Use (and misuse) of the McDonald criteria to diagnose multiple sclerosis

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The McDonald criteria allow the use of MRI to provide evidence of dissemination in space and time to establish a diagnosis of multiple sclerosis (MS), including in people with a single clinical event, or clinically isolated syndrome (CIS) [1]. The original criteria published in 2001 were revised based on evidence from large, multicentre European studies [2]. The high sensitivity and specificity of the McDonald criteria for the development of clinically-definite MS (CDMS) has been confirmed in number of studies. The McDonald criteria allow for an earlier diagnosis of MS, potentially facilitating earlier initiation of disease-modifying treatment [3].

There are several caveats when applying the McDonald criteria [1]. Firstly, the criteria should only be applied in people with a “typical” clinical presentation suggestive of MS (e.g. unilateral optic neuritis, bilateral internuclear ophthalmoplegia). Deciding what constitutes a typical (or atypical) clinical presentation is subjective, although a number of reviews and expert consensus statements are available to guide neurologists [4]. Secondly, MRI findings alone are not enough to diagnose MS – there must be objective clinical evidence of at least one central nervous system lesion. Finally care must be taken to exclude alternative diagnoses. These caveats are essential when applying the McDonald criteria, but are sometimes overlooked.

In this issue of *European Journal of Neurology* Rosencranz and colleagues evaluate the performance of the McDonald criteria in a cohort of patients referred to their centre with a suspected first demyelinating event [5]. The strength of the paper is the use of unselected cohort of patients with suspected MS to test how the McDonald

criteria perform in a “real-world” setting, rather than in highly selected cohorts from specialist MS centres, in which the MRI criteria for diagnosing MS were developed and validated [2]. The limitations include the retrospective design and the use of clinically-acquired data meaning that not all patients had a follow-up MRI, which is important for demonstrating dissemination in time.

The major finding of the study is that over a follow-up period of 2 years, only 1 in 3 CIS patients who fulfilled the McDonald 2010 developed CDMS. The remaining patients had MRI evidence of dissemination in space and time but did not experience a second clinical attack, at least at different site (some patients had recurrent symptoms i.e. clinically-probable MS, but weren’t included in this group). The specificity, accuracy and positive predictive value of the McDonald 2010 criteria was rather lower in this cohort that in previous studies (<70%) leading the authors to question the benefit of the McDonald criteria.

Why did so few patients develop CDMS? The most important factor is the short duration of follow-up. Only half of CIS patients who develop MS have a second clinical attack in the first 2 years after disease onset, and so the number with CDMS will inevitably increase with time [3]. A small number of patients also received disease-modifying therapies, which are known to delay the onset of CDMS in CIS patients. Finally, the authors included patients who presented with non-specific sensory symptoms without objective neurological signs (in whom the rate of CDMS was particularly low) and cognitive presentations, which although well-described in MS are not “typical”. The McDonald criteria have not been validated for use in

patients with non-specific neurological symptoms or in patients with atypical clinical presentations, in whom the pre-test probability of MS is much lower than in young adult patients with unilateral optic neuritis or a partial myelopathy. Somewhat reassuringly when the subgroup of patients without objective neurological signs were excluded from the analysis the performance of the McDonald criteria was similar. However, it remains imperative that the McDonald criteria only be applied in patients with a typical CIS presentation who have objective evidence of at least one lesion. Misdiagnosis of MS is a major contemporary issue in neurological practice. A recent prospective study from North America highlighted the inappropriate application of the McDonald in patients with symptoms not typical of demyelination and without objective evidence of a lesion as major contributors to MS misdiagnosis and mistreatment [6].

Overall the findings of Rosencranz and colleagues do suggest that MS is diagnosed more often in CIS patients using the McDonald criteria, confirming previous observations [3, 7, 8]. A subgroup of CIS patients have MRI evidence of dissemination in space and time on MRI with no further relapses or accumulation of physical disability over follow-up periods as long as 20 years [7]. Changes to the diagnostic criteria may be identifying patients with milder forms of MS and this may favourably impact on the long-term prognosis of relapse-onset MS [8]. This is a reminder that the McDonald criteria are intended to be *diagnostic* rather than *prognostic*. There is an unmet need for robust prognostic markers that can help predict disease course in people with CIS and early MS, including the timing of a second clinical attack, relapse rates and long-term disability.

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