2017 McDonald diagnostic criteria: A review of the evidence

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Abstract:

The diagnosis of Multiple Sclerosis (MS) has continuously evolved, allowing for an earlier and more accurate diagnosis of MS over time. The McDonald Criteria for diagnosis of MS were originally proposed in 2001, with previous revisions in both 2005 and 2010. The International Panel on Diagnosis in MS have recently reviewed the 2010 McDonald Criteria, and made recommendations for the revised 2017 McDonald Criteria. Any revisions made relied entirely on the available evidence, and not expert opinion. In this review, we provide an overview of the recent 2017 revisions to the McDonald Criteria, focusing in particular on the motivating evidence behind the recommendations made. We also review the existing research around misdiagnosis in MS, as well as areas considered to be high priorities of research, currently lacking in sufficient evidence, which may influence future diagnostic criteria in years to come. Finally, we illustrate some clinical examples, to demonstrate the impact of new diagnostic criteria on time to MS diagnosis in a real-world setting.

Introduction:

The diagnosis of MS has continuously evolved over time since its first description in 1868 by Jean Martin Charcot, "La sclerose en plaques". Charcot's clinical and pathological observations recognised the diverse neurological symptoms of a single disease with distinct pathological features, and led to the first diagnostic criteria in MS, "the Charcot triad", of nystagmus, ataxia and dysarthria. (Charcot 1868) Since this initial observational description, evolving diagnostic criteria in MS have been influenced by the increasing availability of

supportive paraclinical assessments, including visual and sensory evoked potentials (Schumacher, Beebe et al. 1965), cerebrospinal fluid oligoclonal bands (CSF OCBs) (Poser, Paty et al. 1983) and most dramatically in relatively recent years, by advancements in magnetic resonance imaging (MRI). The remarkable revelations of early MRI studies in the natural history of MS were the driving force behind the initial McDonald Criteria in 2001 (McDonald, Compston et al. 2001). Subsequent clinical-MRI correlations, with improved MRI technology, have significantly affected revisions in 2005, and 2010 (Polman, Reingold et al. 2005, Polman, Reingold et al. 2011) and most recently in 2017, by the International Panel on Diagnosis in MS (the Panel) (Thompson, Banwell et al. 2017). Each revision of the diagnostic criteria over time has allowed an earlier, accurate diagnosis of MS (Brownlee, Swanton et al. 2015).

Using the McDonald Criteria, relapsing-remitting MS is diagnosed in a patient presenting with appropriate symptoms and with objective clinical evidence of one or more demyelinating lesions, using the additional radiological or laboratory evidence of dissemination in space (DIS) and/or dissemination in time (DIT) if required. We may diagnose progressive MS with evidence of at least one year of clinical evidence of progression using additional radiological and/or laboratory evidence (**Table 1**). Diagnosis of MS always requires careful exclusion of diseases which could better explain the clinical and radiological and laboratory findings. (Miller, Weinshenker et al. 2008) Each revision to the McDonald criteria has particularly concentrated on what defines DIS, and DIT, with MRI definitions illustrated in **Table 2**.

In this review, we examine the core revisions to the 2017 McDonald criteria, looking at the evidence motivating the proposed recommendations. We also assess the existing evidence for misdiagnosis in MS as well as areas of high priority research that may influence future diagnostic criteria in years to come. Finally, we will illustrate some clinical examples, to demonstrate the impact of new diagnostic criteria on time to diagnosis in a real-world setting. The fundamental rules remain: 1) that neurological symptoms and signs are considered to be inflammatory and demyelinating in origin; 2) that no better diagnosis can explain the clinical presentation, and 3) that the integration of the data is done by a neurologist entirely familiar with multiple sclerosis.

Core Revisions to the McDonald Criteria

A clinical diagnosis of MS requires the fulfilment of both DIS and DIT, however the correct identification of patients with very early MS and at high risk for conversion to clinically definite MS (CDMS) is now even more important, with treatments showing a delay in the occurrence of a second attack, as well as better long-term outcomes. (Jacobs 2000, Kavaliunas, Manouchehrinia et al. 2017) The Panel relied on the available evidence for any revisions made to the 2010 McDonald criteria, and not on expert opinion.

CSF examination:

The 2010 McDonald criteria placed little emphasis on the presence of CSF OCBs in the diagnostic criteria of MS, although recognised as an accurate marker of intrathecal IgG synthesis, and therefore of diagnostic support. CSF OCBs (not present in a concomitant serum sample) may now substitute for a second clinical or imaging event and provide evidence of DIT in a clinically isolated syndrome (CIS) where evidence for DIS already exists on MRI. A number of studies show sufficient evidence that in adults with CIS, CSF OCBs are an independent predictor of a second relapse, controlling for clinical, demographic, and radiological variables.

One Spanish study prospectively looked at 112 patients presenting with a CIS, with available CSF OCBs as well as MRI results. In this group the sensitivity, specificity, accuracy, and positive and negative predictive values of CSF OCBs could be determined. Follow-up was over a mean of 31 months (range 12-62), with 23% of patients developing clinically definite MS (CDMS) during the follow-up period. There was a high prevalence of CSF OCBs in this CIS cohort (62.5%). Positive CSF OCBs showed a sensitivity of 81%, specificity of 43%, accuracy of 52%, positive predictive value of 30% and negative predictive value of 87% in this cohort. When combining the presence of CSF OCBs with MRI criteria fulfilling the Barkhof criteria (Barkhof, Filippi et al. 1997), results were even more associated with subsequent conversion to CDMS; with a sensitivity of 62%, a specificity of 77%, an accuracy of 73%, positive predictive value of 47% and negative predictive value of 87%. (Tintore, Rovira et al. 2001) Another Spanish study of 415 CIS patients with available baseline CSF

OCBs and MRI has shown the presence of OCBs to increase the risk of a second clinical event independent of baseline MRI by nearly double, with a hazard ratio (HR) of 1.7. (Tintore, Rovira et al. 2008) A prospective study of over one-thousand patients showed the presence of CSF OCBs to increase risk of conversion to CDMS (HR 1.3), as well as the risk of disability progression (HR 2.0). (Tintore, Rovira et al. 2015) A retrospective study looked at 406 patients presenting with a CIS who had available MRI and were tested for OCBs. 81% had positive OCBs and MRI lesions consistent with DIS, this was associated with a hazard ratio of 2.1 for the development of CDMS over a 25-month period, compared with a 47-month follow-up period in the OCB negative cohort. In those without brain lesions, conversion rate to CDMS was 60% for the OCB positive cohort, and just 21% in the OCB negative cohort. (Huss, Halbgebauer et al. 2016) A large, retrospective, international multicenter study of over one thousand patients showed positive CSF OCBs to have a HR of 2.18 for development of CDMS over a 4.3-year follow-up period, this is compared with a HR of 1.97 for MRI with two to nine hyperintensities, and a HR of 2.74 for MRI with >9 T2 hyperintense demyelinating plaques. (Kuhle, Disanto et al. 2015)

CSF findings may also provide warning signs to suggest alternative diagnosis particularly in atypical CIS presentations, such as a high leucocyte count, or negative OCBs. (Brundin 2016) Thus, in the revised 2017 criteria, the Panel highly recommend lumbar puncture assessment, particularly in the following instances: (i) where there is equivocal clinical and MRI evidence supporting MS, (ii) where there is a non-classical presentation, including progressive MS presentations, (iii) when there is an atypical clinical presentation of MS and (iv) in specific populations.

Quality control with oligoclonal band ascertainment is emphasized, using an experienced laboratory, 2 or more CSF-specific bands and agarose gel electrophoresis with isoelectric focusing and immunoblotting or immunofixation for IgG preferred. Paired serum and CSF samples is mandatory. (Andersson, Alvarez-Cermeno et al. 1994, Freedman, Thompson et al. 2005, Stangel, Fredrikson et al. 2013, Filippi, Rocca et al. 2016)

MRI criteria:

Over time, the role of MRI in the diagnosis of MS has become increasingly more important. MRI may be used to fulfill criteria for DIS and/or DIT in the diagnostic work-up, it may also demonstrate atypical features more suggestive of an alternative diagnosis. The MAGNIMS (Magnetic Resonance Imaging in MS) consortium have described new 2016 criteria for the radiological work-up of MS (Filippi, Rocca et al. 2016).

According to the 2010 McDonald criteria, DIS can be established with at least one T2 lesion in at least two of four locations characteristic for MS (juxtacortical, periventricular, infratentorial and spinal cord). It is now well-known from pathological studies that cortical and deep grey mater involvement is extensive in MS; cortical lesions may be subpial, intracoritcal or leucocortical (on the grey-white mater border), or juxtacortical. (Peterson, Bo et al. 2001) Imaging cortical lesions is difficult and remains primarily an area of research, lesions are not well visualised on conventional 1.5 or 3 Tesla MRI scanners. Because routine clinical MRIs cannot distinguish between cortical, and juxtacortical lesions in MS, it was recommended by MAGNIMS that they be combined to a single term, "cortical/juxtacortical" for the updated criteria. The Panel also considered the evidence for inclusion of visualised of cortical lesions in the diagnostic work-up of MS. When specialized sequences for viewing cortical grey mater disease (such as double inversion recovery) are used, the presence of one or more intracortical lesion was shown to be an independent predictor for the development of CDMS. The accuracy of MRI diagnostic criteria are improved when considering intracortical lesions for DIS, with an accuracy of 81%. (Filippi, Rocca et al. 2010)

Using 2010 McDonald criteria, the demonstration of DIS does not include a symptomatic lesion in the lesion count for consideration of DIS, specifically in brainstem or spinal cord syndromes. DIT could be established in 2010 criteria by; the presence of one or more new T2 or gadolinium-enhancing lesion on follow-up MRI with reference to a baseline scan, or the simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time. Therefore, in patients with a typical CIS, symptomatic lesions corresponding with the clinical deficit did not demonstrate DIS, nor did they contribute to DIT if enhancing. Evidence has since emerged for the incorporation of symptomatic lesions for the demonstration of DIS, and symptomatic enhancing lesions for the demonstration of DIT. A recent retrospective French study of 146 patients with CIS who fulfilled the 2010 McDonald criteria, looked at the effect on time to diagnosis when considering the symptomatic visualised demyelinating lesion as confirmatory diagnostic information. Using these

diagnostic criteria, MS diagnosis could be confirmed in 99.7% of the patients after a single clinical event with initial MRI, time to diagnosis was a mean of 0.03 months (+/- 0.41 months) versus 5.81 months (+/- 15.24 months) using the 2010 McDonald Criteria. (Caucheteux, Maarouf et al. 2015) A second retrospective study of 30 CIS presentations that were followed up for a mean of 7.3 years showed the sensitivity of DIS criteria for 2010 McDonald criteria to be 73%, which increased to 87% when any lesion in the symptomatic region was included, specificity did not change at 73%. (Brownlee, Swanton et al. 2015) A Canadian study looked retrospectively at the effect of including a symptomatic gadolinium enhancing lesion for DIT criteria in 109 CIS patients. 30% of the patients met the 2010 McDonald criteria diagnosis at baseline MRI, this increased to 33%, with three further patients receiving a diagnosis when applying these criteria. All three of these patients already met the 2010 MRI DIS criteria. (Kang, Metz et al. 2014) These results suggest the inclusion of symptomatic lesions in criteria for DIS increase the sensitivity for MS diagnosis without compromising specificity. An exception to this is the optic nerve as an anatomical location for DIS, because insufficient evidence exists regarding symptomatic versus asymptomatic in supporting DIS. One recent study of 129 CIS patients with an optic neuritis presentation, and 29 patients with a non-optic neuritis presentation suggests that use of a symptomatic optic nerve lesion in DIS, increases sensitivity from 83% to 95% however it reduces specificity from 68% to 57% in MS diagnosis. Evidence also exists to suggest CIS presentation with optic neuritis is more likely to remain a monophasic illness than demyelination in other central nervous system locations, in a study of more than one thousand CIS presentations. (Tintore, Rovira et al. 2001)

Primary progressive MS:

Aside from the inclusion of symptomatic lesions for definition of DIS as described above, the definition of primary progressive MS for diagnosis remains unchanged from 2010 McDonald criteria.

Misdiagnosis in MS:

An important issue to consider in the recommendations for the diagnosis of MS, is that of misdiagnosis, an ongoing issue in current medical practice which has been stressed by the Panel in the 2017 review of McDonald criteria. A recent multi-centre study based in across

four centres in the United States (US), looked closely at the spectrum of misdiagnosis in MS. 23 neurologists who sub-specialize in MS reviewed patients previously diagnosed with MS by another neurologist over a 13month period. During this time, 110 patients who had previously received a misdiagnosis were identified. The five most frequent alternative diagnoses reported in over 66% of this patient group were: migraine, fibromyalgia, non-specific neurological symptoms with abnormal MRI, conversion disorder, and neuromyelitis optica. Most of these patients (70%) had been inappropriately exposed to potentially harmful disease modifying therapies over prolonged periods of time. The most common reasons for misdiagnosis were; (i) the inappropriate application of the McDonald criteria in an atypical neurological attack, and (ii) the application of the McDonald criteria to a historical attack without corroborating objective evidence of a lesion on clinical examination, radiologically, or by evoked potentials. (Solomon, Bourdette et al. 2016)

Another US study in 2005, evaluated 281 referrals to MS specialists over a 30-month period. This study showed that whilst 46% of referrals based on clinical symptoms went on to receive a diagnosis of MS or possible MS, only 11% of those referred based on abnormal MRI findings alone ultimately received a diagnosis of MS, or possible MS. (Carmosino, Brousseau et al. 2005) CM Poser was one of the first neurologists to report on the significant number of misdiagnosis in MS due to over-reliance on MRI. (Poser 1997)

It is due to findings in these studies that the Panel in 2017 have stressed the importance of appropriate clinical application of the McDonald criteria, which predominantly apply to patients with a typical CIS at onset, for accurate MS diagnosis. Atypical clinical presentations in MS include; bilateral optic neuritis, optic neuritis with poor visual recovery, complete gaze palsy or fluctuating ophthalmoparesis, intractable nausea vomiting or hiccups, complete transverse myelitis, encephalopathy, subacute cognitive decline, isolated fatigue, headache or meningism, and constitutional symptoms. (Brownlee, Hardy et al. 2017) These clinical presentations require extensive investigation to outrule an alternative diagnosis.

The Panel focus in particular on ruling out neuromyelitis optica spectrum disorder (NMOSD), due to the volume of evidence published since the McDonald criteria were last updated. With widespread testing for serum aquaporin-4 antibody (AQP4); NMOSD is now recognised as an astrocytopathy, thus having a separate pathogenic mechanism to MS, with overlapping clinical features. (Papadopoulos, Bennett et al. 2014) The International Panel for

NMO diagnosis have recently published recommendations for the early and appropriate diagnosis of NMOSD. (Wingerchuk, Banwell et al. 2015) The criteria for diagnosis of NMOSD may be fulfilled with or without positive AQP4. About 20% of those negative for AQP4 will have positive anti-myelin oligodendrocyte antibodies (anti-MOG). Those with anti-MOG or indeed with seronegative NMOSD will typically have a milder disease course; and are more likely to be monophasic. (Sato, Callegaro et al. 2014) The importance of this condition in African-American, Asian, Latin American, and paediatric patients with suspected MS where NMOSD diagnosis is more likely is stressed by the Panel.

High priority areas of research for future diagnostic criteria in MS

MAGNIMS 2016 have recommended that ≥3 periventricular MRI lesions are required for DIS in this location, reminiscent of Barkhof MRI criteria (Barkhof, Filippi et al. 1997) previously used in both 2001 and 2005 McDonald criteria for DIS. The reasoning behind this decision by MAGNIMS was that incidental lesions in the periventricular region are common, they may occur in up to 30% of patients with migraine (Absinta, Rocca et al. 2012), this however does not consider the recommended application of the McDonald criteria in as typical CIS presentation. In an analysis studying the change of the requirement from one periventricular to three or more for DIS fulfillment, the sensitivity reduced from 91% to 85%, although the specificity increased from 33% to 40%. (Filippi, Preziosa et al. 2018) While there is evidence that fulfilling DIS with ≥3 periventricular lesions and a lesion in another region is more predictive of the future development of CDMS (Ruet, Arrambide et al. 2014), the Panel felt insufficient evidence exists to make an evidence-based recommendation on this and have highlighted the point as a high priority area for future research. A single periventricular MS plaque may also be discriminated from focal white matter lesions of vascular lesions, migraineurs or other neurological disorders with more frequent clinical use of MRI systems that operate at higher magnetic rate (≥3 Tesla). Using a combination sequence of susceptibility weighted imaging and T2-weighted fluid-attenuated inversion recovery with 3 Tesla MRI, there is high sensitivity for detection of small central veins in a lesion, and identification of one periventricular lesion with this “central vein sign”, is specific for MS. It is also applicable in other areas, particularly in subcortical lesions. (Sati, Oh et al. 2016)

The role of visual evoked potentials (VEP), as well as optical coherence tomography (OCT) as diagnostic tools in current or prior optic neuritis was also a priority topic for research discussed. OCT correlates with optic neuritis by reduction in retinal nerve fibre layer (RNFL) thickness, with 75% of patients with acute optic neuritis developing a 10-40μm loss within 3-6 months, much higher than that observed in glaucoma or macular oedema. Therefore, OCT may be valuable determine other causes of visual dysfunction if optic neuritis is being considered. (Costello, Coupland et al. 2006) Ganglion cell layer and inner plexiform layer thinning is also observed to reflect MRI grey mater pathology, cognitive and physical disability in MS. (Saidha, Sotirchos et al. 2013) Allowing the optic nerve to be included as a fifth anatomical site using VEP or MRI, improved sensitivity from 91 to 92% but reduced specificity from 33 to 26% in a recent MAGNIMS analysis. (Filippi, Preziosa et al. 2018) The Panel felt that the role of VEP or OCT in MS diagnosis required further research with regard to sensitivity and specificity in diagnostic work-up before inclusion in the McDonald criteria. Somatosensory, motor and brainstem evoked potentials have also been shown to be associated with clinical progression in patients with CIS, and worsened long-term disability in patients with newly diagnosed relapsing-remitting MS. Further research in to their use in MS diagnosis is of importance.

Radiologically isolated syndrome:

The incidental finding of T2 hyperintensities on brain MRI is not uncommon, particularly with broad use of MRI in medical practice. The occurrence of MRI abnormalities highly suggestive of demyelination with no associated neurological manifestations is defined as a radiologically isolated syndrome (RIS). In post-mortem studies, the presence of clinically silent demyelinating plaques is approximately 0.1%. (Engell 1989) The likelihood of RIS patients subsequently developing CDMS has been increasingly investigated. One natural history study looked at outcomes in 30 confirmed RIS patients; whilst radiological progression occurred in 59% of cases, only 10 patients went on to develop either CIS or CDMS. This study observed the presence of contrast-enhancing lesions on initial MRI to be highly predictive of radiological progression in this cohort. (Okuda, Mowry et al. 2009) Another retrospective review of 71 subjects with a confirmed RIS, 25 of whom demonstrated cervical spine T2-hyperintensities. This study showed that 84% of RIS cases with cervical

spine involvement subsequently developed CIS or primary-progressive MS over a median time of 1.6 years. The sensitivity, specificity and positive predictive value of cervical spine demyelination in RIS progressing clinically was 87.5%, 91.5% and 84% respectively. (Okuda, Mowry et al. 2011) The presence of cognitive impairment has also been demonstrated in those with a RIS. One study looked at cognitive function in 26 RIS presentations using a French adaptation of the Brief Repeatable Battery of Neuropsychological tests (Bever Jr, Grattan et al. 1995), and compared results to 26 patients with CDMS as well as 26 healthy control subjects. Cognitive function was significantly lower in both RIS and MS groups across a number of cognitive domains relative to healthy controls. Cognitive function was similar in MS and RIS groups except in two tests of two cognitive domains where MS patients performed significantly worse (memory span and executive function) (Lebrun, Blanc et al. 2010). RIS may not in fact be an entirely asymptomatic presentation. However, the panel felt that clinical manifestations were required to make the diagnosis of MS, despite MRI DIS/DIT and a positive oligoclonal band status; but evidence for DIS and DIT may be used retrospectively from investigations done prior to an index clinical episode. A more recent MAGNIMS RIS consensus recommends that for patients *without* a history of a relapsing neurological presentation and with an unremarkable clinical examination, who have MRI lesions consistent with MS and without red flags suggestive of an alternative diagnosis should be considered "subclinical MS". (De Stefano, Giorgio et al. 2018) This term does not imply "pre-clinical" MS, and treatment initiation is not recommended. It is possible these patients may have an exceptional capacity to repair or do not have maladaptation of functional connectivity, which might explain the lack of neurological symptoms; perhaps why incidental findings of demyelination on post-mortem studies are not uncommon (Engell 1989).

Clinical vignettes:

Case 1:

A 35 year-old woman, with no significant past medical history, presented to the outpatient clinic in 2014, with a one week history of diplopia and left-sided hemisensory symptoms, consistent with a brainstem syndrome. An MRI of brain and cervical spine demonstrated a left periventricular ovoid T2 hyperintensity, a right midbrain and cerebellar lesion, these findings were suggestive of demyelination. Post-contrast imaging did not reveal enhancement

of any of the lesions shown (**Image 1**). A neuroinflammatory blood screen was negative, excluding potential alternative diagnoses to consider in this presentation. A lumbar puncture was performed, and this demonstrated oligoclonal banding was not present in a concomitant serum sample. CSF white cell count was mildly raised at 6 cells per mm^3, and protein and glucose were within normal limits.

At the time of her presentation, this lady was given a diagnosis of CIS. After an initial six-month interval MRI scan, she was followed with annual surveillance MRI imaging and in early 2017 she had radiological conversion on MRI. She was diagnosed with MS according to 2010 McDonald criteria and commenced on disease modifying treatment at this time. Applying the revised 2017 McDonald criteria to this case, a diagnosis of MS would have been made three years earlier, with evidence of DIS by MRI and DIT by CSF OCBs in a patient with a typical CIS presentation.

Case 2:

A 28 year-old woman, presented to the emergency department with sensory symptoms which began in her lower limbs and had spread over a four day period to involve her abdomen and upper limbs. She had no associated weakness, or bladder dysfunction. She was clinically diagnosed with a cervical cord sensory transverse myelitis and possible CIS. She had an MRI of brain and cervical spine which demonstrated a T2 hyperintensity in the left caudo-thalamic groove as well as a subtle lesion in the cerebellum. A C3 cervical cord lesion was seen and shown to have enhancement post-contrast (**Image 2**). Neuroinflammatory blood mimic screen was negative, including AQP4 antibodies. The patient refused a lumbar puncture as part of the diagnostic work-up.

She was subsequently diagnosed with MS according to the 2010 McDonald criteria eight months later, when an interval MRI was performed demonstrating two new supratentorial hyperintensities suggestive of demyelination. Applying the 2017 McDonald criteria to this case, an immediate diagnosis could have been made, DIS was demonstrated on initial MRI as well as DIT, with a symptomatic gadolinium-enhancing spinal cord lesion. The diagnosis is made without the need for lumbar puncture in a typical CIS presentation with clear-cut MRI findings. Treatment could therefore have been initiated eight months earlier using the updated criteria.

Conclusion:

The 2017 McDonald criteria revisions allow for the earliest possible diagnosis of MS in CIS cases with features strongly suggestive of future conversion to CDMS, according to current existing evidence. These revisions should lead to earlier disease modifying treatment initiation and ultimately better long-term outcomes for people with MS. Areas requiring research that could further alter future diagnostic criteria in MS have also been highlighted, these may shorten time to diagnosis even more, but the Panel have been careful to rely on sufficient existing evidence available for any recommendations made, ensuring the accuracy, sensitivity and specificity with which a diagnosis of MS is made by the McDonald criteria. The effect on time to diagnosis by these alterations has been highlighted in two real-world cases illustrated in this review.

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