Diagnosis of Multiple Sclerosis: 2017 Revisions of the "McDonald" Criteria

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Abstract

The 2010 McDonald criteria for diagnosis of multiple sclerosis (MS) are widely used in research and clinical practice. Scientific advances in the past seven years suggest that they may no longer provide the most up-to-date guidance for clinicians and researchers. The International Panel on Diagnosis of Multiple Sclerosis reviewed the 2010 McDonald Criteria and recommended revisions. The 2017 McDonald Criteria continue to apply primarily to patients experiencing a typical clinically isolated syndrome (CIS), define what is needed to fulfill dissemination in time and space, and stress the need for no better explanation for the presentation. The following changes were made: in patients with a typical CIS and clinical or MRI demonstration of dissemination in space, the presence of cerebrospinal-fluid-specific oligoclonal bands allows an MS diagnosis; symptomatic lesions can be used to demonstrate dissemination in space and/or time in patients with supratentorial, infratentorial, or spinal cord syndrome; and cortical lesions can be used to demonstrate dissemination in space. Recommended research to further refine the criteria includes (i) inclusion of optic nerve involvement; (ii) validation in diverse populations; and (iii) incorporation of advanced imaging, neurophysiological, and body fluid markers.

Introduction

Diagnostic criteria for multiple sclerosis (MS) have evolved over time, with the most recent recommendations from the International Panel on Diagnosis of MS (the Panel) appearing more than six years ago.[1-5] The increasing incorporation of paraclinical assessments, especially imaging, to supplement clinical findings has allowed earlier, more sensitive, and more specific diagnosis.[6] New data, emerging technology, and evolving consensus necessitate a periodic re-examination of diagnostic criteria and their utility. The Panel reconvened under the auspices of the International Advisory Committee on Clinical Trials in MS (sponsored by the U.S. National MS Society and the European Committee for Treatment and Research in MS) for two meetings (November 2-5, 2016, Philadelphia and May 20-21, 2017, Berlin). Herein, we discuss issues related to misdiagnosis, differential diagnosis, and appropriate application of the McDonald (International) Criteria, with a particular emphasis on diagnosis in diverse populations and in patients with atypical presentations. We present recommendations concerning the MS diagnostic process, recommend specific revisions to the McDonald Criteria, and outline future research to refine the McDonald Criteria.

Conduct of the Panel meetings and considerations related to the 2017 revisions to the McDonald Criteria

Convening the Panel meetings was motivated by new data concerning (i) the performance of the 2010 McDonald Criteria in diverse populations; (ii) the relationship between MS and other diseases with potentially overlapping clinical and imaging features such as is seen in neuromyelitis optica spectrum disorders (NMOSD); (iii) challenges in making the diagnosis in individuals with non-classical presentations; (iv) the frequency and consequences of misdiagnosis; and (v) cerebrospinal fluid (CSF) and other paraclinical tests related to diagnosis

of MS. The meetings were further informed by the proposed 2016 revisions of magnetic resonance imaging (MRI) criteria for diagnosis of MS by the European Magnetic Resonance Imaging in MS network (2016 MAGNIMS Criteria).[7]

The Panel included international representation and expertise in clinical, imaging, and laboratory aspects of MS diagnosis. At the meetings, Panel members reviewed past criteria and made brief presentations covering proposed revisions. Relevant published and unpublished data guided subsequent group discussion and consensus building on proposed revisions. *A priori* rules to handle issues for which consensus could not be reached were specified.

The Panel agreed that the 2010 McDonald Criteria performed well based on their utilization in clinical and research settings and in regulatory approval of multiple MS medications; major changes were not anticipated. Rather, the proposed changes outlined below were intended to (i) simplify or clarify components of the 2010 McDonald Criteria (Panels 1 and 2); (ii) facilitate earlier diagnosis of MS when MS was likely but not diagnosable with the 2010 McDonald Criteria; and (iii) preserve the specificity of the 2010 McDonald Criteria and promote their appropriate application to reduce the frequency of misdiagnosis. The Panel strived to ensure that proposed changes did not weaken the Criteria and were supported by reasonable evidence, not merely expert opinion.

Utility and applicability of the McDonald Criteria

Before considering potential revisions of the 2010 McDonald Criteria, the Panel reviewed issues related to MS diagnosis, appropriate utilization of the McDonald Criteria, and their applicability across patient populations.

Misdiagnosis and differential diagnosis

Misdiagnosis of MS remains an issue in clinical practice.[8-11] The Panel identified several factors that potentially increase this risk. MS has heterogeneous clinical and imaging manifestations, which differ between patients and change within individual patients over time. There is no single pathognomonic clinical feature or diagnostic test; diagnosis of MS relies on the integration of clinical, imaging, and laboratory findings. MRI abnormalities associated with other diseases and non-specific MRI findings, which are common in the general population, can be mistaken for MS. The increasingly strong focus on timely diagnosis to alleviate uncertainty for patients and allow initiation of disease-modifying therapy (DMT) also may increase the risk of misdiagnosis.[12]

As with any diagnostic criteria, a tradeoff exists between sensitivity (to allow efficient diagnosis in patients having MS) and specificity (avoiding erroneous diagnosis in patients who do not have MS).[12] The positive and negative predictive power of diagnostic tests depend on the pre-test probability (likelihood) of the disorder, which has important implications for interpreting the available data concerning the utility of such tests (Panel 2).

The clinician must remain vigilant for clinical features or diagnostic test results that suggest the possibility of an alternative diagnosis, so-called red flags.[13-16] A recent multicenter case series demonstrated that a wide range of conditions can be mistaken for MS.[11] Aside from NMOSD, the most frequent reason for misdiagnosis as MS was misinterpretation of nonspecific symptoms, neurologic signs, or MRI findings in common disorders (for example, migraine), which when reviewed carefully, in most patients, would not fulfill the 2010 McDonald Criteria. Misdiagnosis had harmful consequences in some patients, emphasizing the importance of appropriate application of the McDonald Criteria (Panel 3).

Interpretation and integration of the history, physical examination, and results of imaging and laboratory testing by a clinician with expertise in MS remain fundamental in making a reliable diagnosis of MS or an alternative diagnosis. It is important to re-emphasize that the McDonald Criteria should only be applied in patients with a typical clinically isolated syndrome (CIS, Panel 1), that is, patients who already have a high likelihood of having MS. Care should

be exercised in accepting historical events in the absence of contemporaneous or current objective evidence providing corroboration of those events (Panel 3). As with past McDonald Criteria, the Panel's discussion emphasized rigor in interpreting clinical features and results of diagnostic studies to ensure the absence of atypical features and that there is no better diagnosis.

Applicability of the McDonald Criteria in diverse populations

Development of the McDonald Criteria was largely based on data from adult Caucasian European and North American populations with a typical CIS[14] and age less than 50 years. The applicability of the 2010 McDonald Criteria has been reported in patients from Canada,[17] Italy,[18] the Netherlands,[19] Spain,[20] and Russia.[21] Additional studies concerning the applicability of the 2010 McDonald Criteria in Asian,[22-24] Middle Eastern,[25,26] and Latin American[27] populations have been published since 2010, though tended to be small. Based on those data, there is no evidence that the 2010 McDonald Criteria cannot be used in these populations. Vigilance is needed to exclude alternative diagnoses, particularly NMOSD in higher risk populations. In Latin America, infectious diseases and nutritional deficiencies also remain important.[28]

Several studies support the applicability of the 2010 McDonald Criteria in children.[29-36] The McDonald Criteria are generally most applicable for patients 11 years of age or older; special care is needed in patients younger than 11 years old in whom the likelihood of MS is lower.[30] Acute disseminated encephalomyelitis (ADEM) is more common in children than in adults. Although ADEM typically is monophasic, some children with ADEM have recurrent clinical episodes and/or MRI evidence of accrual of new lesions, leading to MS diagnosis.[37] The Panel agreed that the McDonald Criteria should not be applied to children at the time of ADEM presentation and that occurrence of a subsequent attack characteristic of MS is necessary to diagnose MS.[38] Alternative diagnoses, including NMOSD, need to be excluded in all children in whom the diagnosis of MS is being considered. In the future, testing for antibodies reactive with

myelin-oligodendrocyte glycoprotein (MOG) may be useful to aid diagnosis of children with NMOSD who are aquaporin-4 (AQP4)-seronegative, children with ADEM followed by recurrent optic neuritis, and children with chronic relapsing optic neuritis.[39-41] Children with syndromes having features overlapping ADEM, NMOSD, and MS require particular care to reach a final diagnosis.

Although MS typically presents at age 20-50 years, approximately 0.5% of adults with MS have symptom onset at age 60 years or older.[42,43] Older individuals are more likely to have a progressive course at presentation, either progressive from onset or following retrospectively recognized attacks, but occasionally they present with an acute attack. Careful attention to alternative diagnoses and particularly comorbidities is necessary. Age-related vascular white matter lesions may occasionally be periventricular, and seeking more than one periventricular lesion with morphology characteristic of MS may be prudent in this setting. Also, consideration of MS in an older individual is an example of a diagnostic scenario for which spinal cord MRI and/or CSF examination looking for findings supportive of MS or suggesting a different diagnosis are advised. With these caveats, the Panel agreed that the 2017 McDonald Criteria are likely to be applicable in older patients, but recommended further studies to support this conclusion.

Neuromyelitis optica spectrum disorders

Substantial data concerning NMOSD have emerged since publication of the 2010 McDonald Criteria. Although clinical, imaging, and CSF features of MS and NMOSD may overlap, they are now understood to be distinct disorders.[44] Diagnosis of NMOSD has been facilitated by the development and use of serologic testing for antibodies reactive with the AQP4 water channel and validation of the antibodies not only as a marker of NMOSD but also as a pathogenic factor.[45,46] The range of recognized clinical and MRI manifestations of AQP4-associated NMOSD is wide and still evolving. Recent data suggest that some AQP4-seronegative patients

with NMOSD features have antibodies reactive with MOG.[47-51] However, testing for anti-MOG antibodies is not yet commercially available, and diagnostic sensitivity and specificity have not been fully validated.

Panel members agreed that the 2010 McDonald Criteria and 2015 International Panel for NMO Diagnosis Criteria[52] largely distinguish MS and NMOSD, though uncertain cases can occur, particularly with AQP4-seronegative patients. Because the treatments for MS and NMOSD are different (for example, interferon-beta, fingolimod, and natalizumab can exacerbate NMOSD[53]), the Panel recommended that NMOSD should be considered in any patient being evaluated for MS. Serologic testing for AQP4 and, when commercially available, MOG should be performed in all patients with features suggesting NMOSD (such as bilateral optic neuritis, severe brainstem involvement, longitudinally extensive spinal cord lesions, large cerebral lesions, or normal brain MRI or findings not fulfilling dissemination in space [DIS]), and considered in groups at higher risk for NMOSD (such as African-American, Asian, Latin American, and pediatric patients).

Role of MRI in MS diagnosis

MRI has been increasingly utilized to support the diagnosis of MS and to look for atypical radiological features arguing against MS. MAGNIMS and the Consortium of MS Centers recently proposed standardized MRI protocols for the diagnostic process, to determine prognosis, and for follow-up.[54-56] Brain and spinal cord MRI remain the most useful paraclinical tests to aid the diagnosis of MS and can substitute for clinical findings in determination of dissemination in space (DIS) and/or time (DIT) in patients with a typical CIS. Involvement in four areas (periventricular, cortical/juxtacortical, infratentorial, and spinal cord) are characteristic of MS and can be utilized to fulfill the criteria for DIS. See Rovira A et al.[55] for a description of typical MS lesion morphology.

The Panel recommended that brain MRI be obtained in all patients being considered for an MS diagnosis, recognizing it may at times not be possible because of availability, cost, or contraindication. There was general agreement that, although spinal MRI is not mandatory in all cases, it is advisable when the presentation suggests a spinal cord localization, when there is a primary progressive course, when considering MS in a population in which MS is less common (for example, older individuals or non-Caucasians), or when additional data are needed to increase diagnostic confidence (for example when brain MRI findings only just fulfill the criteria for DIS).[55,56] Spinal MRI appears less useful in the diagnosis of MS in children.[34]

Role of CSF examination in MS diagnosis

Although CSF examination has been de-emphasized in successive iterations of the McDonald Criteria, it remains a valuable diagnostic test.[57] In the appropriate clinical setting, evidence of intrathecal antibody synthesis, though not specific for MS, supports the diagnosis.[58] Conversely, CSF findings atypical of MS (for example, markedly elevated protein >100 mg/dL; pleocytosis with >50 cells/mm^3; or presence of neutrophils, eosinophils, or atypical cells) suggest other diseases.[59]

The Panel's discussion of CSF recognized the importance of using appropriate and standardized technology.[58-60] The qualitative demonstration of two or more CSF-specific oligoclonal bands (OCBs) more reliably indicates intrathecal antibody synthesis than other tests, such as IgG Index.[58-60] Positive IgG Index results should be interpreted with caution when testing for OCBs is negative or not performed. The sensitivity of OCB testing depends on the method used; agarose gel electrophoresis with isoelectric focusing and immunoblotting or immunofixation for IgG is the most sensitive at present.[58-60] Importantly, analysis of paired CSF and serum samples is essential to confirm that the OCBs are unique to CSF.

While CSF examination is not mandatory in all cases (for instance, a typical CIS supported by characteristic MRI findings [Panel 1], unequivocal demonstration of DIS and DIT, and absence of atypical clinical or imaging features), there should be a low threshold for CSF examination to increase diagnostic confidence. CSF examination is strongly recommended: (i) when there is insufficient clinical and MRI evidence supporting a diagnosis of MS, particularly if initiation of long-term DMT is being considered; (ii) when there is a non-classical presentation, including patients with a progressive course at onset (primary progressive MS); (iii) when there are clinical, imaging, or laboratory features atypical of MS; and (iv) in populations in which diagnosing MS is less common (for example, children, older individuals, or non-Caucasians). While negative CSF OCBs does not rule out MS, particularly early in the condition and in children,[58,59] caution should be exercised in diagnosing MS when CSF OCBs are not detected and, certainly, in the presence of atypical clinical, imaging, or CSF findings.

2017 Revisions to the McDonald Diagnostic Criteria for multiple sclerosis

The Panel reviewed the 2010 McDonald Criteria and made recommendations for revisions (Panels 4, 5, and 6; Table 1).

Presence of CSF oligoclonal bands allows the diagnosis of MS in selected patients

Multiple studies provide evidence that in adult patients with CIS, CSF OCBs are an independent predictor of the risk of a second attack when controlling for demographic, clinical, treatment, and MRI variables.[61-69] After considering these data, the Panel recommended that with a typical CIS, fulfillment of clinical or MRI criteria for DIS, and no better explanation for the clinical presentation, demonstration of CSF OCBs in the absence of atypical CSF findings allows a diagnosis of MS to be made, even if the MRI findings on the baseline scan do not meet the criteria for DIT and in advance of either a second attack or MRI evidence of a new or active

lesion on serial imaging.[69] This consensus recommendation allows the presence of CSF OCBs to substitute for the requirement for fulfilling DIT in this situation. This criterion is similar to the laboratory-supported definite MS category in the earlier Poser criteria.[2]

Incorporation of the symptomatic lesion in providing evidence for dissemination in space and time

Previously, the symptomatic lesion in a patient presenting with brainstem or spinal cord syndrome could not be included as MRI evidence of DIS or DIT, to avoid "double counting." Recent studies showed that inclusion of symptomatic lesions in the MRI determination of DIS or DIT increases MS diagnostic sensitivity with little or no reduction in specificity[70,71] and was proposed in the 2016 MAGNIMS Criteria.[7,72] On the basis of these data, the Panel recommended including symptomatic and asymptomatic MRI lesions in the determination of DIS and DIT. An exception relates to lesions in the optic nerve in a patient presenting with optic neuritis, for which there was felt to be insufficient supportive evidence to include as a site in determining DIS.

Cortical lesions equivalent to juxtacortical lesions

Juxtacortical lesions (Panel 1) are an area of predilection in MS, incorporated into the MRI criteria for DIS in the 1997 Barkhof imaging criteria.[73] Based on histopathological studies, cortical lesions and juxtacortical lesions extending into the cortex are known to be typical of MS.[74,75] With development of better techniques to identify cortical lesions, their potential to make a contribution to diagnosis has been appreciated.[72,76,77] The Panel recommended that, in addition to juxtacortical lesions, cortical lesions can be used in fulfilling MRI criteria for DIS, although it recognized that standard MRI currently has limited ability to demonstrate cortical lesions or distinguish cortical lesions in MS from other etiologies. Care is needed to distinguish potential cortical lesions from artifacts.

Primary progressive MS

About 15% of patients with MS have a course characterized by gradual progression from onset (primary progressive MS).[78] The McDonald Criteria were developed to make the diagnosis in patients with a CIS at onset then modified for use in patients with progression from onset. The diagnostic criteria for primary progressive MS remain the same in the 2017 McDonald Criteria as those outlined in the 2010 McDonald Criteria,[5] aside from removal of the distinction between symptomatic and asymptomatic MRI lesions and that cortical lesions can be used (Panel 6).

Integrating the disease course phenotypes with the McDonald Diagnostic Criteria

The 2013 revised classification of MS clinical phenotypes and disease course maintained the distinction between MS with an attack onset versus a progressive course from onset.[78] The revised classification incorporated further categorization as active or not (based on recent clinical relapse and/or MRI lesion activity) and progressive or not (based on clinical assessment of disability). The intent was for patients to be assessed over time and classified (and reclassified as needed) according to the disease course in a preceding time period, e.g. one year. The Panel recommended that a provisional disease course should be specified as soon as the MS diagnosis is made, and periodically re-evaluated based on accumulated information.

Key proposals that require further evidence if they are to be adopted into diagnostic criteria

Number of periventricular lesions

The 2001 and 2005 McDonald Criteria required three or more periventricular lesions as one of the anatomic locations that could fulfill MRI criteria for DIS.[3,4] In the 2010 McDonald Criteria, this requirement was changed to one or more periventricular lesions as one of the four anatomic

locations (periventricular, juxtacortical, and infratentorial brain regions, and spinal cord).[5] However, non-specific white matter lesions are common in older individuals and in those with vascular risk factors including migraine; a single periventricular lesion is not uncommon.[16] Therefore, the 2016 MAGNIMS Criteria suggested that a single lesion might be insufficiently specific and proposed increasing the requirement to three periventricular lesions.[7] In a recent analysis, changing the requirement from one periventricular lesion to three improved specificity of DIS from 0.37 to 0.46 but decreased sensitivity from 0.88 to 0.83.[72] The Panel felt the modest improvement in specificity, comparable to that achieved when DIS and DIT are considered in combination,[79,80] did not justify the added complexity of requiring a different number of lesions in different anatomic regions. Therefore, the Panel recommended the 2017 McDonald Criteria maintain the requirement for one periventricular lesion. For some patients, for example, older individuals or those with vascular risk factors including migraine, it may be prudent for the clinician to seek a higher number of periventricular lesions.

Incorporation of the anterior visual system into the diagnostic criteria

The visual system often provides an early and eloquent clinical sign of MS.[81] The 2016 MAGNIMS Criteria proposed the optic nerve as a fifth anatomic location to fulfill MRI criteria for DIS.[7] In the 2017 Diagnostic Panel deliberations, there was substantial discussion concerning the potential advantages and disadvantages of MRI, visual evoked potentials (VEP), and optical coherence tomography (OCT) to objectively demonstrate optic nerve involvement and support a clinical suspicion of current or prior optic neuritis, including changes in the sensitivity of all three tests over time relative to the optic neuritis event.[81] The recent MAGNIMS analysis showed that adding optic nerve involvement detected by MRI or VEP as a fifth anatomic site led to a minor improvement in sensitivity from 0.88 to 0.91 but substantially reduced specificity from 0.52 from 0.41.[72] The analysis did not include OCT.

Despite recognizing optic nerve involvement as an important feature of MS, the Panel felt the data concerning the diagnostic sensitivity and specificity of MRI, VEP, or OCT to demonstrate optic nerve lesions in patients without a clear-cut history or clinical evidence of optic neuritis were insufficient to support incorporation into the McDonald Criteria at this time. Studies to validate MRI, VEP, or OCT in fulfilling DIS or DIT in support of MS diagnosis were identified as a high priority.

Applicability of the McDonald Criteria in patients with non-classical presentations

Radiologically isolated syndrome

With increasing availability and utilization of MRI, patients with incidental T2 hyperintensities on brain imaging are common[82] and include individuals with MRI findings strongly suggestive of MS lesions but with no neurologic manifestations or other clear-cut explanation, a condition termed radiologically isolated syndrome (RIS).[83] Data concerning the population-based incidence and prevalence of RIS are limited but suggest that RIS is uncommon (in Sweden, incidence of 0.8 cases of RIS per 100,000 person-years compared to 10.2 cases of MS per 100,000 person-years[84]), but increased in healthy relatives of patients with MS.[85] Approximately one-third of RIS cases are diagnosed with MS within five years of presentation, most often with a relapsing-remitting course[83,86] but occasionally with a primary progressive course.[87,88] The factors predicting increased risk of subsequent MS diagnosis are similar to those predicting MS diagnosis after a CIS: younger age, higher cerebral lesion load, asymptomatic infratentorial or spinal cord lesions, gadolinium-enhancing lesions, presence of CSF OCBs, and abnormal VEP.[87,89]

Some Panel members argued that individuals with RIS have a high likelihood of having MS and may already exhibit evidence of putative MS pathobiology, including fatigue,[90] cognitive impairment,[91] and thalamic atrophy,[92] and that postponing an MS diagnosis and initiation of DMT might increase the risk of disability. Others argued that the risk of misdiagnosis is high in

patients with MRI abnormalities only,[11] and two-thirds of these patients will not receive an MS diagnosis within five years. The Panel reached consensus to continue to require clinical manifestations to make the diagnosis of MS and, as in the 2010 McDonald Criteria, to allow utilizing historical radiologic evidence for DIS and DIT in patients with RIS to support the diagnosis of MS once a typical CIS occurs. While the Panel considered allowing diagnosis of MS in patients with RIS and demonstration of DIS and DIT by MRI and demonstration of CSF OCBs, there was not general support for this proposal. It was identified as a high priority area for further research.

Solitary sclerosis

The Panel discussed rare patients who have an inflammatory lesion of the cerebral white matter, cervicomedullary junction, or spinal cord who develop progressive disability clinically indistinguishable from progressive forms of MS; may have CSF OCBs; but have no clinical or radiologic evidence of new lesion formation – a condition which has been termed progressive solitary sclerosis.[93] The Panel agreed that, despite a progressive course, such patients do not satisfy the McDonald Criteria for MS, as they do not have DIS. Like RIS, solitary sclerosis was identified as a high priority area for further research.

Possible MS

Previous versions of the McDonald Criteria included a diagnostic category of "possible MS," defined as a suspicion of MS (i.e., a patient with a CIS but not meeting the full criteria).[5] The Panel considered expanding the category of possible MS to include patients with non-classical presentations, but did not reach consensus. The ability of revised criteria to differentiate between and inform about presentations that may eventually evolve to include clinical or MRI features confirmatory of MS (such as RIS, solitary sclerosis, or other non-classical presentations for which the MS criteria may be partially but not unequivocally fulfilled) needs more focused

collaborative studies, in particular because such presentations are uncommon.

Other high priority areas of research

Many of the elements of the McDonald Criteria have come from data from academic MS specialty centers and have been derived largely from adult patients of Western European genetic/ethnic origins presenting with a typical CIS (i.e., with a high likelihood of MS). Validation of the 2017 McDonald Criteria will be needed in diverse populations, either prospectively or retrospectively, including those from Asia, Latin America, the Middle East, Africa, and other relatively less studied geographic locations; in suspected pediatric and late-onset MS; in patients with comorbidities with clinical or imaging manifestations that overlap those of MS; and in non-specialty and general practice clinical settings.

The Panel identified further studies to validate the 2016 MAGNIMS Criteria in aggregate as a high priority. New MRI approaches also will need to be considered for future iterations of McDonald Criteria. Currently, the only feature to assess the chronicity of MRI lesions at the time of first assessment is presence or absence of gadolinium enhancement. Chronic T1-hypointense lesions ("black holes") were shown not to aid in determination of DIT.[94] The role in MS diagnosis of more sensitive imaging methods to detect gray matter pathology (particularly to demonstrate subpial cortical and deep gray matter lesions[74]) and techniques to distinguish MS lesions from T2 hyperintensities in other conditions (e.g. central vein sign on T2*-weighted/FLAIR* images[95] or paramagnetic rim on T2*/phase/susceptibility-weighted images[96,97]) are being explored. The role of higher field strength imaging requires detailed investigation to determine if it is useful and practical, particularly in non-academic settings, given its improved ability to detect lesions and reveal their anatomic features.

Currently, no laboratory test in isolation confirms the diagnosis of MS. While AQP4 serologic testing generally differentiates NMOSD from MS,[45] less is known about the performance of testing for MOG antibodies.[41,47-49] Other diagnostic biomarkers have been

proposed to differentiate between MS phenotypes or to monitor CNS damage, but none has been shown to reliably diagnose MS in individual patients, representing a major unmet need and area for future research. Finally, the possible contribution of evoked potential investigations besides VEP (e.g. somatosensory or motor) to diagnostic criteria should be further explored. With the growing interest in precision medicine and rapidly evolving technologies, it will be critical that the community develop an approach to validation of all paraclinical tests for MS diagnosis and incorporation into practice when appropriate.

Conclusions

Early MS diagnostic criteria were based primarily on clinical evidence.[1] Subsequent criteria incorporated imaging and other paraclinical markers in response to technological advances and new data.[2-5] The proposed 2017 revisions to the well established McDonald Criteria go beyond prior versions by revitalizing the role of CSF analysis, by reconsidering the value of imaging findings previously not included, such as symptomatic and cortical lesions, and by articulating more clearly cautions about misdiagnosis and differential diagnosis, all of which were supported by a sound evidence base.

The 2017 McDonald Criteria should prove useful both in research settings and clinical practice. None of these changes invalidate the diagnosis of MS according to previous versions of the McDonald Criteria (any patient diagnosed with prior Criteria should also fulfill the 2017 Criteria). It was recognized that application of new diagnostic criteria can have an impact on future recruitment into and interpretation of clinical trials and observational studies[98] but should not affect registration of already-approved medications. Ability to accurately and more rapidly diagnose MS should facilitate enrolment in prospective clinical trials, and could increase the populations of subjects eligible for observational and natural history studies.

While increasingly based on paraclinical tests, optimal diagnosis of MS requires the judgment of a clinician with MS-related expertise, aided by appropriate radiologic and other paraclinical assessments. The goal is to make a rapid and accurate diagnosis of MS, keeping fully in mind the potential dangers of misdiagnosis in an era with increasing numbers of treatment options for MS, which carry varying degrees of risk. The importance of correct diagnosis is further heightened by the observation that certain MS DMTs are contraindicated in some of the more common differential diagnoses, for example, NMOSD. The Panel is mindful of the challenges many patients experience in gaining access to clinicians with MS-related expertise and advocates a concerted global effort to address this critical workforce gap.

Search strategy and selection criteria

In preparation for the meetings, the Panel conducted literature searches (completed 15 April 2017) in PubMed (English language, using search terms “multiple sclerosis” and “diagnosis” with a focus on publications since 2010 but also including earlier publications as appropriate). It reviewed papers on topics including, but not limited to, the role in diagnosis of magnetic resonance imaging, optical coherence tomography, evoked potentials, and cerebrospinal fluid analysis; of diagnosis in diverse populations (pediatric, Asian, and Latin American); in patients with non-classical presentations (e.g. radiologically isolated syndrome and solitary sclerosis); of differential diagnosis between multiple sclerosis, neuromyelitis spectrum disorders, and other neurological disorders; and the intersection of diagnosis with disease phenotype designation.

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Contributors

JA Cohen, AJ Thompson, and SC Reingold drafted Panel meeting agendas, with review and agreement by all Panel members. BL Banwell, F Barkhof, G Comi, J Correale, M Filippi, K Fujihara, SL Galetta, FD Lublin, DH Miller, X Montalban, EM Mowry, M Tintoré, AL Traboulsee, and BG Weinshenker made specific topic-related presentations at the meetings. All Panel members attended both meetings, and actively participated in discussion and reaching consensus. JA Cohen, AJ Thompson, and SC Reingold prepared the initial drafts of this manuscript. All Panel members were given the opportunity to review drafts and make revisions prior to finalization, and approved the manuscript for submission.

Declaration of interests

Alan J Thompson reports personal fees and other from MedDay, Novartis, Eisai Ltd, Biogen Idec and TEVA, outside the submitted work; Editorial Board membership, *The Lancet Neurology,* receiving free subscription; Editor-in-Chief, *Multiple Sclerosis Journal,* honorarium from SAGE Publications; Chair, Scientific Advisory Board, International Progressive MS Alliance (PMSA), support for travel to international meetings; member, National MS Society (USA), Research Programs Advisory Committee, support for travel to international meetings; Chair, International Medical and Scientific Board, and Board Member (2005-2015) for Multiple Sclerosis International Federation (MSIF), support for travel to international meetings; member of MSIF International Medical and Scientific Board (2015-). He received honoraria and support for travel for lecturing from EXCEMED.

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Panel 1: Glossary

Attack: Attack, relapse, exacerbation, and (when it is the first episode) CIS are synonyms. See CIS and relapse for descriptions.

Clinically isolated syndrome: A monophasic clinical episode with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection; similar to an MS relapse (attack, exacerbation) but in a patient not known to have MS.[14,78,99] Thus, if the patient subsequently is diagnosed with MS (by fulfilling DIS and DIT and ruling out other diagnoses), the CIS was that patient's first attack. A CIS may be monofocal (reflecting pathology in a single location) or multifocal; the specific manifestations of a CIS depend on the anatomic location(s) of the pathology. Typical presentations include unilateral optic neuritis, focal supratentorial syndrome, focal brainstem/cerebellar syndrome, or partial myelopathy. Examples of atypical presentations include bilateral optic neuritis, complete ophthalmoplegia, complete myelopathy, encephalopathy, headache, alteration of consciousness, meningismus, or isolated fatigue. See Brownlee WJ et al.[6] for further discussion of typical and atypical presentations.

Cortical MRI lesion: Lesion within the cerebral cortex. Typically, special MRI techniques such as double inversion recovery, phase-sensitive inversion recovery, magnetization-prepared rapid acquisition with gradient echo sequences are required to visualize these lesions.[72,76,77] The lesions detected by these techniques are primarily of the leukocortical type; subpial lesions are rarely detected. Care is needed to distinguish potential cortical lesions from artifacts. See Filippi M et al.[7] for illustrative examples.

Dissemination in space: Development of lesions in distinct anatomic locations within the CNS, i.e. indicating a multifocal CNS process.

Dissemination in time: Development/appearance of new CNS lesions over time.

Exacerbation: Attack, relapse, exacerbation, and (when it is the first episode) CIS are synonyms. See CIS and relapse for descriptions.

Infratentorial MRI lesion: T2-hyperintense lesion in the brainstem (typically near the surface), cerebellar peduncles, or cerebellum. See Brownlee WJ et al.[6] for illustrative examples.

Juxtacortical MRI lesion: T2-hyperintense cerebral white matter lesion abutting the cortex, without intervening white matter. See Aliaga ES and Barkhof,[16] Brownlee WJ et al.,[6] and Filippi M et al.[7] for illustrative examples.

Objective clinical or paraclinical evidence (as it relates to a current or historical attack): Abnormality on neurologic examination, imaging (MRI or OCT), or neurophysiologic testing (VEP) that corresponds to the anatomic location suggested by the symptoms of the CIS, for example, optic disc pallor or a relative afferent pupillary defect, optic nerve T2 hyperintensity on MRI, retinal nerve fiber layer thinning on OCT, or P100 latency prolongation on VEP in a patient reporting a previous episode of self-limited, painful, monocular visual impairment. Caution should be exercised in accepting symptoms accompanied only by patient-reported subjective alteration on examination as evidence of a current or prior attack.

Periventricular MRI lesion: T2-hyperintense cerebral white matter lesion abutting the lateral ventricles without intervening white matter; includes lesions in the corpus callosum; excludes

lesions in deep gray matter structures. See Aliaga ES and Barkhof[16] and Brownlee WJ et al.[6] for illustrative examples.

Progressive course: An MS course characterized by steadily increasing objectively documented neurologic disability independent of relapses. Fluctuations, periods of stability, and superimposed relapses may occur. Primary progressive MS (a progressive course from disease onset) and secondary progressive MS (a progressive course following an initial relapsing-remitting course) are distinguished.[78]

Relapse: A monophasic clinical episode with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. Attack, relapse, exacerbation, and (when it is the first episode) CIS are synonyms.

Radiologically isolated syndrome: MRI findings strongly suggestive of MS in a patient with no neurologic manifestations or other clear-cut explanation.

Relapsing-remitting course: An MS course characterized by relapses with stable neurologic disability between episodes.[78]

Spinal cord MRI lesion: Hyperintense lesion in the cervical, thoracic, or lumbar spinal cord seen on T2 plus STIR, proton-density images, or other appropriate sequence; or in two planes on T2 images. See Rovira A et al.,[55] Brownlee WJ et al.,[6] and Filippi M et al.[7] for illustrative examples.

CIS = clinically isolated syndrome, CNS = central nervous system, DIS = dissemination in space, DIT = dissemination in time, DMT = disease-modifying therapy, MRI = magnetic resonance imaging, MS = multiple sclerosis, OCT = optical coherence tomography, VEP = visual evoked potentials

Panel 2: Validation of the McDonald Criteria

In the context of validation of proposed diagnostic criteria for MS, the typical approach is to study (retrospectively or, preferably, with prospective follow-up) a population of patients experiencing a first symptom suggestive of MS (i.e., a CIS) and categorize them based on whether or not they fulfill the proposed diagnostic criteria and subsequently develop a second clinical attack typical of an MS relapse and indicating involvement of an anatomic location distinct from the initial attack. The need is to determine the rates of true positives (patients who fulfill the proposed diagnostic criteria and develop a second attack); false positives (patients who fulfill the proposed diagnostic criteria and do not develop a second attack); true negatives (patients who do not fulfill the proposed diagnostic criteria and do not develop a second attack); and false negatives (patients who do not fulfill the proposed diagnostic criteria and develop a second attack). Sensitivity = true positives / (true positives + false negatives). Specificity = true negatives / (true negatives + false positives).

The performance of a diagnostic test (or, in this example, a proposed diagnostic criteria) in terms of positive and negative predictive value depends on the likelihood of the condition of interest (in this example, MS) in the study population. The McDonald Criteria and proposed revisions have largely been validated in patient populations that have a high likelihood of MS by virtue of their demographic features, mode of recruitment, and having had a typical CIS. Their positive predictive value will be lower in populations with a lower likelihood of MS.

CIS = clinically isolated syndrome, DMT = disease-modifying therapy, MS = multiple sclerosis,

Panel 3: Considerations to help avoid misdiagnosis of multiple sclerosis

- Recognize that the McDonald Criteria were not developed to differentiate MS from other conditions but to identify MS or high likelihood of MS in patients with a typical CIS once other diagnoses have been deemed unlikely.
- Integration of the history, examination, imaging, and laboratory evidence by a clinician with MS-related expertise remains fundamental in making a reliable diagnosis of MS or an alternative diagnosis. In addition to confirming DIS and DIT, diagnostic rigor in the interpretation of clinical data, imaging findings, and test results is necessary.
- In the absence of a clear-cut typical CIS (see Glossary), caution should be exercised in making the diagnosis of MS, and it should be confirmed by further clinical and radiological follow-up. In such cases, the clinician should consider postponing making a definitive diagnosis and institution of long-term DMT, pending longer follow-up to accumulate additional evidence supporting the diagnosis.
- Caution should be taken in accepting historical events as an attack in the absence of contemporaneous or current objective evidence providing corroboration.
- There should be a low threshold for additional testing, including spinal cord MRI and/or CSF examination (i) when there is insufficient clinical and brain MRI evidence supporting a diagnosis of MS, particularly if initiation of long-term DMT is being considered; (ii) when there is a non-classical presentation, including patients with a progressive course at onset (primary progressive MS); (iii) when there are clinical, imaging, or laboratory features atypical of MS; and (iv) in populations in which diagnosing MS is less common (for example, children, older individuals, or non-Caucasians).

CIS = clinically isolated syndrome, CSF = cerebrospinal fluid, DIS = dissemination in space, DIT = dissemination in time, DMT = disease modifying therapy, MRI = magnetic resonance imaging, MS = multiple sclerosis

Panel 4: 2017 revisions to the McDonald Diagnostic Criteria for multiple sclerosis

- In a patient with a typical CIS and fulfillment of clinical or MRI criteria for DIS and no better explanation for the clinical presentation, demonstration of CSF-specific OCBs in the absence of other CSF findings atypical of MS allows a diagnosis of MS to be made. This recommendation is an addition to the 2010 McDonald Criteria.[5]
- Symptomatic and asymptomatic MRI lesions can be considered in the determination of DIS or DIT. MRI lesions in the optic nerve in a patient presenting with optic neuritis remain an exception and, due to insufficient evidence, cannot be utilized in fulfilling the McDonald Criteria. In the 2010 McDonald Criteria, the symptomatic lesion in a patient presenting with brainstem or spinal cord syndrome could not be included as MRI evidence of DIS or DIT.[5]
- Cortical and juxtacortical lesions can be used in fulfilling MRI criteria for DIS. Cortical lesions could not be used in fulfilling MRI criteria for DIS in the 2010 McDonald Criteria.[5]
- The diagnostic criteria for primary progressive MS in the revised 2017 McDonald Criteria remain the same as those outlined in the 2010 McDonald Criteria,[5] aside from removal of the distinction between symptomatic and asymptomatic MRI lesions and that cortical lesions can be used.
- At the time of diagnosis, a provisional disease course should be specified (relapsing-remitting, primary progressive, or secondary progressive) and whether the course is active or not, and progressive or not based on the prior year's history. The phenotype should be periodically re-evaluated based on accumulated information. This recommendation is an addition to the 2010 McDonald Criteria.[5]

CIS = clinically isolated syndrome, CSF = cerebrospinal fluid, DIS = dissemination in space, DIT = dissemination in time, MRI = magnetic resonance imaging, MS = multiple sclerosis, OCBs = oligoclonal bands

Panel 5: 2017 McDonald Criteria for demonstration of DIS and DIT by MRI in a patient with a CIS

DIS can be demonstrated by ≥1 T2-hyperintense lesions[a] characteristic of MS in ≥2 of four areas of the central nervous system:

- Periventricular[b]
- Cortical/juxtacortical
- Infratentorial
- Spinal cord

DIT can be demonstrated by:

- Simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time[a]

OR

- A new T2-hyperintense and/or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

CIS = clinically isolated syndrome, CNS = central nervous system, DIS = dissemination in space, DIT = dissemination in time, MRI = magnetic resonance imaging, MS = multiple sclerosis

[a] Unlike the 2010 McDonald Criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.

[b] For some patients, for example, older individuals or those with vascular risk factors, it may be prudent for the clinician to seek a higher number of periventricular lesions.

Table 1: The 2017 McDonald Criteria for diagnosis of multiple sclerosis in patients with an attack[a] at onset

CLINICAL PRESENTATION	ADDITIONAL DATA NEEDED FOR MS DIAGNOSIS
≥2 clinical attacks and objective clinical evidence of ≥2 lesions; or ≥2 clinical attacks and objective clinical evidence of 1 lesion and clear-cut historical evidence of a prior attack involving a lesion in a distinct anatomic location[b]	None[c]
≥2 clinical attacks and objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: An additional clinical attack implicating a different CNS site **OR** Demonstration of DIS by MRI[d]
1 clinical attack and objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: A second clinical attack **OR** Demonstration of DIT by MRI[e] **OR** Demonstration of CSF-specific OCBs[f]
1 clinical attack and objective clinical evidence of 1 lesion	Dissemination in space and time, demonstrated by: For DIS: A second clinical attack implicating a different CNS site

	OR Demonstration of DIS by MRI[d] **AND** For DIT: A second clinical attack **OR** Demonstration of DIT by MRI[e] **OR** Demonstration of CSF-specific OCBs[f]

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS. If MS is suspected by virtue of a CIS but the 2017 McDonald Criteria are not completely met, the diagnosis is “possible MS.” If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is “not MS.”

CNS = central nervous system, CSF = cerebrospinal fluid, DIS = dissemination in space, DIT = dissemination in time, MRI = magnetic resonance imaging, MS = multiple sclerosis, OCBs = oligoclonal bands

[a] An attack is defined in Panel 1: Glossary.

[b] Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic

for a prior inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed.

[c] No additional tests are required to demonstrate DIS and DIT. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of MS is being considered. In addition, spinal cord MRI and/or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting MS, with a non-classical presentation, or with atypical features. If imaging or other tests (e.g. CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of MS, and alternative diagnoses should be considered. There must be no better explanation for the clinical presentation and objective evidence must be present to support a diagnosis of MS.

[d] The MRI criteria for DIS are described in Panel 5.

[e] The MRI criteria for DIT are described in Panel 5.

[f] The presence of CSF OCBs does not demonstrate DIT *per se* but can substitute for demonstration of DIT.

Panel 6: 2017 McDonald Criteria for diagnosis of MS in patients with a disease course characterized by progression from onset (primary progressive MS)

Primary progressive MS may be diagnosed in patients with:

- One year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus 2 out of 3 of the following criteria:

- ≥1 T2-hyperintense lesions in ≥1 areas in the brain characteristic of MS (periventricular, cortical/juxtacortical or infratentorial)[a]
- ≥2 T2-hyperintense lesions in the spinal cord[a]
- Presence of CSF-specific OCBs

CSF = cerebrospinal fluid, MS = multiple sclerosis, OCBs = oligoclonal bands

[a] Unlike the 2010 McDonald Criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.