Misdiagnosis of multiple sclerosis

Impact of the 2017 McDonald criteria on clinical practice

Andrew J. Solomon, MD, Robert T. Naismith, MD, and Anne H. Cross, MD

Neurology® 2019;92:26-33. doi:10.1212/WNL.0000000000006583

Correspondence

Dr. Solomon
andrew.solomon@uvm.edu

RELATED ARTICLE

Editorial

Misdiagnosis of multiple sclerosis: If you have a hammer, everything looks like a nail?

Page 15

Abstract

Misdiagnosis of multiple sclerosis (MS) (the incorrect assignment of a diagnosis of MS) remains a problem in contemporary clinical practice. Studies indicate that misdiagnosed patients are often exposed to prolonged unnecessary health care risks and morbidity. The recently published 2017 revision of the McDonald criteria for the diagnosis of MS provides an opportunity to consider the effect of these revisions on the problem of MS misdiagnosis. The 2017 McDonald criteria include several new recommendations to reduce potential for misdiagnoses. The criteria should be used for the types of patients in which validation studies were performed, specifically those patients who present with typical demyelinating syndromes. MRI lesion characteristics were defined for which McDonald criteria would be expected to perform with accuracy. However, 2017 revisions, which now include assessment for cortical lesions, and the inclusion of symptomatic lesions and positive oligoclonal bands for the fulfillment of diagnostic criteria, may have the potential to lead to misdiagnosis of MS if not applied appropriately. While the 2017 McDonald criteria integrate issues relating to MS misdiagnosis and incorporate specific recommendations for its prevention more prominently than prior criteria, the interpretation of clinical and radiologic assessments upon which these criteria depend will continue to allow misdiagnoses. In patients with atypical clinical presentations, the revised McDonald criteria may not be readily applied. In those situations, further evaluation or monitoring rather than immediate diagnosis of MS is prudent.

Introduction

The McDonald criteria for the diagnosis of multiple sclerosis (MS), first introduced in 2001 with revisions in 2005, 2010, and 2017, continue to evolve. The recently published 2017 revisions¹ may facilitate earlier fulfillment of the diagnostic criteria for relapsing-remitting MS.²⁻⁴ However, confirming a diagnosis of MS is not always straightforward. Clinical heterogeneity along with a lengthy differential diagnosis⁵ results in the not infrequent incorrect assignment of a diagnosis of MS.⁶⁻⁸ While MS is a common disease, affecting around 900,000 persons in the United States, the astute clinician needs to be aware of alternative diagnoses, such as functional neurologic disorders, migraine, and vascular disease, along with uncommon inflammatory, infectious, and metabolic disorders that may mimic MS.

Studies have indicated that, of all new referrals to MS subspecialty centers with a question of MS diagnosis, 30%–67% were ultimately determined not to have MS. Regrettably, misdiagnosis and initiation of MS disease-modifying therapy (DMT) had already occurred in some of these patients.⁸⁻¹¹ A multicenter case series consisting of patients who had been incorrectly diagnosed with MS¹¹ revealed that over 50% carried the misdiagnosis for at least 3 years, and more than 5% were misdiagnosed for over 20 years. In this study, 31% incurred unnecessary morbidity as a direct result of misdiagnosis.¹¹ The primary reasons for MS misdiagnosis included inappropriate application of McDonald criteria in syndromes atypical for demyelination or lacking objective clinical findings consistent with MS, and the misinterpretation of or overreliance on MRI abnormalities in the setting of nonspecific neurologic symptoms.¹¹

From the Department of Neurological Sciences (A.J.S.), Larner College of Medicine at The University of Vermont, University Health Center, Burlington; and Department of Neurology (R.T.N., A.H.C.), Washington University in St. Louis, MO.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

DIS = dissemination in space; **DIT** = dissemination in time; **DMT** = disease-modifying therapy; **Gd+** = gadolinium-enhancing; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **OCB** = oligoclonal bands; **PPMS** = primary progressive multiple sclerosis; **VEP** = visual evoked potentials.

Thus, many cases of misdiagnosis are not a failure of the McDonald criteria, but its inappropriate application to patients for whom they were not intended.^{12,13} In 65%, the inappropriate application of the criteria for neurologic symptoms atypical for a demyelinating attack was a contributor to misdiagnosis.¹¹ Evidence supporting the benefit of early initiation of DMT has created urgency surrounding a prompt diagnosis of MS, and this has potentially increased misdiagnoses further.^{14,15} The 2017 update¹ to the McDonald criteria provides an opportunity to formulate updated recommendations to prevent the misdiagnosis of MS.

Diagnostic criteria for MS were created over 50 years ago to aid research. In the 1965 Schumacher criteria, MS was defined as “symptoms and signs of neurological dysfunction indicating multiple and separate lesions in the central nervous system. Symptoms appear longitudinally.”¹⁶ These 4 principles have persisted through multiple subsequent iterations of MS diagnostic criteria: a symptomatic demyelinating syndrome, objective neurologic findings, dissemination in space (DIS), and dissemination in time (DIT). The 2017 McDonald criteria outline the measures to fulfill these elements. The risk for misdiagnosis is higher when these 4 principles are incompletely satisfied. All versions of the McDonald criteria have required “no better explanation” for the clinical picture before making a diagnosis of MS. However, the converse of this statement does not apply; when the possibility of MS cannot be excluded, the diagnosis should not be made prematurely. Rather, the patient should be followed until there is sufficient evidence to support the diagnosis. Since implementation of the latest 2017 criteria will continue to depend on the interpretation of clinical and radiologic data for the fulfillment of DIS and DIT, and a determination of no better explanation, the misdiagnosis of MS remains a risk.

Typical demyelinating syndromes

The authors of the 2017 McDonald criteria emphasize its application only in syndromes typical for MS-related demyelination (table 1).¹⁷ Validation studies to determine the sensitivity and specificity of MS diagnostic criteria, including the 2017 criteria,¹⁸ largely comprised patients with these specific clinical presentations. Nonetheless, studies indicate that the most frequent disorders mistaken for MS were diagnoses such as functional neurologic disorders and migraine, in which presentations typical of MS-related demyelination are unlikely.^{6,9–11,19} This suggests that some clinicians may be unaware that McDonald criteria are intended for application only in typical demyelinating syndromes, or may incorrectly identify

migrainous or functional presentations as being typical of demyelination. The 2017 MS McDonald criteria provide a helpful glossary that specifies typical and atypical presentations of MS-related demyelination to guide clinicians on proper application of the criteria¹; table 1 also enumerates these presentations.

Validation studies for the 2017 McDonald criteria were conducted largely in “patients under 50 within Europe, United States, and Canada.”¹ Therefore, application of the criteria should be approached cautiously in patients over 50 years old (or under 11) and in non-Caucasian populations. While patients of these demographic profiles may fulfill clinical and radiographic elements of the 2017 McDonald criteria, they not only were underrepresented in the validation studies, but are also at higher risk for alternative diagnoses that may mimic MS. Consideration of disorders including acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorder, neurosarcoidosis, and vascular disease are important considerations in these groups to avoid misdiagnoses.

Identification of a syndrome typical for MS-related demyelination in a patient with an appropriate demographic profile is not sufficient to confirm a diagnosis of MS using McDonald criteria. Thoughtful evaluation of the differential diagnosis with specific assessment for the presence of clinical or radiologic red flags, findings that are may be atypical for a diagnosis of MS,⁵ is also critical. A number of excellent reviews contain detailed lists of red flags in the setting of MS diagnosis.^{5,20–22} In particular, recent studies have characterized the many syndromes presenting with transverse myelopathy that may be mistaken for demyelination,^{23,24} or with vision loss that can be misdiagnosed as optic neuritis.^{25–27} Spinal cord lesions associated with MS are most commonly one segment or less in length, asymmetric, partial, and peripherally located.²⁸ Optic neuritis associated with MS tends to be unilateral, mild, and associated with partial or complete recovery. Atypical presentations (table 1) necessitate further consideration before making the diagnosis of MS. For example, neuromyelitis optica spectrum disorder (NMOSD) and syndromes associated with myelin oligodendrocyte glycoprotein antibody each can present with optic neuritis or transverse myelitis that may be mistaken for MS.^{6,11,29–31} Red flags for such disorders may include severe nonremitting optic neuritis, MRI evidence of longitudinally extensive transverse myelitis, and intractable hiccoughs or vomiting. When using McDonald criteria to make a diagnosis of MS, it is necessary to consider alternative diagnoses even in the setting of syndromes typical for MS, and to recognize clinical and radiographic red flags that suggest an alternative diagnosis.

Table 1 Clinical syndromes typical and atypical for multiple sclerosis (MS)-related demyelination

Typical for MS	Atypical for MS
Unilateral optic neuritis, mild and with partial or full recovery	Bilateral optic neuritis; severe optic neuritis; poor recovery from optic neuritis
Diplopia due to internuclear ophthalmoplegia	Headache, with or without diplopia or visual obscuration
Facial sensory loss or trigeminal neuralgia in young patient	Acute or subacute cognitive impairment
Cerebellar syndromes that include ataxia and nystagmus	Dizziness or vertigo without brainstem or cerebellar findings
Sensory impairment or motor weakness localizing to the spinal cord, with partial or full recovery	Sensory loss in extremities without a clear CNS pattern
	Complete transverse myelopathy

Corroboration of prior symptoms with objective neurologic findings

Relying on a history of neurologic symptoms without objective evidence to meet McDonald criteria for DIT was previously shown to contribute to almost 50% of MS misdiagnoses.¹¹ The first McDonald criteria (2001) stated that “Historical accounts of symptoms...cannot be sufficient on their own for a diagnosis of MS.”³² However, the 2017 criteria now specify that “reasonable historical evidence for one past attack, in the absence of documented objective neurologic findings...can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack.”¹

We feel it is necessary to obtain objective evidence to confirm prior events of suspected demyelination because determining that historical symptoms are typical of demyelination is challenging.¹¹ We recommend that historical symptoms of vision loss, diplopia, vertigo, limb weakness, walking impairment, and sensory disturbance are inadequate to fulfill DIT criteria. Objective evidence of CNS dysfunction on neurologic examination or as the result of paraclinical testing such as MRI or visual evoked potentials (VEP) must be present and localize to the prior symptoms.

Furthermore, the specificity of objective evidence supporting a historical episode of demyelination may vary in level of support. Examples of strongly supportive objective findings include an internuclear ophthalmoplegia in a patient with a history of diplopia or a relative afferent pupillary defect or optic disk pallor in a patient with a history suggestive of optic neuritis. Objective findings of CNS dysfunction that are less specific for MS such as a Babinski sign, asymmetric hyperreflexia, upper motor neuron pattern weakness, and cerebellar ataxia that correspond with prior symptoms constitute only a moderate level of support. Low level supportive evidence would include findings that might be attributable to either central or peripheral nervous system dysfunction, or subjective evidence such as sensory deficits. We recommend that low level evidence not be used to fulfill DIT criteria.

The results of paraclinical testing can also provide objective evidence of a prior episode. The 2017 McDonald criteria

affirm that now, in addition to prolonged VEP latency, an optic nerve T2-weighted hyperintensity on MRI or temporal retinal nerve fiber thinning on optical coherence tomography can provide objective evidence corroborating a prior episode of symptomatic optic neuritis. MRI lesions that localize to other regions of the CNS that would explain a historical episode of neurologic dysfunction may also provide objective evidence. Examples would include a lesion in the medial longitudinal fasciculus corresponding to a prior episode of diplopia characteristic of an internuclear ophthalmoplegia or a spinal cord lesion corresponding to a prior episode of motor, sensory, or urologic symptoms characteristic of transverse myelitis. Somatosensory evoked potentials are another modality that might suggest the presence of a spinal cord lesion, although this test has been largely replaced in MS with spinal cord MRI.

MRI lesions and their characteristics

Misinterpretation of abnormal MRI findings is a frequent contributor to misdiagnosis of MS.¹¹ One study found that only 11% of patients who were referred to a MS subspecialty center based primarily on an abnormal MRI were subsequently diagnosed with MS.¹⁰ In particular, the incorrect interpretation of what constitutes a periventricular or juxtacortical lesion location contributed to MS misdiagnosis.¹¹ The 2017 McDonald criteria define juxtacortical and periventricular lesions as abutting the ventricles and cortex, respectively, without intervening white matter. This clarification distinguishes MS from disorders associated with T2 white matter hyperintensities that appear near but not touching the cortex or the ventricles. For example, a study of headache patients discovered that over half had brain MRI T2 white matter hyperintensities, but most of these patients had hyperintensities falling short of these definitions.³³

Lesion location, morphology, and number are important considerations when assessing MRI for fulfillment of MS criteria, particularly in patients with older age at presentation, atypical syndromes, and red flags atypical for MS. Using the 2017 diagnostic criteria, a single periventricular lesion can serve as one of the 2 regions required to fulfill MRI DIS. Yet periventricular hyperintensities are also associated with small

vessel ischemic disease and normal aging, and are present in over 60% of patients by their early 60s.³⁴ Periventricular capping and rims are not uncommon in healthy individuals.³⁵ By contrast, lesions involving the callosal septal interface, best observed on the midsagittal T2-weighted sequence, are reported to have better specificity for MS because the rich vascular supply of this region renders it resistant to ischemia.³⁶ Recent data suggest that a requirement of more than one periventricular lesion for fulfillment of MRI DIS criteria could improve specificity for MS.^{37,38} The authors of the 2017 criteria decided that the small improvement in specificity associated with additional lesions did not justify the increased complexity of including a different number of lesions for different regions to fulfill MRI DIS criteria. However, we strongly suggest considering a requirement of 3 periventricular lesions or callosal lesions in older populations and in patients with known comorbidities associated with MRI white matter T2-weighted hyperintensities to help prevent misdiagnoses.

With incorporation of MRI for the first time into DIS and DIT criteria, the 2001 McDonald criteria suggested a size threshold for MRI lesions, specifying “lesions will ordinarily be larger than 3 mm in cross section.”³² The derivation of this 2001 lesion size threshold is unclear. Interval revisions to the McDonald criteria did not recommend a lesion size threshold. However, the 2017 revisions define a lesion as an “area of hyperintensity on a T2W or proton-density-weighted MRI scan that is at least 3 mm in long axis.”¹ Renewed consideration of lesion size may lessen the risk of misdiagnosis, as the use of punctate lesions to fulfill MRI criteria for MS is a factor in misdiagnoses.¹¹ Furthermore, the growing implementation of clinical MRI scanners with higher resolution (e.g., 3T with 1 mm slices) will likely increase identification of small T2-weighted hyperintensities. One study found that the majority of healthy individuals with a mean age 44 ± 8 years had at least one T2-weighted hyperintensity on 3T brain imaging, but the typical diameter was only 2–4 mm.³⁵ We would not recommend diagnosing MS when only punctate lesions are present, as MS lesions are usually at least 3 mm and often more than 6 mm. To improve the accuracy of MS MRI diagnostic criteria, we advocate future studies to assess MS lesion size thresholds using current MRI technologies.

Identification of cortical lesions may facilitate the earlier diagnosis of MS.^{37,39,40} Inclusion of cortical lesions in diagnostic criteria may reduce MS misdiagnoses by differentiating MS from migraine and NMOSD.^{41–44} The 2017 McDonald criteria recommend that such lesions be considered equivalent to juxtacortical lesions. The 2017 criteria also acknowledge that using conventional MRI for the visualization of cortical lesions is challenging.⁴⁵ Recent studies³⁷ and consensus guidelines⁴⁶ have stressed that cortical lesion detection is best accomplished using advanced imaging techniques at specialized centers to prevent false-positive findings. Intracortical and subpial cortical lesions are especially difficult to visualize on MRI; we recommend that such lesions be used for the diagnosis of MS only by centers experienced in their detection.

Symptomatic MRI lesions for fulfillment of DIS and DIT

Using 2010 McDonald criteria, fulfillment of DIT to diagnose MS with a single clinical event was possible if an asymptomatic gadolinium-enhancing (Gd+) lesion was present with additional nonenhancing T2-weighted lesions fulfilling DIS.⁴⁷ In the 2017 revisions, DIT can be fulfilled with presence of any Gd+ lesion (including symptomatic lesions) together with at least one nonenhancing T2-weighted hyperintense lesion. The allowance of symptomatic lesions in the 2017 McDonald criteria is based on data from 2 cohorts indicating increased sensitivity with minimal reduction in specificity for MS compared to the 2010 criteria.^{48,49} This change effectively reduces the number of lesions required to fulfill McDonald criteria. For instance, in a patient presenting with transverse myelitis, MRI with a symptomatic (Gd+) spinal cord lesion and a single nonenhancing periventricular lesion would potentially fulfill McDonald criteria, yet could be found in numerous inflammatory or infectious spinal cord disorders other than MS.^{23,24} We recommend caution in making a diagnosis of MS in patients with this presentation, especially when additional comorbidities known to cause MRI T2 white matter hyperintensities such as hypertension, migraine, or vascular disease are present.

CSF evaluation

The 2017 revisions to the McDonald criteria now permit positive CSF-restricted oligoclonal bands (OCB) to fulfill DIT criteria, providing another avenue to establish the MS diagnosis with a single clinical episode of demyelination and a single brain MRI. These changes are at least in part based on recent data in a large cohort⁵⁰ suggesting that in patients meeting DIS criteria, the additional presence of positive OCB increases specificity and has a high positive predictive value for MS diagnosis. The 2017 McDonald criteria specify that “CSF-specific” OCB should be identified in the absence of “atypical CSF findings” (e.g., absence of atypically high CSF leukocyte numbers or protein levels). The 2017 diagnostic criteria emphasize that the accuracy of CSF OCB testing depends on the methodology used. Sending CSF to a high-quality laboratory that performs agarose gel electrophoresis with isoelectric focusing and immunoblotting or immunofixation for immunoglobulin G is recommended.¹

Recent retrospective application of 2017 McDonald criteria^{2,3,51} found that the revised criteria enabled earlier diagnosis of MS, primarily through use of CSF OCB for fulfillment of DIT. However, it should also be noted that CSF findings typical of MS are not specific to MS. CSF-restricted OCB may be elevated in other inflammatory and infectious etiologies including monophasic syndromes with clinical and radiographic overlap with MS.^{51,52} Use of CSF-restricted OCB to meet DIT in patients with syndromes atypical for MS-related demyelination could potentially lead to misdiagnosis of MS in patients with

inflammatory CNS disorders. To prevent MS misdiagnoses, we recommend that CSF OCB be used to fulfill DIT criteria only in patients similar to the population from which these data were validated,⁵³ that is, younger patients (<50 years) presenting primarily with optic neuritis, brainstem, or spinal cord syndromes typical for MS. Studies in additional cohorts and with long-term follow-up are needed to better evaluate the specificity of incorporating OCB as a substitution for DIT. On the other hand, CSF-restricted OCB have been shown in several studies⁵⁴ to have a high negative predictive value, and thus their absence should be a red flag suggesting the possibility of an alternative diagnosis.

Primary progressive MS

The diagnosis of primary progressive MS (PPMS) can be particularly challenging. Diagnostic criteria for PPMS were not changed in the 2017 revisions except for inclusion of cortical and symptomatic lesions for fulfillment of DIS criteria. 2017 McDonald criteria define a progressive course as “steadily increasing objectively documented neurologic disability independent of relapses” and note that “fluctuations, periods of stability, and superimposed relapses might occur.”¹ Several different neurodegenerative and vascular diseases might mimic the course of PPMS. As mentioned previously, nonspecific white matter abnormalities might fulfill MRI DIS criteria. As in the original McDonald criteria (2001),³² we recommend spinal fluid evaluation before finalizing PPMS diagnosis. Although CSF-restricted OCB are not specific to MS, making a PPMS diagnosis in the absence of CSF-restricted OCB is particularly hazardous. Even in those with positive CSF OCB, alternative inflammatory and paraneoplastic disorders⁵ should be considered.

Table 2 highlights recommendations that may prevent MS misdiagnoses in the application of 2017 McDonald criteria.

Clinical presentations in which 2017 McDonald criteria are insufficient for MS diagnosis

The expert panel that formulated the 2017 McDonald criteria acknowledged that the current criteria “were not developed to differentiate MS from other conditions”¹ but rather to facilitate earlier diagnosis of MS in patients presenting with typical demyelinating syndromes. The use of McDonald criteria in atypical syndromes, or any clinical presentations other than optic neuritis, brainstem/cerebellar syndromes, or transverse myelitis, diminishes accuracy.^{13,55}

Nonetheless, a small proportion of patients who are eventually diagnosed with MS will have presented initially with atypical syndromes.²² Criteria are needed to aid in the diagnosis of MS in patients with an atypical presentation or a typical presentation accompanied by clinical or radiographic

red flags. The McDonald criteria for MS would not be expected to perform with precision in these situations. We agree with the authors of the 2017 criteria that validation will be needed in a large prospective real-world cohort of patients.

In atypical and challenging clinical presentations, fulfillment of more than the minimum requirements of the McDonald criteria, or additional clinical or radiographic data, would help avoid misdiagnoses. In many such cases, history and examination findings accompanied only by abnormal brain MRIs may not be sufficient. Table 3 provides guidance for an approach to diagnosis of MS in patients with atypical and challenging clinical presentations.

In patients with a history of migraine, vascular risk factors, or examination findings suggestive of a functional neurologic disorder who fulfill McDonald criteria, evaluation for CSF-restricted OCB or spinal cord lesions should be pursued to support the diagnosis of MS. MRI criteria using a lesion threshold of 6 mm⁵⁶ may improve specificity for MS in atypical syndromes and older patients, as even healthy controls can have T2 abnormalities in the 2–4 mm range. The identification of callosal lesions may help to differentiate MRI demyelination from vascular changes. Diagnosis of MS, especially in atypical syndromes, should not rely on questionable spinal cord lesions observed only on sagittal view. Lesions should be confirmed on axial images and on at least 2 different MRI sequences (such as proton density, T2, or short tau inversion recovery). In equivocal cases, repeat imaging may be necessary to confirm a spinal cord lesion. Repeating CSF evaluation may also be prudent in patients with atypical or challenging syndromes. Initially negative CSF may subsequently reveal positive OCB.⁵⁷ Likewise, the presence of CSF OCB may be transient in self-limited inflammatory non-MS CNS disorders.⁵⁸

Guidance is also needed for clinicians when confronted with a patient with a questionable previous diagnosis of MS. There may be reluctance to revisit a MS diagnosis, particularly if it is decades old.⁵⁹ McDonald criteria have not been tested in such patients. Objective evidence of a prior attack may no longer be present. Reliance on historical information can perpetuate a misdiagnosis. Brain MRIs that previously met DIS may subsequently develop the appearance of small vessel ischemic disease due to the confluence of discrete demyelinating lesions over time. However, the periodic reassessment of a preexisting diagnosis of MS is a component of optimal care of patients with MS.

Ultimately, in patients presenting with atypical or non-specific neurologic syndromes, or typical syndromes with concurrent red flags, the 2017 McDonald criteria do not apply. Additional clinical and radiographic monitoring are necessary before making a definitive diagnosis of MS. Despite data supporting the benefit of early initiation of DMTs in relapsing MS, it is also important not to miss another diagnosis

Table 2 Recommendations for prevention of multiple sclerosis (MS) misdiagnosis when applying 2017 McDonald criteria

Typical demyelinating syndromes
MS diagnostic criteria should be applied only in the typical demyelinating syndromes in which they have been validated
Caution should be taken in patients over 50 years old (or under 11) and in non-Caucasian populations
Continue to consider a broad differential diagnosis, with vigilance for red flags, even in patients with typical syndromes
Use of prior symptoms for fulfillment of DIT criteria
Objective evidence on neurologic examination or as the result of paraclinical testing (VEP, MRI, OCT) must corroborate symptoms
Objective evidence specific for CNS demyelination, such as internuclear ophthalmoplegia or afferent pupillary defect, is preferred over nonspecific evidence such as hyperreflexia
MRI lesions and their characteristics
Juxtacortical lesions must abut the cortex, without intervening white matter
Periventricular lesions must abut the ventricles, without intervening white matter
Lesions should be 3 mm or larger in diameter
Small punctate lesions should not be used to fulfill MRI criteria
Use of intracortical and subpial cortical lesions to fulfill criteria should be restricted to experienced imaging centers
Symptomatic MRI lesions for fulfillment of DIS and DIT
In patients with monophasic syndrome of a single symptomatic brainstem or spinal cord lesion where only 1 additional MRI DIS region is satisfied, consider awaiting appearance of an additional MRI lesion or additional clinical event to meet DIS criteria, especially when comorbidities are present
CSF evaluation
CSF evaluation is recommended before finalizing a diagnosis of PPMS
OCB restricted to the CSF should be used with caution in the presence of high numbers of polymorphonuclear cells or highly elevated protein
Positive OCB should be used to substitute for DIT criteria only in patients younger than 50 presenting with optic neuritis, brainstem, or spinal cord syndromes typical for MS, and without evidence of another inflammatory CNS condition
If CSF is negative for findings typical of MS, a diagnosis of MS should be made with caution
Abbreviations: DIS = dissemination in space; DIT = dissemination in time; OCB = oligoclonal bands; OCT = optical coherence tomography; PPMS = primary progressive multiple sclerosis; VEP = visual evoked potentials.

and to avoid unnecessary exposure to DMTs. We recommend objective evidence to support at least 2 episodes of demyelination typical for MS in the patient who presents with atypical or nonspecific symptoms or red flags, despite having a MRI meeting DIS.

Discussion

The misdiagnosis of MS can be associated with serious risks and potential morbidity. The correct identification of a syndrome typical for MS-related demyelination in a patient with

Table 3 Recommended approach to diagnosis of multiple sclerosis (MS) in patients with atypical and challenging clinical presentations

Fulfillment of more than the minimum requirements of the McDonald criteria is necessary to avoid misdiagnoses in the setting of red flags or an atypical presentation
Evaluation for CSF-restricted OCB or spinal cord lesions in patients with migraine, vascular risk factors, or examination findings suggestive of a functional neurologic disorder
In OCB-negative patients, consider repeat CSF evaluation at a later date
Consider a lesion threshold of 6 mm for MRI criteria in patients with atypical syndromes and advanced age
Presence of callosal lesions may help differentiate MRI demyelination from vascular changes
Re-evaluate preexisting diagnoses of MS in patients who transfer care from another provider
Additional clinical and radiographic monitoring for objective evidence supporting at least 2 episodes of demyelination typical for MS may be necessary
Abbreviation: OCB = oligoclonal bands.

an appropriate demographic profile is integral to making an accurate diagnosis of MS and preventing misdiagnosis. More prominently than prior criteria, the 2017 revisions to the McDonald criteria integrate issues relating to the problem of MS misdiagnosis and provide specific recommendations for prevention of misdiagnoses. Detailed specification of the “typical” demyelinating syndromes and MRI lesion characteristics required to fulfill 2017 McDonald criteria are expected to help prevent MS misdiagnoses. However, if not applied carefully, 2017 revisions that incorporate cortical lesions and include symptomatic MRI lesions in MRI criteria, and allow positive OCB to fulfill DIS and DIT criteria, may result in misdiagnoses. As previous authors have noted,⁶⁰ important cautionary comments, modifiers, and clarifications that are contained in the McDonald criteria are unlikely to be reproduced fully in textbooks, journals, lectures, or abbreviated pocket cards that contain condensed versions of the MS diagnostic criteria. Some clinicians may not read the qualifiers and expansive footnotes in the original document. As a result, educational efforts surrounding proper use of the 2017 McDonald criteria remain critical for the prevention of MS misdiagnosis.

Author contributions

Andrew J. Solomon: drafting/revising the manuscript, data acquisition, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Robert T. Naismith: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Anne H. Cross: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval.

Study funding

No targeted funding reported.

Disclosure

A. Solomon has received honoraria for consulting for Biogen and Genentech and research funding from Biogen. R. Naismith has received honoraria for consulting for Acorda, Alkermes, Biogen, EMD Serono, Genentech, Genzyme, Novartis, and Teva. A. Cross has received honoraria for consulting for Biogen, EMD Serono, Genentech/Roche, Genzyme, and Novartis. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* February 19, 2018. Accepted in final form July 30, 2018.

References

- Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162–173.
- McNicholas N, Lockhart A, Yap SM, et al. New versus old: implications of evolving diagnostic criteria for relapsing-remitting multiple sclerosis. *Mult Scler Epub* 2018 Apr 1.
- Beesley R, Anderson V, Harding KE, et al. Impact of the 2017 revisions to McDonald criteria on the diagnosis of multiple sclerosis. *Mult Scler Epub* 2018 May 1.
- Schwenkenbecher P, Wurster U, Sühs KW, Stangel M, Skripuletz T. Applying the 2017 McDonald diagnostic criteria for multiple sclerosis. *Lancet Neurol* 2018;17:498.
- Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler* 2008;14:1157–1174.
- Solomon AJ, Klein EP, Bourdette D. “Undiagnosing” multiple sclerosis: the challenge of misdiagnosis in MS. *Neurology* 2012;78:1986–1991.
- Solomon AJ, Weinshenker BG. Misdiagnosis of multiple sclerosis: frequency, causes, effects, and prevention. *Curr Neurol Neurosci Rep* 2013;13:403.
- Kaisey MGB. Misdiagnosis of multiple sclerosis and common alternate diagnoses. *Mult Scler J* 2017;23:680–975.
- Yamout BI, Khoury SJ, Ayyoubi N, et al. Alternative diagnoses in patients referred to specialized centers for suspected MS. *Mult Scler Relat Disord* 2017;18:85–89.
- Carmosino MJ, Brousseau KM, Arciniegas DB, Corboy JR. Initial evaluations for multiple sclerosis in a university multiple sclerosis center: outcomes and role of magnetic resonance imaging in referral. *Arch Neurol* 2005;62:585–590.
- Solomon AJ, Bourdette DN, Cross AH, et al. The contemporary spectrum of multiple sclerosis misdiagnosis: a multicenter study. *Neurology* 2016;87:1393–1399.
- Hawkes CH, Giovannoni G. The McDonald criteria for multiple sclerosis: time for clarification. *Mult Scler* 2010;16:566–575.
- Brownlee WJ. Use (and misuse) of the McDonald criteria to diagnose multiple sclerosis. *Eur J Neurol* 2018;25:209–210.
- Miller AE, Pelletier D. Multiple sclerosis: rapid diagnosis or right diagnosis? *Neurology* 2016;87:652–653.
- Solomon AJ, Corboy JR. The tension between early diagnosis and misdiagnosis of multiple sclerosis. *Nat Rev Neurol* 2017;13:567–572.
- Schumacher GA, Beebe G, Kibler RF, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Ann NY Acad Sci* 1965;122:552–568.
- Brownlee WJ, Hardy TA, Fazekas F, Miller DH. Diagnosis of multiple sclerosis: progress and challenges. *Lancet* 2016;389:1336–1346.
- Filippi M, Preziosa P, Meani A, et al. Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study. *Lancet Neurol* 2018;17:133–142.
- Murray TJ, Murray SJ. Characteristics of patients found not to have multiple sclerosis. *Can Med Assoc J* 1984;131:336–337.
- Charil A, Yousry TA, Rovaris M, et al. MRI and the diagnosis of multiple sclerosis: expanding the concept of “no better explanation”. *Lancet Neurol* 2006;5:841–852.
- Toledano M, Weinshenker BG, Solomon AJ. A clinical approach to the differential diagnosis of multiple sclerosis. *Curr Neurol Neurosci Rep* 2015;15:57.
- Kelly SB, Chaila E, Kinsella K, et al. Using atypical symptoms and red flags to identify non-demyelinating disease. *J Neurol Neurosurg Psychiatry* 2012;83:44–48.
- Barreras P, Fitzgerald KC, Mealy MA, et al. Clinical biomarkers differentiate myelitis from vascular and other causes of myelopathy. *Neurology* 2018;90:e12–e21.
- Zalewski NL, Flanagan EP, Keegan BM. Evaluation of idiopathic transverse myelitis revealing specific myelopathy diagnoses. *Neurology* 2018;90:e96–e102.
- Voss E, Raab P, Trebst C, Stangel M. Clinical approach to optic neuritis: pitfalls, red flags and differential diagnosis. *Ther Adv Neurol Disord* 2011;4:123–134.
- Hoorbakht H, Bagherkashi F. Optic neuritis, its differential diagnosis and management. *Open Ophthalmol J* 2012;6:65–72.
- Stunkel L, Kung NH, Wilson B, McClelland CM, Van Stavern GP. Incidence and causes of overdiagnosis of optic neuritis. *JAMA Ophthalmol* 2018;136:76–81.
- Tartaglino LM, Friedman DP, Flanders AE, Lublin FD, Knobler RL, Liem M. Multiple sclerosis in the spinal cord: MR appearance and correlation with clinical parameters. *Radiology* 1995;195:725–732.
- Reindl M, Di Pauli F, Rostasy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. *Nat Rev Neurol* 2013;9:455–461.
- Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. *J Neuroinflammation* 2016;13:279.
- Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. *Brain* 2017;140:3128–3138.
- 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.
- Liu S, Kullnat J, Bourdette D, et al. Prevalence of brain magnetic resonance imaging meeting Barkhof and McDonald criteria for dissemination in space among headache patients. *Mult Scler* 2013;19:1101–1105.
- Wen W, Sachdev P. The topography of white matter hyperintensities on brain MRI in healthy 60- to 64-year-old individuals. *Neuroimage* 2004;22:144–154.
- Neema M, Guss ZD, Stankiewicz JM, Arora A, Healy BC, Bakshi R. Normal findings on brain FLAIR MRI scans at 3T. *AJNR Am J Neuroradiol* 2009;30:911–916.
- Gean-Martón AD, Vezina LG, Marton KI, et al. Abnormal corpus callosum: a sensitive and specific indicator of multiple sclerosis. *Radiology* 1991;180:215–221.
- Arrambide G, Tintore M, Auger C, et al. Lesion topographies in multiple sclerosis diagnosis: a reappraisal. *Neurology* 2017;89:2351–2356.
- Brownlee WJ, Miszkil KA, Altmann DR, Ciccarelli O, Miller DH. Periventricular lesions and MS diagnostic criteria in young adults with typical clinically isolated syndromes. *Mult Scler* 2017;23:1031–1034.
- Geurts JJ, Barkhof F. Grey matter pathology in multiple sclerosis. *Lancet Neurol* 2008;7:841–851.
- Filippi M, Rocca MA, Calabrese M, et al. Intracortical lesions: relevance for new MRI diagnostic criteria for multiple sclerosis. *Neurology* 2010;75:1988–1994.

41. Eshaghi A, Wottschel V, Cortese R, et al. Gray matter MRI differentiates neuromyelitis optica from multiple sclerosis using random forest. *Neurology* 2016;87:2463–2470.
42. Absinta M, Rocca MA, Colombo B, et al. Patients with migraine do not have MRI-visible cortical lesions. *J Neurol* 2012;259:2695–2698.
43. Liu Y, Jiang X, Butzkueven H, et al. Multimodal characterization of gray matter alterations in neuromyelitis optica. *Mult Scler* 2018;24:1308–1316.
44. Watts R, Solomon A, Koeller K, Nickerson J. Z-score approach to the detection of cortical lesions in multiple sclerosis. Proceedings of the 25th Annual Meeting of the International Society for Magnetic Resonance in Medicine (ISMRM). Concord, CA: International Society for Magnetic Resonance in Medicine; 2017.
45. Calabrese M, Castellaro M. Cortical gray matter MR imaging in multiple sclerosis. *Neuroimaging Clin N Am* 2017;27:301–312.
46. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol* 2016;15:292–303.
47. 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.
48. Tintore M, Otero-Romero S, Rio J, et al. Contribution of the symptomatic lesion in establishing MS diagnosis and prognosis. *Neurology* 2016;87:1368–1374.
49. Brownlee WJ, Swanton JK, Miszkil KA, Miller DH, Ciccarelli O. Should the symptomatic region be included in dissemination in space in MRI criteria for MS? *Neurology* 2016;87:680–683.
50. Arrambide G, Tintore M, Espejo C, et al. The value of oligoclonal bands in the multiple sclerosis diagnostic criteria. *Brain* 2018;141:1075–1084.
51. Etemadifar M, Sabeti F. Applying the 2017 McDonald diagnostic criteria for multiple sclerosis. *Lancet Neurol* 2018;17:497.
52. Chu AB, Sever JL, Madden DL, et al. Oligoclonal IgG bands in cerebrospinal fluid in various neurological diseases. *Ann Neurol* 1983;13:434–439.
53. Tintore M, Rovira A, Rio J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain* 2015;138:1863–1874.
54. Tintore M, Rovira A, Martinez MJ, et al. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. *AJNR Am J Neuroradiol* 2000;21:702–706.
55. Rosenkranz SC, Kaulen B, Neuhaus A, et al. Low clinical conversion rate in clinically isolated syndrome patients: diagnostic benefit of McDonald 2010 criteria? *Eur J Neurol* 2018;25:247–e9.
56. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997;120:2059–2069.
57. Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. *Arch Neurol* 2005;62:865–870.
58. Jacob A, Weinshenker BG. An approach to the diagnosis of acute transverse myelitis. *Semin Neurol* 2008;28:105–120.
59. Solomon AJ, Klein E. Disclosing a misdiagnosis of multiple sclerosis: do no harm? *Continuum* 2013;19:1087–1091.
60. Poser CM, Brinar VV. Problems with diagnostic criteria for multiple sclerosis. *Lancet* 2001;358:1746–1747.

Share Your Artistic Expressions in *Neurology* ‘Visions’

AAN members are urged to submit medically or scientifically related artistic images, such as photographs, photomicrographs, and paintings, to the “Visions” section of *Neurology*®. These images are creative in nature, rather than the medically instructive images published in the NeuroImages section. The image or series of up to six images may be black and white or color and must fit into one published journal page. Accompanying description should be 100 words or less; the title should be a maximum of 96 characters including spaces and punctuation.

Please access the Author Center at Npub.org/authors for full submission information.

Visit the *Neurology*® Resident & Fellow Website

Click on Residents & Fellows tab at Neurology.org.

Now offering:

- *Neurology*® Resident & Fellow Editorial team information
- “Search by subcategory” option
- E-pearl of the Week
- RSS Feeds
- Direct links to Continuum®, Career Planning, and AAN Resident & Fellow pages
- Recently published Resident & Fellow articles
- Podcast descriptions

Find *Neurology*® Residents & Fellows Section on Facebook: <http://tinyurl.com/o8ahsys>

Follow *Neurology*® on Twitter: <http://twitter.com/GreenJournal>