination) are sometimes seen in patients with migraine, small vessel cerebrovascular disease or even with healthy ageing.[1] Similarly, CSF-specific oligoclonal bands can be found in other neuroinflammatory disorders (e.g. neuromyelitis optica spectrum disorder, vasculitis). In the face of diagnostic tests with high sensitivity but limited specificity it is essential that the McDonald criteria are applied only in patients with symptoms typical of MS (e.g. unilateral optic neuritis, brainstem syndromes, partial myelopathy), after excluding alternative diagnoses.[3] Misdiagnosis of MS can arise as a consequence of misapplication of the McDonald criteria in patients with symptoms not typical of MS.[6] Migraine, fibromyalgia and functional neurological disorders account for nearly half of patients misdiagnosed with MS.[6] While these disorders can produce clinical symptoms that overlap with MS (e.g. visual disturbance, sensory symptoms, pain), the nature of the symptoms, their evolution and the absence of abnormal neurological signs would normally point to an alternative diagnosis. Misdiagnosis of MS in patients with these conditions doesn't represent a failing of our

diagnostic criteria, but rather a failure to identify another (more common) neurological disorder that has clinical features distinct from MS.

A number of established MRI measures with greater pathological specificity for MS than brain T2-hyperintense lesions are already included in the McDonald criteria. Short-segment spinal cord lesions are seen in most people with MS but are not in patients with cerebrovascular disease, migraine or healthy aging.[1] Spinal cord MRI can be especially helpful in making a diagnosis of MS in patients with atypical clinical presentations, in older adults and in those with comorbidities. Routine spinal cord imaging is controversial[7], and spinal cord MRI may be an under-utilised in the work-up of patients with suspected MS. Cortical grey matter lesions, detected using double Inversion Recovery (DIR), are also a highly specific MRI finding that can help differentiate MS from common mimics.[9] Cortical grey matter lesions were included in the most recent revisions to the McDonald criteria.[3] However, despite considerable effort over the last 10 years or more, DIR is not routinely available outside highly specialist centres. Given the potential value of cortical grey matter lesions in MS diagnosis and differential diagnosis the

in order to maximise the impact of this well-established MRI biomarker in clinical practice.

Neurologists diagnosing and treating MS are fortunate in that we have a robust set of diagnostic criteria that allow for an early and accurate diagnosis of MS. These criteria are likely undergo further revision in the future as new evidence becomes available. However, the active consideration and exclusion of other disorders, a caveat that has been at the heart of diagnostic criteria for MS over the last 50 years, will almost certainly remain. This requires

careful integration of the patient's symptoms and signs, focussed investigation and clinical acumen, not new diagnostic criteria to distinguish MS from other conditions.

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