The new MS diagnostic criteria in practice

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Abstract

The diagnosis of multiple sclerosis, after exclusion of its mimics, is based on the objective evidence of central nervous system involvement and dissemination of demyelinating lesions in time and space. The correct application of the current diagnostic criteria enables early diagnosis of MS and prompt commencement of disease-modifying therapies. We provide a diagram that summarises the McDonald 2017 diagnostic criteria, which may serve both MS experts and general neurologists in the diagnostic process of multiple sclerosis. We also briefly comment on the advantages of using the new diagnostic criteria and stress the uncertain fields that warrant further research.

Background

The diagnostic criteria for multiple sclerosis (MS), first developed in the 1950s, have since undergone several revisions, all focused on three main requirements for a diagnosis of MS: 1) objective clinical evidence of central nervous system (CNS) involvement; 2) evidence of lesions disseminated in time (DIT) and space (DIS); 3) exclusion of other conditions that could better explain the clinical and paraclinical findings. Before the widespread use of magnetic resonance imaging (MRI), DIT and DIS were fulfilled by two attacks involving different parts of the CNS and clinical evidence of two lesions separated in time, or one attack with additional paraclinical evidence of another lesion. In 2001, McDonald et al. fully integrated the use of MRI into the diagnostic schema as an alternative to clinical evidence for DIS and DIT, allowing an earlier diagnosis of MS.[1] Based on new evidence for the role of MRI, the McDonald criteria were revised in 2005, 2010, and 2017.[2–4] Given the increasing focus on the importance of early treatment of MS with disease-modifying therapies, a prompt and accurate diagnosis of MS has never been more important.

Previous diagnostic criteria

The 2010 revisions to the McDonald criteria simplified the requirements for DIS and DIT on MRI and removed neurophysiological and cerebrospinal fluid (CSF) testing from the diagnostic criteria (for relapsing-remitting MS). DIS on MRI required at least one T2 lesion in at least two of four locations characteristic of MS (periventricular, juxtacortical, infratentorial and spinal cord), and DIT required the simultaneous presence of gadolinium-enhancing and non-enhancing lesions, or a new T2 or gadolinium-enhancing lesion on a follow-up MRI. For the first time, a diagnosis of MS could be made in some clinically isolated

syndrome (CIS) patients with a single contrast-enhanced MRI scan. However, there were two main caveats: 1) the criteria would only be applied when MS was already the most likely diagnosis, and where this was not the case, then both neurophysiological and CSF studies still had a clear role; 2) the criteria treated symptomatic and asymptomatic lesions differently: only asymptomatic lesions could contribute to DIS and DIT using MRI.

The main changes in the new diagnostic criteria

The 2017 revision of the McDonald criteria (Figure 1) further simplify the diagnostic process in patients with CIS. The first major change is the reintroduction of CSF oligoclonal bands, which have been shown to predict a second clinical attack following a CIS in patients with MRI evidence of DIS. [5] In a typical CIS patient with DIS, the presence of unmatched CSF oligoclonal bands now permits a diagnosis of MS, even without DIT on MRI or a second attack (Figure 2). Moreover, there is no longer a distinction between symptomatic or asymptomatic lesions, and both, with the exception of optic nerve lesions, can contribute to the MRI determination of DIS or DIT. The 2017 Criteria also allow for cortical lesions, which are common in MS, to contribute to the determination of MRI DIS. The requirements for the diagnosis of primary progressive MS have not changed compared to past versions, apart from the removal of the distinction between symptomatic and asymptomatic lesions and the inclusion of cortical lesions.

Commentary

MRI can demonstrate DIT and DIS, which are at the core of MS diagnosis, and the revised criteria now recognise cortical involvement in MS while also simplifying the MRI DIS and DIT requirements. However, MRI lesions similar to that found in MS can be seen in other

disorders, and MRI criteria should not be applied in patients with atypical clinical presentations.[6] If there is doubt regarding the nature of symptoms or signs, further evaluation should be carried out.[7] The 2017 criteria should be applied with caution in geographical areas with a lower incidence of MS, in younger children and older adults, and those with comorbidities (e.g. migraine or small vessel disease) in order to avoid misdiagnosis. Particular attention is necessary to rule out neuromyelitis optica spectrum disorder, especially in African-American, Asian, Latin American, and paediatric populations, where this disease is relatively more common. There remains further scope for the current 2017 diagnostic criteria to be further refined, for example, despite the specificity of cortical lesions for MS they still cannot be detected as easily as white matter lesions using MRI techniques available clinically. The visual system is also often involved in MS, yet the role of optic nerve MRI, visual evoked potentials, or optical coherence tomography in fulfilling DIS or DIT remains uncertain. Moreover, the incidental finding of MRI white matter lesions that fulfil MS radiological diagnostic criteria (termed a radiologically isolated syndrome [RIS]), remains a cause of clinical uncertainly that the 2017 criteria have not resolved [8].

Changes in MS diagnostic criteria have also raised questions about the use of DMTs following a CIS. The evidence for DMT use following a CIS comes from clinical trials that used pre-2010 diagnostic criteria, i.e. where a significant proportion of those enrolled in studies would now fulfil diagnostic criteria for MS, and so it is unclear if their efficacy would be the same in people now classified as having a CIS rather than MS. This point has recently been a matter of discussion for the National Institute for Health and Care Excellence." [9]

In conclusion, the new diagnostic criteria can be applied easily and allow for a more stream-lined diagnosis of MS. However, they do not replace physicianly judgement and should never be applied without careful clinical evaluation.

Competing interests

Dr De Angelis has nothing to disclose.

Dr Brownlee reports personal fees from Roche and personal fees from Merck Serono outside the submitted work.

Dr Chard has received, within the last two years, honoraria (paid to his employer) from Excemed for faculty-led education work; and meeting expenses from Novartis and Société des Neurosciences outside the submitted work.

Dr Trip reports a personal fee from Roche, a personal fee and non-financial support from Novartis, a personal fee from Merck Serono, personal fees and non-financial support from Teva, non-financial support from Biogen, all outside the submitted work.

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References

[1] 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. *Ann Neurol* 2001; 50: 121–127.

[2] Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58: 840–846.

[3] Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis:

2010 Revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.

[4] Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. Epub ahead of print 21 December 2017. DOI: 10.1016/S1474-4422(17)30470-2.

[5] Arrambide G, Tintore M, Espejo C, et al. The value of oligoclonal bands in the multiple sclerosis diagnostic criteria. *Brain* 2018; 141: 1075–1084.

[6] Geraldes R, Ciccarelli O, Barkhof F, et al. The current role of MRI in differentiating multiple sclerosis from its imaging mimics. *Nat Rev Neurol* 2018; 14: 199–213.

[7] Brownlee WJ, Hardy TA, Fazekas F, et al. Diagnosis of multiple sclerosis: progress and challenges. *Lancet* 2017; 389: 1336–1346.

[8] Okuda DT, Siva A, Kantarci O, et al. Radiologically Isolated Syndrome: 5-Year Risk for an Initial Clinical Event. *PLoS One* 2014; 9: e90509.

[9] National Institute for Health and Care Excellence (NICE). Beta interferons and glatiramer acetate for treating multiple sclerosis. Technology appraisal guidance (published date 27 June 2018). www.nice.org.uk Accessed date 17 July 2018.

Figure legend

- **Figure 1. Diagram or visual summary of the last revision of the MS Diagnostic Criteria**

  According to the glossary provided by Thompson et al. [4], in the figure, the term "lesion(s)" refers to "an area of hyperintensity on a T2-weighted or proton-density weighted MRI scan that is at least 3 mm in long axis."

  CIS= clinically isolated syndrome. CNS= central nervous system. CSF= cerebrospinal fluid. DIS= dissemination in space. DIT= dissemination in time. MRI= magnetic resonance imaging. MS= multiple sclerosis. WM= white matter.

- **Figure 2. Case Scenario**

  Adapted clinical case showing different diagnostic outcomes after the application of the old and the new diagnostic criteria.

  *The presence of CSF-specific oligoclonal bands does not conclusively demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

  CE= contrast enhancement. CSF= cerebrospinal fluid. Gad: gadolinium. *MRI= magnetic resonance imaging.* OCBs= oligoclonal bands.

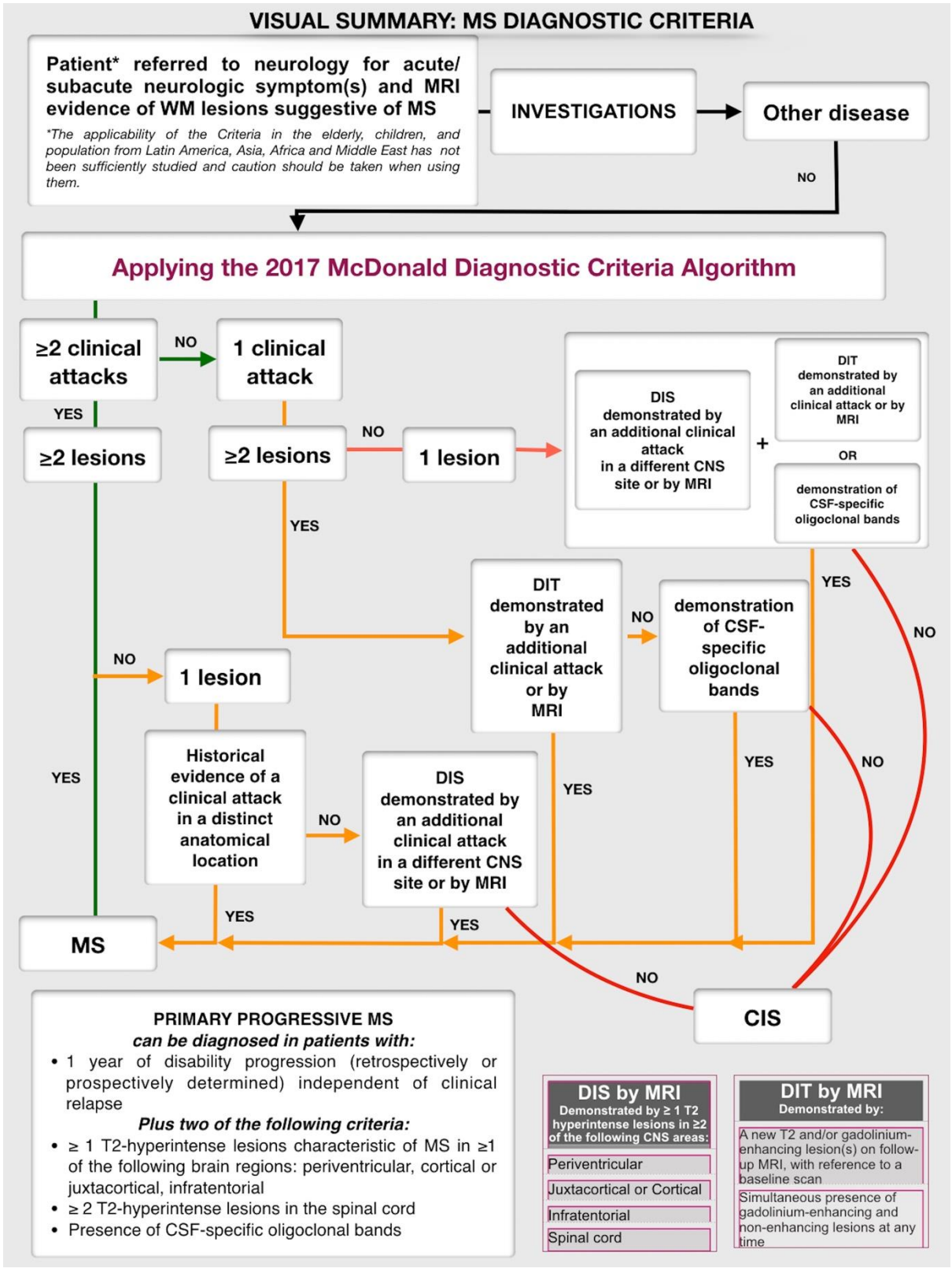
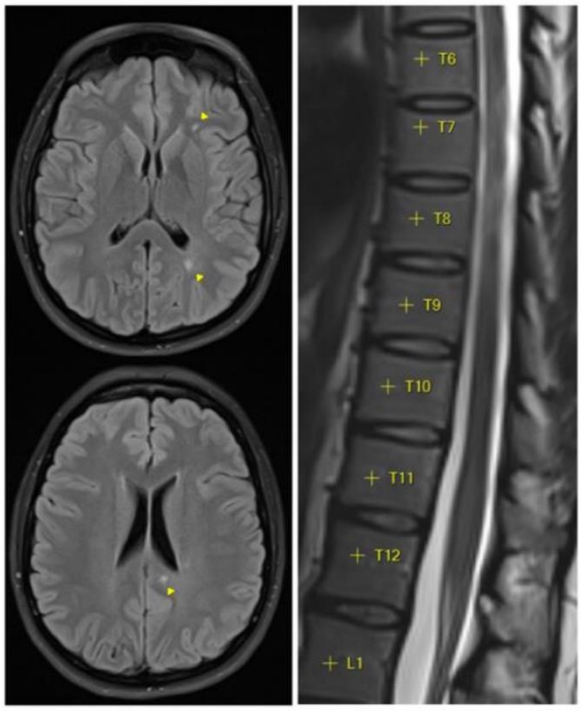


Figure 1. Diagram or visual summary of the last revision of the MS Diagnostic Criteria

CASE SCENARIO

Demographics	27-year-old woman
Presenting complaint	Numbness and paraesthesia from the right side of the trunk down to right foot lasting 10 days, followed by the Lhermitte phenomenon
Examination	Brisk reflexes in right lower limb.
Investigations	***FBC, U&Es, CRP, bone profile, B12***: normal. ***ANA, ANCA, ds-DNA, antiphospholipid, ENA, anti-aquaporin 4, anti-MOG Abs***: negative. ***Folate*** and ***vitamin D***: low (replacement therapy started). ***MRI without Gad (Nov 2016):*** T2 hyperintensity in the body of the corpus callosum, left splenium and left peritrigonal area. Cord lesions at T6/T7, T11-T12. ***MRI with Gad (Jan 18):*** No enhancing lesions. No new lesions. ***CSF:*** unmatched oligoclonal bands.



APPLICATION OF THE 2010 MCDONALD CRITERIA		***APPLICATION OF THE 2017 MCDONALD CRITERIA***	
Dissemination in space > 1 T2 periventricular lesions; > 1 T2 spinal cord lesions but cannot be counted as symptomatic.	✗	**Dissemination in space** > 1 T2 periventricular lesions; > 1 T2 spinal cord lesions, which can now be counted despite being symptomatic	✓
Dissemination in time No new MRI lesions, no relapses	✗	**Dissemination in time** No new MRI lesions, no relapses Positive CSF-specific OCBs*	✓
FINAL DIAGNOSIS Clinically Isolated Syndrome		**FINAL DIAGNOSIS** Multiple Sclerosis	

Figure 2. Case Scenario