Diagnosis, Differential Diagnosis, and Misdiagnosis of Multiple Sclerosis

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ABSTRACT

PURPOSE OF REVIEW: **The diagnosis of multiple sclerosis (MS) is often challenging. This article discusses approaches to the clinical assessment for MS that may improve diagnostic accuracy.**

RECENT FINDINGS: **Contemporary diagnostic criteria for MS continue to evolve, while knowledge about diseases that form the differential diagnosis of MS continues to expand. Recent data concerning causes of MS misdiagnosis (the incorrect assignment of a diagnosis of MS) have further informed approaches to syndromes that may mimic MS and the accurate diagnosis of MS.**

SUMMARY: **This article provides a practical update on MS diagnosis through a discussion of recently revised MS diagnostic criteria, a renewed consideration of MS differential diagnosis, and contemporary data concerning MS misdiagnosis.**

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INTRODUCTION

Multiple sclerosis (MS) is a complex disease, and its clinical and radiologic heterogeneity[1] often make its diagnosis challenging. No highly specific and sensitive biomarker for MS has been identified,[2] and many diseases can mimic its appearance. Efforts to develop MS diagnostic criteria commenced over 50 years ago,[3] and the continued refinement of criteria, including the 2017 revisions to the McDonald criteria,[4] have enabled earlier diagnosis of MS. However, MS misdiagnosis (the assignment of an incorrect diagnosis of MS), remains an important contemporary problem, with considerable consequences for patients.[5,6] A clinical approach combining knowledgeable attention to the appropriate application of 2017 McDonald criteria, thoughtful consideration of the differential diagnosis of MS and the presence of potential red flags for alternative diagnoses, and an understanding of common contemporary causes of MS misdiagnosis will improve accuracy of MS diagnosis.

DIAGNOSIS OF RELAPSING-REMITTING MULTIPLE SCLEROSIS

Beginning with the Schumacher criteria[3] in 1965, diagnostic criteria have relied on five principles to confirm of the diagnosis of MS: (1) the identification of a

syndrome "typical" of MS-related demyelination, (2) objective evidence of central nervous system (CNS) involvement, (3) demonstration of dissemination in space, (4) demonstration of dissemination in time, and (5) "no better explanation" other than MS.

Over the past 20 years, evolving data have supported the incorporation of laboratory and radiologic assessments to complement what were previously solely clinical assessments to fulfill these principles. The revisions to the McDonald criteria have enabled earlier diagnosis of MS.[7] Yet MS diagnosis, including the application of the 2017 McDonald criteria,[4] continues to rely on the fulfillment of these five key principles.

Typical Syndromes

The evaluation for a diagnosis of MS begins with an assessment of whether a patient's clinical presentation is typical for MS-related demyelination.[8] A broad spectrum of neurologic symptoms may prompt a clinical evaluation for MS. Similarly, patients with a confirmed MS diagnosis may have an assortment of chronic and paroxysmal symptoms that are sequelae of the CNS damage associated with the disease. However, confirmation of a diagnosis of MS using the current diagnostic criteria requires first the identification of the presentation of a one of a limited number of syndromes typical for an MS-related demyelinating attack or relapse.[4,8] Typical syndromes include optic neuritis, brainstem syndromes such as internuclear ophthalmoplegia and trigeminal neuralgia, cerebellar syndromes, and transverse myelitis. Clinical acumen and experience are often necessary for this first critical step in approaching the diagnosis of MS, as distinguishing a noninflammatory optic neuropathy or myelopathy from optic neuritis or myelitis may be challenging at times (refer to the section "No Better Explanation": the Differential Diagnosis of Relapsing-Remitting Multiple Sclerosis later in this article).

Importantly, the McDonald criteria were validated only in cohorts of patients presenting with attacks or relapses consisting of these typical syndromes. Since the specificity for MS of the McDonald criteria has not been evaluated in other syndromes, their application alone for diagnosis of MS in patients with other clinical presentations is not recommended. If a patient's clinical presentation is determined to be atypical, further clinical, laboratory, and radiologic assessments beyond the minimum requirements of the McDonald criteria are necessary to confirm a diagnosis of MS (refer to the section Atypical Syndromes, Typical Syndromes With Red Flags, and Evaluation of Long-standing Diagnoses later in this article).

Objective Evidence

Objective clinical evidence of at least one CNS lesion corresponding to the presentation of an attack typical for MS-related demyelination is also necessary to fulfill MS diagnostic criteria.[4] Objective evidence may include a relative afferent pupillary defect in a patient presenting with visual symptoms suggestive of optic neuritis, internuclear ophthalmoplegia in a patient presenting with diplopia, or detection of a hemisensory level in a patient with sensory or motor symptoms suggestive of myelitis.

The authors of the 2017 revisions to the McDonald criteria also affirm that paraclinical or radiographic evidence of a CNS abnormality that corresponds to the anatomic location suggested by symptoms may substitute for clinical objective evidence for diagnosis of MS. For example, P100 latency prolongation

on a visual evoked potential or a T2 hyperintensity on MRI in the optic nerve might provide objective evidence of an episode of optic neuritis, or a T2 hyperintensity in the spinal cord might provide objective evidence of an episode of myelitis.

In patients presenting with symptoms concerning for a syndrome typical for MS but without objective clinical, paraclinical, or radiographic evidence of a corroborating CNS lesion, caution is especially warranted before making a diagnosis of MS. For example, patients often present for MS evaluation with neurologic symptoms accompanied by a normal neurologic examination and a brain MRI with abnormalities that would not explain the presenting symptoms. The McDonald criteria have not been tested in such patients, and their application without objective evidence would likely diminish specificity for MS. Further clinical evaluation and radiographic monitoring is often necessary in such patients to avoid misdiagnosis and to accurately confirm a diagnosis of MS.

Dissemination in Space and Time

Confirmation of objective evidence for a single attack typical for MS-related demyelination is the first step in an evaluation for a diagnosis of MS. Such a patient has a *clinically isolated syndrome*[4,9] if the patient has no further fulfillment of MS diagnostic criteria. Subsequent assessment for evidence of both dissemination in space and dissemination in time of CNS involvement characteristic of MS is the next step toward the confirmation of a MS diagnosis. Evidence of dissemination in space is defined as detection of lesions in more than one distinct anatomic location within the CNS.[4] Multifocal CNS involvement is characteristic of MS. Fulfillment of dissemination in time requires confirmation of new CNS lesions over time, suggesting an ongoing disease process typical of MS rather than a monophasic disease.

Objective evidence of a second attack typical for MS in a different location than the first would fulfill dissemination in space and dissemination in time criteria. The authors of the 2017 revisions to the McDonald criteria reaffirm that prospective confirmation of objective clinical findings for two attacks disseminated in both space and time typical for an MS diagnosis remains most secure.[4] However, in a patient with objective evidence of a single typical attack, evolving data[10,11] have suggested that the results of CSF and MRI assessments may substitute for clinical evidence to demonstrate dissemination in space and dissemination in time without diminishing specificity and sensitivity for the diagnosis of MS.

MRI Demonstration of Dissemination in Space

Recent studies continue to support[11,12] the 2017 McDonald criteria recommendations for MRI demonstration of dissemination in space[4] by detection of the presence of T2-hyperintense MRI lesions in four areas of the CNS, including (1) periventricular, (2) cortical or juxtacortical, and (3) infratentorial brain regions and (4) the spinal cord. The presence of at least one T2-hyperintense MRI lesion in two of these regions demonstrates dissemination in space.

As a result of new data,[13] the 2017 revisions to the McDonald criteria now include symptomatic lesions for demonstration of dissemination in space.[4] For example, in a patient presenting with myelitis and MRI evidence of a corresponding spinal cord lesion (objective evidence of a "symptomatic lesion"), a single additional T2-hyperintense MRI lesion in the periventricular, cortical or

KEY POINTS

- **Diagnosis of relapsing-remitting multiple sclerosis begins with confirmation of objective evidence of a syndrome typical for multiple sclerosis.**
- **Knowledge of the recent revisions to the 2017 McDonald criteria is essential for the proper use of paraclinical (ie, visual evoked potentials, CSF examination) and radiographic data to substitute for a second clinical attack for the demonstration of dissemination in space and dissemination in time for the diagnosis of multiple sclerosis.**

juxtacortical, or infratentorial region would demonstrate MRI dissemination in space. Of note, although MRI may provide paraclinical objective evidence of an attack of optic neuritis, the anterior visual system was not included as a region for demonstration of MRI dissemination in space in the 2017 criteria. In a patient presenting with optic neuritis, evidence of lesions in two of the four aforementioned regions remains necessary to demonstrate MRI dissemination in space.

The 2017 McDonald criteria also for the first time include cortical lesions (considered equivalent to juxtacortical lesions) as a region that may provide MRI demonstration of dissemination in space.[4] The detection of cortical lesions remains challenging, particularly using MRI scanners and sequences typically employed in clinical practice. Recent studies[12] and consensus guidelines[14]

TABLE 2-1 **The 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis in Patients With an Attack at Onset[a,b]**

Number of Clinical Attacks	Number of Lesions With Objective Clinical Evidence	Additional Data Needed for a Diagnosis of Multiple Sclerosis
≥2	≥2	None[c]
≥2	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomic location[d])	None[c]
≥2	1	Dissemination in space demonstrated by an additional clinical attack implicating a different central nervous system site or by MRI
1	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI *or* demonstration of CSF-specific oligoclonal bands[e]
1	1	Dissemination in space demonstrated by an additional clinical attack implicating a different central nervous system site or by MRI *And* Dissemination in time demonstrated by an additional clinical attack or by MRI *or* demonstration of CSF-specific oligoclonal bands[e]

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.

[a] Modified with permission from Thompson AJ, et al, Lancet Neurol.[4] © 2017 Elsevier Ltd.

[b] If the 2017 McDonald criteria are fulfilled and no better explanation exists for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis.

[c] No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other test (eg, CSF) is undertaken and is negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered.

[d] 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 neurologic findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed.

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

recommend the use of advanced imaging techniques available at specialized centers for cortical lesion detection. MRI evaluation for cortical lesions to meet dissemination in space may be best limited to physicians experienced in using such techniques.

MRI and CSF Demonstration of Dissemination in Time

Similar to previous revisions, the 2017 McDonald criteria specify that MRI dissemination in time can be demonstrated on a single MRI scan by the presence of any gadolinium-enhancing and nonenhancing lesions or by the appearance of a new T2-hyperintense or gadolinium-enhancing lesion on a follow-up MRI compared to a baseline scan, irrespective of the timing of either scan.[4] In a change from the 2010 criteria, previously excluded gadolinium-enhancing symptomatic lesions often responsible for the syndrome prompting evaluation (eg, a gadolinium-enhancing brainstem lesion in a patient with internuclear ophthalmoplegia) may now be included for consideration of fulfillment of MRI dissemination in time.

In a change from previous revisions and based on recent data[10] suggesting CSF-specific oligoclonal bands are an independent predictor of a second clinical attack, the 2017 McDonald criteria recommend that demonstration of two or more oligoclonal bands may substitute for demonstration of clinical or MRI dissemination in time. This notable revision enables earlier diagnosis of MS in a patient with objective evidence of a single clinical attack typical for MS with an MRI that only demonstrates dissemination in space. The authors of the 2017 McDonald criteria emphasize that the accuracy of oligoclonal band testing depends on the methodology employed, and a laboratory that performs agarose gel electrophoresis with isoelectric focusing and immunoblotting or immunofixation for IgG is recommended.[4]

Patients presenting for evaluation for MS often report a history of prior neurologic symptoms that may, at times, aid in diagnosis. When objective evidence exists of a single clinical attack typical for MS, the description of historical symptoms compatible with an additional prior syndrome typical for MS may support demonstration of dissemination in time. In such instances, evaluation for objective evidence of a CNS lesion to confirm a suspected prior syndrome by neurologic examination or paraclinical testing such as evoked potentials or by MRI identification of a lesion is highly recommended. Consideration of prior symptoms alone for the demonstration of dissemination in time may increase the risk of MS misdiagnosis.[5] The authors of the 2017 criteria recommend caution when considering historical symptoms for the demonstration of dissemination in time in the absence of supportive objective evidence of a CNS lesion.[4] **TABLE 2-1** summarizes the 2017 McDonald criteria for the diagnosis of relapsing-remitting MS, including requirements of demonstration of dissemination in space and dissemination in time. **CASE 2-1** and **CASE 2-2** demonstrate application of the revised criteria.

"No Better Explanation": the Differential Diagnosis of Relapsing-Remitting Multiple Sclerosis

Objective evidence of a demyelinating syndrome typical for MS demonstrating dissemination in space and dissemination in time is insufficient for the diagnosis of MS. As no single biomarker for MS exists, each revision of MS diagnostic criteria has also specified that there must be a determination of "no better explanation"[4] for the clinical presentation under consideration. This final key

KEY POINT

- **Objective evidence of a demyelinating syndrome typical for multiple sclerosis demonstrating both dissemination in space and dissemination in time must be accompanied by a search for "no better explanation" to confirm a diagnosis of multiple sclerosis.**

CASE 2-1

A 21-year-old woman presented for evaluation after 5 days of vision loss in her right eye. She described gradual onset and progression of symptoms and reported periocular pain worsened by eye movements. She had no additional history of medical problems or prior neurologic symptoms.

Her neurologic examination was notable for a relative right afferent pupillary defect and visual acuity of 20/70 in the right eye. The remainder of her ophthalmic and neurologic examination was normal. Brain MRI revealed enhancement of the right optic nerve and four ovoid T2 hyperintense lesions. One of these was a juxtacortical lesion, while the remaining three lesions were in the subcortical or deep white matter. MRI of the cervical and thoracic spinal cord demonstrated a small T2-hyperintense lesion at the C6 disk level located posteriorly. The thoracic spinal cord was normal. None of the lesions demonstrated contrast enhancement. Subsequent CSF evaluation demonstrated nine oligoclonal bands restricted to the CSF and a white blood cell count of 11 cells/mm^3 with lymphocytic predominance; the CSF was otherwise normal. Serum and CSF evaluation for inflammatory, metabolic, and infectious diagnoses other than multiple sclerosis (MS) was nonrevealing. No clinical or radiographic red flags suggested diagnoses other than MS.

COMMENT

This patient presented with objective evidence of an attack of optic neuritis, a syndrome typical for MS. Vision loss alone would have been inadequate to make this diagnosis; the presence of an afferent pupillary defect and an MRI demonstrating enhancement of the optic nerve served as objective evidence of this single attack typical for MS. Her clinical history and presentation did not demonstrate dissemination in space by two clinical attacks. Brain MRI only fulfills one (juxtacortical) out of four regions for MRI dissemination in space according to the 2017 McDonald criteria, as the optic nerve is excluded from consideration.

This case highlights that spinal cord lesions are not always symptomatic. The patient had no prior history of neurologic symptoms or neurologic examination findings that localized to the spinal cord. The case also demonstrates the importance of baseline spinal cord imaging to aid in MS diagnosis. Inclusion of the cervical spinal cord lesion results in MRI demonstration of dissemination in space. The clinical history and presentation did not demonstrate dissemination in time by two clinical attacks, and the patient's brain MRI did not demonstrate enhancing and nonenhancing T2 lesions to fulfill dissemination in time, as the optic nerve is excluded according to 2017 McDonald criteria. However, her positive CSF substituted for clinical or MRI dissemination in time based on the 2017 McDonald criteria revisions. The case also highlights that CSF evaluation may now facilitate earlier diagnosis of MS in some patients.

This patient had objective evidence of a single attack typical for MS and fulfilled 2017 McDonald criteria for demonstration of dissemination in space and dissemination in time, and, as no better evidence for her clinical presentation existed, she was diagnosed with MS.

CASE 2-2

A 34-year-old man presented with 3 days of gradual worsening paresthesia starting at his right chest and ending at his toes on his right side. He had no additional history of medical problems or prior neurologic symptoms.

Neurologic examination revealed diminished pinprick from the T4 dermatome and below on the right side and mild diminished vibration in the right first toe. General and neurologic examinations were otherwise unremarkable. MRI of his thoracic spinal cord demonstrated a T2-hyperintense contrast-enhancing lesion at the T4 vertebral disk level visualized on both sagittal and axial images. Brain MRI demonstrated six T2-hyperintense lesions, including one ovoid periventricular lesion, with the remainder located in the subcortical or deep white matter. None demonstrated contrast enhancement. Cervical spinal cord MRI was normal. Serum evaluation for inflammatory, metabolic, and infectious diagnoses other than MS was nonrevealing. CSF evaluation demonstrated four oligoclonal bands restricted to the CSF, a white blood cell count of 3 cells/mm^3 with lymphocytic predominance, and protein elevation to 65; the CSF was otherwise normal. No clinical or radiographic red flags suggested diagnoses other than MS. Serum and CSF evaluation for inflammatory, metabolic, and infectious diagnoses was nonrevealing.

COMMENT

This patient presented with objective evidence of a single attack of myelitis, a syndrome typical for multiple sclerosis (MS). Neurologic examination revealed a sensory level, and MRI provided objective corroboration of the central nervous system lesion responsible for his symptoms. His presentation demonstrated MRI dissemination in space and dissemination in time according to 2017 McDonald criteria, because the symptomatic thoracic spinal cord lesion can count toward both MRI demonstration of dissemination in space and dissemination in time (reflecting a change from prior criteria); the periventricular and spinal cord lesions demonstrated MRI dissemination in space, and the presence of contrast-enhancing and nonenhancing lesions demonstrated dissemination in time. CSF evaluation was most suggestive of myelitis caused by MS, rather than alternative inflammatory or infectious diagnoses, based on the presence of CSF-restricted oligoclonal bands, a normal white blood cell count, and mildly elevated protein.
This patient had objective evidence of a single attack typical for MS and fulfilled 2017 McDonald criteria for dissemination in space and dissemination in time. After evaluation, no better evidence for his presentation was identified, and he was diagnosed with MS.

element of MS diagnosis requires an astute consideration of the differential diagnosis of MS, with particular attention to the presence of red flags, before the confirmation of MS diagnosis.

Better Explanation for Typical Syndromes

A variety of disorders may present with objective evidence of a syndrome typical for MS and demonstrate clinical or radiographic dissemination in space and dissemination in time, thus appearing to fulfill MS diagnostic criteria. Disorders such as neuromyelitis optica spectrum disorder (NMOSD), syndromes associated with myelin oligodendrocyte glycoprotein (MOG) antibody (anti-MOG), neurosarcoidosis, and CNS manifestations of systemic rheumatologic and oncologic disease may present with optic neuritis or transverse myelitis.[15–18] Yet in many instances, these disorders are accompanied by a red flag,[19,20] that is, clinical, laboratory, or radiographic findings atypical for MS and suggestive of an alternative diagnosis that may offer a better explanation than MS for the clinical presentation. Thoughtful assessment for such red flags may avoid a misdiagnosis of MS.

Although optic neuritis or transverse myelitis may be typical for MS, specific characteristics atypical for MS may alert the astute clinician that an alternative diagnosis should be investigated. For example, severe or bilateral optic neuritis may suggest NMOSD. Longitudinally extensive transverse myelitis may suggest NMOSD, neurosarcoidosis, anti-MOG–associated myelitis, systemic rheumatologic disease, or a paraneoplastic disorder. Complete spinal cord lesions or a history of intractable vomiting may also suggest NMOSD. Transverse myelitis associated with prodromal symptoms or MRI T2 signal abnormality confined to spinal cord gray matter may suggest anti-MOG–associated myelitis.[21] Multiple cranial nerve involvement might suggest neurosarcoidosis. Transverse myelitis or optic neuritis accompanied by high CSF pleocytosis should also prompt investigation into infectious or inflammatory disorders other than MS. Systemic symptoms such as joint pain, skin changes, and weight loss might suggest either rheumatologic or paraneoplastic disease. A variety of additional non-neurologic red flags accompanying a typical syndrome might also suggest specific alternative diagnoses.[18]

A comprehensive review of red flags suggesting alternative diagnoses in patients presenting with syndromes otherwise typical for MS is beyond the scope of this article. Several excellent review articles expand further on the differential diagnosis that should be considered in such patients before determining that a typical syndrome has no better explanation other than MS.[15–19]

Validation of the 2017 McDonald Criteria

Knowledge of the characteristics of patients included in the studies on which the 2017 revisions to the McDonald criteria relied is also important for the consideration of "no better explanation" in an evaluation for MS. These studies included predominantly white patients from Europe, the United States, and Canada who were younger than 50 years old. The authors of the 2017 McDonald criteria also recommend application with caution in diverse populations[4] and patients younger than 11 years of age, in whom the 2017 McDonald criteria have not been evaluated.

Thus, a presentation of optic neuritis, a brainstem or cerebellar syndrome, or transverse myelitis in a very young, older, or nonwhite patient would be a

potential red flag that should prompt further evaluation before a diagnosis of MS. Alternative diagnoses may be more common in patients with this demographic profile. For instance, MS is less common in nonwhites, whereas NMOSD[22] and neurosarcoidosis[23] are comparatively more common in such populations.[1] Although children may present with MS, evaluation for other pediatric demyelinating syndromes, particularly acute disseminated encephalomyelitis (ADEM),[24,25] is essential in young children. A first clinical attack typical of MS demyelination is less common after the age of 50. In an older patient, vascular disease or a neoplasm might prove a better explanation than MS for neurologic syndromes or MRI abnormalities that appear to fulfill MS diagnostic criteria.

Expanding the Differential Diagnosis and Red Flags to Noninflammatory Disorders

Some disorders often included in the broad differential diagnosis of MS do not usually present with syndromes typical for demyelination. The explanation for this is that the symptoms caused by these syndromes (eg, visual or sensory symptoms) may be mistaken for symptoms typical of MS. The determination that objective evidence exists of a syndrome typical for MS, a clinical assessment reliant on the expertise of the examining neurologist, can often be challenging. Nondemyelinating and noninflammatory syndromes are frequently mistaken for a presentation typical of MS.[5]

Knowledge of the specific disorders frequently mistaken for optic neuritis[26,27] and myelitis[28,29] and the skills to facilitate their diagnosis are critical in the evaluation for MS. Nonarteritic anterior ischemic optic neuropathy may frequently be mistaken for optic neuritis[26,27]; other optic neuropathies, migrainous visual symptoms, functional vision loss, retinal or macular disorders, and neoplasms must also often be differentiated from optic neuritis.[27] Patients with myelopathies with vascular, spondylotic, or compressive etiology frequently present for evaluation of myelitis,[28,29] and infectious, metabolic, or neoplastic myelopathies may also mimic transverse myelitis.[15] Several recent large cohort studies[26–29] have provided guidance on a number of clinical, paraclinical, or radiographic red flags that may help identify a noninflammatory diagnosis in patients with ophthalmic or spinal cord syndromes. FIGURE 2-1, FIGURE 2-2, and TABLE 2-2 present approaches and the differential diagnosis of clinical presentations that may mimic syndromes typical for MS.

Studies spanning 30 years that evaluated the characteristics of patients referred to MS subspecialty centers[30–32] and data concerning MS misdiagnosis[5,33] have identified migraine and functional neurologic disorders as diagnoses frequently prompting MS evaluation. Diagnosis requires special attention to history and clinical examination, as MRI abnormalities accompanying nonspecific neurologic symptoms often prompt an initial evaluation for MS in such patients. White matter abnormalities associated with migraine[34] or small vessel ischemia may demonstrate MRI dissemination in space, and interval symptoms may appear to demonstrate dissemination in time if attention to an initial confirmation of an MS-specific typical syndrome is neglected. The presence of migraine or risk factors for small vessel ischemia in any patient seen for an evaluation for MS should prompt caution for the interpretation of MRI abnormalities. Important initial red flags that should prompt further evaluation for common noninflammatory diagnoses that may result in brain MRI abnormalities and neurologic symptoms include the

KEY POINTS

- A syndrome typical for multiple sclerosis may also exhibit characteristics atypical for multiple sclerosis, suggesting a specific alternative diagnosis.
- The demographic profile of patients presenting with syndromes typical for multiple sclerosis may provide an important red flag prompting evaluation for alternative diagnoses.
- Noninflammatory conditions may also be mistaken for a typical presentation of multiple sclerosis. Knowledge of broad red flags suggesting a structural, functional, metabolic, infectious, neoplastic, or other disease may lead to a specific alternative diagnosis.

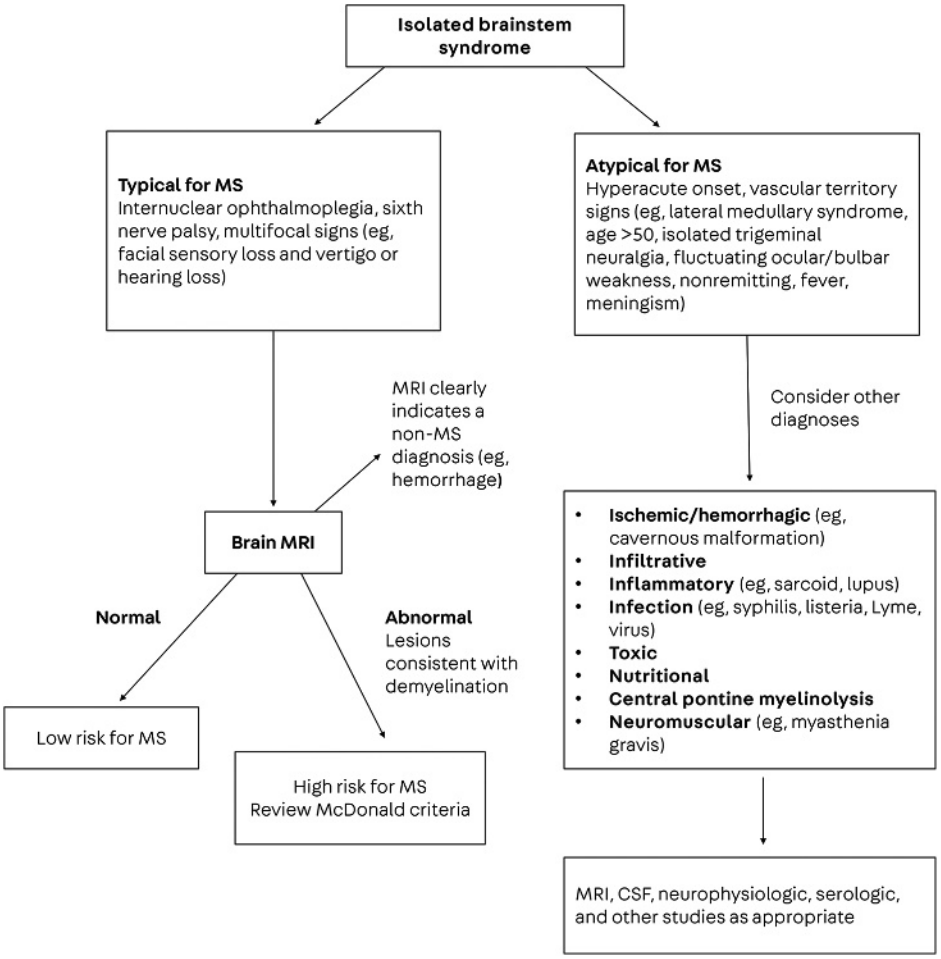

FIGURE 2-1
An approach to the evaluation of a brainstem syndrome.
CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MS = multiple sclerosis.
Modified from Miller DH, et al, Mult Scler.[19] © 2008 SAGE Publications.

absence of clinical or radiographic spinal cord involvement or of CSF-restricted oligoclonal bands.

Comprehensive knowledge of every red flag for the disorders that may mimic MS[19,20] is not easy, and misdiagnosis of a rare syndrome presenting with an infrequently seen red flag may be difficult to avoid. TABLE 2-3 presents a list of important red flags that may suggest diagnoses other than MS, including a number of rare syndromes. A stepwise clinical approach to MS differential diagnosis, such as that suggested by FIGURE 2-1, FIGURE 2-2, and TABLE 2-2 and recent authors,[35] may aid in the initial identification of alternative broad categories of disease other than MS before ultimately leading to the confirmation of a specific diagnosis. CASE 2-3 demonstrates an approach to the evaluation for MS incorporating the consideration of red flags.

Atypical Syndromes, Typical Syndromes With Red Flags, and Evaluation of Long-Standing Diagnoses

The authors of the 2017 McDonald criteria reaffirmed that the criteria "were not developed to differentiate MS from other conditions"[4] but to confirm the

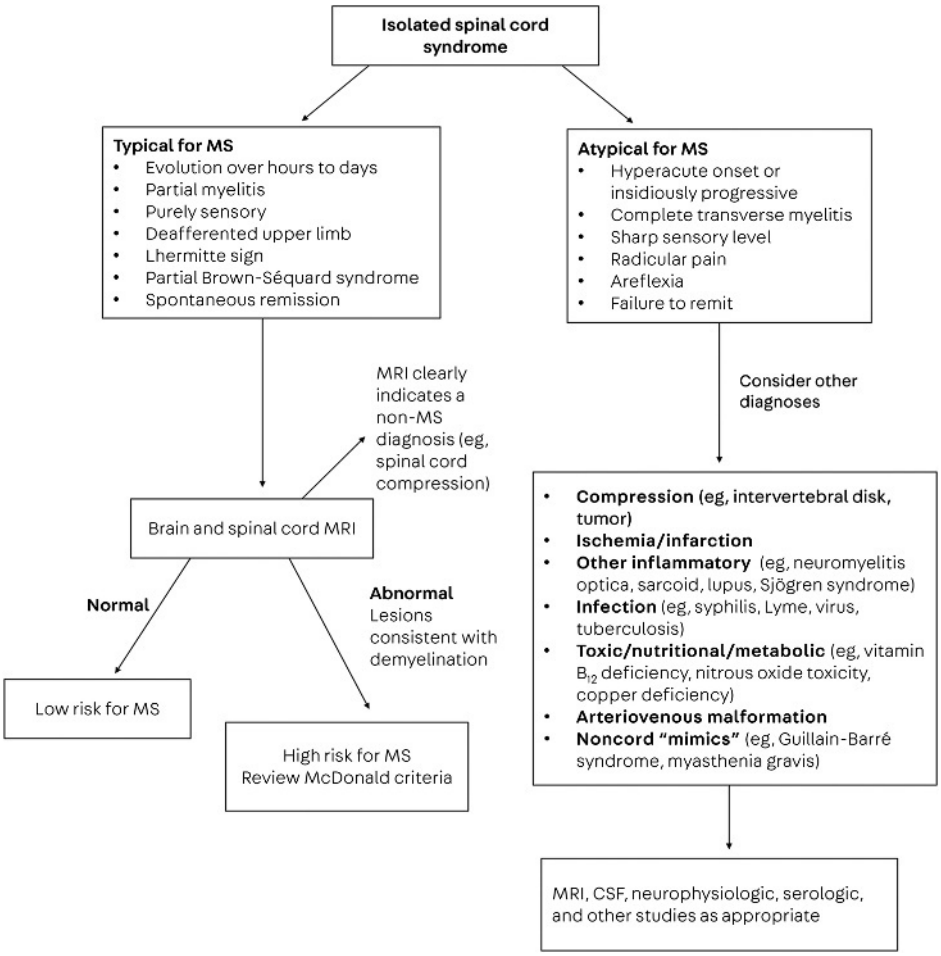

FIGURE 2-2

An approach to the evaluation of a spinal cord syndrome.

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; MS = multiple sclerosis.
Modified from Miller DH, et al, Mult Scler.[19] © 2008 SAGE Publications.

diagnosis of MS in patients presenting with typical demyelinating syndromes. Application of the McDonald criteria in patients presenting with atypical syndromes (presentations other than optic neuritis, brainstem/cerebellar syndromes, or myelitis) likely diminishes their accuracy.[36] The criteria were not validated in patients with atypical syndromes or in patients presenting with typical syndromes accompanied by red flags. However, a small proportion of patients eventually diagnosed with MS do present with such atypical syndromes or a clinical, paraclinical, or radiographic red flag.[37] In such patients, further data complementing fulfillment of the McDonald criteria are advised to confirm a diagnosis of MS. Monitoring for new radiographic changes suggestive of MS, repeating CSF evaluation to confirm the subsequent appearance of CSF-restricted oligoclonal bands, or waiting for an additional attack typical for MS-related demyelination may be necessary to confirm a diagnosis of MS in patients presenting with atypical syndromes or red flags.

Clinicians also often encounter patients presenting for evaluation with a previous diagnosis of MS made by another provider. Evidence of a remote attack

typical for MS can be difficult to confirm as symptom history may be challenging to recall, and symptoms, neurologic examination findings, and radiologic abnormalities may change, evolve, or even resolve over time. The McDonald criteria have not been evaluated in patients with a prior long-standing diagnosis of MS. Yet some proportion of such patients presenting to establish care for a preexisting diagnosis of MS may not have MS.[5,38] The hindsight potentially provided by a duration of time since initial diagnosis in such patients may reveal red flags for alternative diagnoses.[5,38] Although clinicians may be reluctant to reevaluate a preexisting MS diagnosis, particularly if it is long-standing,[33,39] confirmation is necessary before proceeding with care. If objective evidence of a prior attack is no longer present, radiographic or paraclinical (eg, visual evoked potential) confirmation of a historical episode is an important first step in evaluation. Records and prior imaging confirming the presence of spinal cord lesions and CSF-specific oligoclonal bands also make a diagnosis of MS more

TABLE 2-2 **Differential Diagnosis of Optic Neuritis**[a]

Diagnosis	Usual Clinical Features in Each Category	Tests to Consider in Each Category
Corticosteroid-responsive optic neuropathies		
Sarcoidosis, systemic lupus erythematosus, autoimmune optic neuritis, chronic relapsing inflammatory optic neuropathy, optic perineuritis, Behçet disease, neuromyelitis optica (NMO, Devic disease)	Progressive severe visual loss; may be very painful; often bilateral (simultaneous or sequential); isolated or as part of a multisystem disorder; more frequent in Africans or Afro-Caribbeans (sarcoidosis); relapse when corticosteroids withdrawn	MRI orbits and brain with contrast; lumbar puncture; anti-aquaporin-4 antibodies; anti-myelin oligodendrocyte glycoprotein antibodies; antinuclear antibodies; serum angiotensin-converting enzyme; chest radiograph; ^{67}Gallium scan; biopsy of accessible tissue (sarcoid)
Other inflammatory optic neuropathies		
Postinfectious, postvaccination, acute disseminated encephalomyelitis (ADEM)	Bilateral and simultaneous; often in childhood; usually excellent prognosis	MRI orbits and brain with contrast; lumbar puncture
Neuroretinitis	Swollen optic disc and macular star; spontaneous recovery	Bartonella, borrelia, and syphilis serology
Compressive optic neuropathies		
Primary tumors (eg, meningiomas, gliomas, and pituitary tumors), metastases, tuberculomas, thyroid ophthalmopathy, arterial aneurysms, sinus mucoceles	Painless (rarely painful—eg, aneurysms and mucoceles); progressive visual loss; optic atrophy at presentation; past history of, or evidence for, primary tumor (metastases)	CT or MRI orbits and brain with contrast; biopsy if appropriate
Infectious optic neuropathies		
Syphilis, tuberculosis, Lyme disease, viral optic neuritis	Progressive visual loss with exposure to infectious agent; severe optic disc edema; cellular reaction in vitreous	Appropriate serology, lumbar puncture, chest radiograph, tuberculin test

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likely but require consideration of alternative inflammatory disorders. TABLE 2-4 summarizes an approach to the diagnosis of MS in patients with atypical and challenging clinical presentations.[40]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS

Approximately 10% to 15% of patients with MS have a progressive course from the onset of symptoms.[1] The diagnostic criteria for primary progressive MS differ from the criteria for relapsing-remitting MS. A small proportion of patients with primary progressive MS may have infrequent attacks or relapses. The diagnosis of primary progressive MS first requires confirmation of at least 1 year of gradual disability progression, independent of any disability associated with a clinical relapse, determined either retrospectively or prospectively. In addition to 1 year of progression, primary progressive MS diagnostic criteria require fulfillment of

CONTINUED FROM PAGE 622

Diagnosis	Usual Clinical Features in Each Category	Tests to Consider in Each Category
Ischemic optic neuropathies		
Anterior ischemic optic neuropathy, posterior ischemic optic neuropathy, giant cell arteritis, diabetic papillopathy	Usually older age groups; sudden onset; painless (except giant cell arteritis); swollen optic disc (except posterior ischemic optic neuropathy); altitudinal field defect	Erythrocyte sedimentation rate
Toxic and nutritional optic neuropathies		
Vitamin B_{12} deficiency, copper deficiency, tobacco-alcohol amblyopia, methanol intoxication, ethambutol toxicity, Cuban and Tanzanian epidemic optic neuropathies	Bilateral and symmetric; painless; poor prognosis	Serum vitamin B_{12}, copper
Inherited optic neuropathies		
Leber hereditary optic neuropathy	Family history; sequential (or simultaneous) bilateral painless; visual loss	Genetic testing for Leber mutation
Ocular causes		
Posterior scleritis	Severe pain; fewer visual symptoms	B-mode ultrasound of orbits
Maculopathies and retinopathies, including central serous retinopathy	Painless; metamorphopsia; preserved color vision	Electroretinogram, fluorescein angiogram
Big blind spot syndrome and acute zonal occult outer retinopathy	Visual field loss and photopsias; normal fundus; preserved color vision	ECG

CT = computed tomography; ECG = electrocardiogram; MRI = magnetic resonance imaging.
[a] Modified with permission from Hickman SJ, et al, Lancet.[18] © 2002 Elsevier Ltd.

TABLE 2-3 **Clinical or MRI Red Flags That May Suggest Diagnoses Other Than Multiple Sclerosis**[a]

Sign, Symptom, or Finding	Red Flag[a]	Examples of Alternative Diagnosis
Bone lesions	Major	Histiocytosis, Erdheim-Chester disease
Lung involvement	Major	Sarcoidosis, lymphomatoid granulomatosis
Multiple cranial neuropathies or polyradiculopathy	Major	Chronic meningitis, including sarcoidosis and tuberculosis; Lyme disease
Peripheral neuropathy	Major	Vitamin B_{12} deficiency, adrenoleukodystrophy, metachromatic leukodystrophy, Lyme disease
Tendon xanthomas	Major	Cerebrotendinous xanthomatosis
Cerebral venous sinus thrombosis	Major	Behçet disease, vasculitis, chronic meningitis, antiphospholipid or anticardiolipin antibody syndromes
Cardiac disease	Major	Multiple cerebral infarcts, brain abscesses with endocarditis or right-to-left cardiac shunting
Myopathy	Major	Mitochondrial encephalomyopathy (eg, MELAS), Sjögren syndrome
Renal involvement	Major	Vasculitis, Fabry disease, systemic lupus erythematosus
Cortical infarcts	Major	Embolic disease, thrombotic thrombocytopenic purpura, vasculitis
Hemorrhages/microhemorrhages	Major	Amyloid angiopathy, moyamoya disease, CADASIL, vasculitis
Meningeal enhancement	Major	Chronic meningitis, sarcoidosis, lymphomatosis, central nervous system (CNS) vasculitis
Extrapyramidal features	Major	Whipple disease, multisystem atrophy, Wilson disease
Livedo reticularis	Major	Antiphospholipid antibody syndrome, systemic lupus erythematosus, Sneddon syndrome
Retinopathy	Major	Mitochondrial encephalomyopathy, Susac syndrome and other vasculitides (retinal infarction), neuronal ceroid lipofuscinosis
Calcifications on CT	Major	Cysticercosis, toxoplasmosis, mitochondrial disorders
Diabetes insipidus	Major	Sarcoidosis, histiocytosis, neuromyelitis optica (NMO)
Increased serum lactate level	Major	Mitochondrial disease
Selective involvement of the anterior temporal and inferior frontal lobe	Major	CADASIL
Hematologic manifestations	Major	Thrombotic thrombocytopenic purpura, vitamin B_{12} deficiency, Wilson disease (hemolytic anemia), copper deficiency
Lacunar infarcts	Major	Hypertensive ischemic disease, CADASIL, Susac syndrome
Persistent gadolinium enhancement and continued enlargement of lesions	Major	Lymphoma, glioma, vasculitis, sarcoidosis
Mucosal ulcers	Major	Behçet disease
Myorhythmia	Major	Whipple disease
Hypothalamic disturbance	Major	Sarcoidosis, NMO, histiocytosis

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Sign, Symptom, or Finding	Red Flag[a]	Examples of Alternative Diagnosis
Recurrent spontaneous abortion or thrombotic events	Major	Antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura, metastatic cancer with hypercoagulable state
Simultaneous enhancement of all lesions	Major	Vasculitis, lymphoma, sarcoidosis
Rash	Major	Systemic lupus erythematosus, T-cell lymphoma, Lyme disease, Fabry disease
T2 hyperintensity in the dentate nuclei	Major	Cerebrotendinous xanthomatosis
Arthritis, polyarthralgia, myalgia	Major	Systemic lupus erythematosus, Lyme disease, fibromyalgia
Amyotrophy	Major	Amyotrophic lateral sclerosis, syringomyelia, polyradiculopathy
Headache or meningismus	Major	Venous sinus thrombosis, chronic meningitis, lymphoma or glioma, vasculitis, systemic lupus erythematosus
T1 hyperintensity of the pulvinar	Major	Fabry disease, hepatic encephalopathy, manganese toxicity
Persistently monofocal manifestations	Major	Structural lesion (eg, Chiari malformation), cerebral neoplasm
Large and infiltrating brainstem lesions	Major	Behçet disease, pontine glioma
Predominance of lesions at the cortical/subcortical junction	Major	Embolic infarction, vasculitis, progressive multifocal leukoencephalopathy
Hydrocephalus	Intermediate	Sarcoidosis or other chronic meningitis, lymphoma or other CNS neoplasm
Punctiform parenchymal enhancement	Intermediate	Sarcoidosis, vasculitis
Sicca syndrome	Intermediate	Sjögren syndrome
T2 hyperintensities of U fibers at the vertex, external capsule, and insular regions	Intermediate	CADASIL
Gastrointestinal symptoms	Intermediate	Whipple disease, celiac disease, and other malabsorptive states that lead to vitamin B_{12} or copper deficiency
Regional atrophy of the brainstem	Intermediate	Behçet disease, adult-onset Alexander disease
Diffuse lactate increase on brain magnetic resonance spectroscopy	Intermediate	Mitochondrial disease
Marked hippocampal and amygdala atrophy	Intermediate	Hyperhomocysteinemia
Loss of hearing	Intermediate	Susac syndrome, glioma, vertebrobasilar infarction
Fulminant course	Intermediate	Thrombotic thrombocytopenic purpura, intravascular lymphoma, acute disseminated encephalomyelitis (ADEM)
Symmetrically distributed lesions	Intermediate	Leukodystrophy
T2 hyperintensities of the basal ganglia, thalamus, and hypothalamus	Intermediate	Behçet disease, mitochondrial encephalomyopathies, Susac syndrome, ADEM

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Sign, Symptom, or Finding	Red Flag[a]	Examples of Alternative Diagnosis
Diffuse abnormalities in the posterior columns of the cord	Intermediate	Vitamin B_{12} deficiency, copper deficiency, paraneoplastic disorder
Increased serum angiotensin-converting enzyme level	Intermediate	Sarcoidosis, histiocytosis
Prominent family history	Intermediate	Depending on pattern of inheritance suggested by family history: hereditary spastic paraparesis, leukodystrophy, Wilson disease, mitochondrial disorders, CADASIL
Constitutional symptoms	Intermediate	Sarcoidosis, Whipple disease, vasculitis
Lesions across gray matter/white matter boundaries	Intermediate	Hypoxic-ischemic conditions, vasculitis, systemic lupus erythematosus
T2 hyperintensities of the temporal pole	Intermediate	CADASIL
Complete ring enhancement	Intermediate	Brain abscess, glioblastoma, metastatic cancer
Progressive ataxia alone	Intermediate	Multisystem atrophy, hereditary spinocerebellar ataxia, paraneoplastic cerebellar syndrome
Central brainstem lesions	Intermediate	Central pontine myelinolysis, hypoxic-ischemic conditions, infarct
Predominant brainstem and cerebellar lesions	Intermediate	Behçet disease, pontine glioma
Neuropsychiatric syndrome	Intermediate	Susac syndrome, systemic lupus erythematosus, Wilson disease, GM2 gangliosidosis
Lesions in the center of corpus callosum, sparing the periphery	Intermediate	Susac syndrome
Seizure	Intermediate	Whipple disease, vasculitis, metastases
Dilation of the Virchow-Robin spaces	Intermediate	Hyperhomocysteinemia, primary CNS angiitis
Uveitis	Intermediate	Sarcoidosis, lymphoma, Behçet disease
Cortical/subcortical lesions crossing vascular territories	Intermediate	Ischemic leukoencephalopathy, CADASIL, vasculitis
Pyramidal motor involvement alone	Intermediate	Primary lateral sclerosis variant of amyotrophic lateral sclerosis, hereditary spastic paraparesis

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Sign, Symptom, or Finding	Red Flag[a]	Examples of Alternative Diagnosis
Large lesions with absent or rare mass effect and enhancement	Intermediate	Progressive multifocal leukoencephalopathy
Gradually progressive course from onset	Intermediate	Human T-cell lymphotrophic virus type I (HTLV-I)–associated myelopathy, adrenomyeloneuropathy, adrenoleukodystrophy, metachromatic leukodystrophy, vitamin B_{12} deficiency
No "occult" changes in normal-appearing white matter	Intermediate	Lyme disease, isolated myelitis, CADASIL
Brainstem syndrome	Minor	Pontine glioma, cavernous malformation, vertebrobasilar ischemia
No enhancement	Minor	Progressive multifocal leukoencephalopathy, ischemic lesions, metachromatic leukodystrophy
Myelopathy alone	Minor	Chiari malformation type 1, cord compression (including cervical spondylosis), vitamin B_{12} or copper deficiency, HTLV-I
No optic nerve lesions	Minor	Metastatic carcinoma, gliomatosis cerebri, toxoplasmosis
Onset before age 20	Minor	Mitochondrial encephalomyopathy, leukodystrophy, Friedreich ataxia
No spinal cord lesions	Minor	Multiple infarcts, vasculitis, progressive multifocal leukoencephalopathy
Abrupt onset	Minor	Cerebral infarction, cerebral hemorrhage, cerebral venous sinus thrombosis
Large lesions	Minor	Glioblastoma, lymphoma, progressive multifocal leukoencephalopathy
No T1-hypointense lesions (black holes)	Minor	Ischemic degenerative leukoencephalopathy, progressive multifocal leukoencephalopathy
Onset after age 50	Minor	Cerebral infarction, amyloid angiopathy, lymphoma
Marked asymmetry of white matter lesions	Minor	Glioblastoma, lymphoma, cerebral infarction

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CT = computed tomography; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; MRI = magnetic resonance imaging.

[a] Modified from Miller DH, et al, Mult Scler.[19] © 2008 SAGE Publications.

[b] Red flags are ordered from the most "major" to the most "minor" as per subgroup rankings. Major red flags point fairly definitively to a non-multiple sclerosis (MS) diagnosis; minor red flags may be consistent with MS or an alternative diagnosis. Intermediate red flags are those for which there was poor agreement and uncertainty among raters about the weighting of the flag for differential diagnosis in MS, especially in isolation of other informative symptoms, signs, and assays. Minor red flags suggest that a disease other than MS should be considered and fully explored, but an MS diagnosis is not excluded.

CASE 2-3

A 56-year-old woman presented with episodes of nausea and vertigo accompanied by visual obscuration involving both eyes. She described a mild unilateral throbbing headache that accompanied these episodes. She had several episodes lasting less than 24 hours over the week before evaluation. The patient also described a prior history of intermittent right leg numbness radiating from the buttocks to the toes that had occurred approximately 3 years earlier and had resolved after a month. She did not seek care for this symptom at the time. Her past medical history was significant for hypertension and chronic tobacco use.

General and neurologic examinations were normal. MRI of the brain demonstrated numerous T2-hyperintense lesions located predominantly in the subcortical and deep white matter, but several periventricular and juxtacortical lesions were noted. None demonstrated contrast enhancement. MRI of the cervical and thoracic spinal cord was normal, and CSF examination was normal.

COMMENT

The age of this patient should prompt caution in the evaluation for multiple sclerosis (MS) as an initial presentation of MS is less common in patients of this age. Application of McDonald criteria may also result in diminished specificity, as the criteria were not tested in patients older than the age of 50 and such patients are known to have an increased risk for comorbidities causing MRI white matter abnormalities. This patient did not present with a syndrome typical of MS and also, despite MRI abnormalities, had no objective evidence of a central nervous system lesion that correlated with present or prior symptoms. Despite MRI demonstration of dissemination in space, the McDonald criteria cannot be applied.

This patient also presented with numerous clinical red flags, including brief duration of symptoms atypical for demyelination; a normal neurologic examination; no MRI lesions corresponding to vision loss, vertigo, or prior leg symptoms; and comorbid conditions that included suspected migraine by current history, hypertension, and tobacco use—all known to cause MRI abnormalities that may mimic the appearance of MS. Although normal spinal cord imaging and CSF do not rule out MS, they should be considered red flags suggesting evaluation for a diagnosis other than demyelination in a patient presenting with an atypical syndrome.

This patient presented with historical neurologic symptoms without objective evidence on neurologic examination of the prior sensory disturbance or on MRI of a spinal cord lesion corresponding to symptoms. Prior symptoms without such objective corroborating evidence of a central nervous system lesion should prompt caution before inclusion for demonstration of dissemination in time. This patient had a better explanation than MS for her symptoms and MRI abnormalities, including migraine and vascular disease, especially after a thorough evaluation including CSF and spinal cord imaging.

two of the following: (1) at least one T2-hyperintense MRI lesion in the periventricular, cortical or juxtacortical, or infratentorial brain regions; (2) two or more T2-hyperintense spinal cord lesions; or (3) detection of CSF-specific oligoclonal bands. The criteria for the diagnosis of primary progressive MS remain the same in the 2017 McDonald criteria as in the previous criteria, with the exception of the incorporation of cortical and symptomatic lesions as discussed for the criteria for relapsing MS. TABLE 2-5 presents the updated criteria for primary progressive MS.

The differential diagnosis for primary progressive MS[41] is considerably shorter than that of relapsing-remitting MS and includes compressive myelopathy and a limited number of hereditary, metabolic, inflammatory, infectious, neuromuscular, vascular, paraneoplastic, and toxic disorders (TABLE 2-6). In many cases, completion of laboratory, radiographic, and CSF evaluation may provide red flags suggesting these alternative diagnoses.

MISDIAGNOSIS OF MULTIPLE SCLEROSIS

Misdiagnosis of MS (the incorrect assignment of a MS diagnosis) remains a contemporary problem.[5,6,33,38,42] MS misdiagnosis is associated with unnecessary long-term risk and morbidity for patients and considerable costs to health care systems.[5] Although the prevalence of MS misdiagnosis is unknown, neurologists endorse having frequently evaluated patients who had been previously misdiagnosed with MS.[33] Recent data concerning the characteristics of misdiagnosed patients[5,38] provide important guidance on its prevention.

Accurate diagnosis of MS relies on an initial clinical assessment to determine if a presentation is typical for MS in order to proceed with the diagnostic process described above. If objective evidence of a syndrome typical for MS is not seen, the 2017 McDonald criteria do not apply. However, many of the clinical diagnoses mistaken for MS are diagnoses that do not

Recommended Approach to Diagnosis of Multiple Sclerosis in Patients With Atypical and Challenging Clinical Presentations[a]

TABLE 2-4

- 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 oligoclonal bands or spinal cord lesions in patients with migraine, vascular risk factors, or examination findings suggestive of a functional neurologic disorder
- In oligoclonal band–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 callososeptal lesions may help differentiate MRI demyelination from vascular changes
- Reevaluate preexisting diagnoses of multiple sclerosis in patients who transfer care from another provider
- Additional clinical and radiographic monitoring for objective evidence supporting at least two episodes of demyelination typical for multiple sclerosis may be necessary

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.
[a] Reprinted with permission from Solomon AJ, et al, Neurology.[40] © 2018 American Academy of Neurology.

usually present with such typical syndromes.[5] These include migraine, functional neurologic disorders, fibromyalgia, and nonspecific symptoms that do not localize to the CNS.[5] This suggests either that, in some cases, the evaluating providers are either unaware that MS diagnostic criteria require objective confirmation of a limited number of specific syndromes for their application or that patient syndromes are often incorrectly identified as typical of MS-related demyelination. Thus, the first step in the prevention of MS misdiagnosis may be broader education surrounding the diagnosis of presentations typical for MS.

Abnormal brain MRI findings prompt an evaluation for MS in many patients. Overreliance on such MRI abnormalities, particularly in patients with atypical, nonspecific, or non–CNS-localizing clinical presentations, is an important contributor to MS misdiagnosis.[5] Demonstration of MRI dissemination in space is possible in a number of common disorders, such as migraine[34] and small vessel ischemic disease, and lack of attention to the presence of atypical syndromes in patients with these diagnoses leads to misdiagnosis.[5] Furthermore, studies have suggested that some providers either misunderstand[34] or have difficulty correctly applying MRI dissemination in space criteria to juxtacortical and periventricular lesions.[5] Careful and correct application of MRI dissemination in space criteria, now further specified in 2017 McDonald criteria,[4,5,34] would likely also prevent many cases of MS misdiagnosis.

Although the identification of prior episodes of demyelination may aid in the demonstration of dissemination in time and confirm a diagnosis of MS, the assessment of historical episodes of neurologic symptoms without objective evidence of a lesion has been noted to be a frequent contributor to MS misdiagnosis.[5] Authors of the 2017 criteria state that if such historical events include "symptoms and evolution characteristic for a previous inflammatory demyelinating attack,"[4] they may be considered for demonstration of dissemination in time in the absence of objective evidence. Determining

TABLE 2-5

2017 McDonald Criteria for Diagnosis of Multiple Sclerosis in Patients With a Disease Course Characterized by Progression From Onset (Primary Progressive Multiple Sclerosis)[a]

Primary progressive multiple sclerosis can be diagnosed in patients with:

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

Plus two of the following criteria:

- One or more T2-hyperintense lesions[b] characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions[b] in the spinal cord
- Presence of CSF-specific oligoclonal bands

CSF= cerebrospinal fluid.

[a] Reprinted with permission from Thompson AJ, et al, Lancet Neurol.[4] © 2017 Elsevier Ltd.

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

Differential Diagnosis of Progressive Multiple Sclerosis[a]

TABLE 2-6

Cord Compression

- Cervical spondylosis
- Intrinsic or extrinsic tumor

Hereditary

- Hereditary spastic paraplegia
- Friedreich ataxia
- Leukodystrophies (adrenomyeloneuropathy, Krabbe disease)

Metabolic

- Vitamin B_{12} deficiency
- Phenylketonuria
- Copper deficiency

Inflammatory

- Neurosarcoidosis
- Central nervous system vasculitis

Infection

- Human T-cell lymphotrophic virus type I (HTLV-I)
- Schistosomiasis
- Syphilis
- HIV
- Brucellosis

Degenerative

- Motor neuron disease

Toxic

- Lathyrism
- Nitrous oxide

Vascular

- Dural arteriovenous malformation
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

Paraneoplastic

HIV = human immunodeficiency virus.

[a] Reprinted with permission from Miller DH, Leary SM, Lancet Neurol.[41] © 2007 Elsevier Ltd.

TABLE 2-7

Recommendations for Prevention of Multiple Sclerosis Misdiagnosis When Applying the 2017 McDonald Criteria[a]

Typical Demyelinating Syndromes

- Multiple sclerosis (MS) diagnostic criteria should be applied only in the typical demyelinating syndromes in which they have been validated
- Caution should be taken in patients older than 50 years of age (or younger than 11 years of age) and in nonwhite 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 Dissemination in Time Criteria

- Objective evidence on neurologic examination or as the result of paraclinical testing (visual evoked potentials, MRI, optical coherence tomography) must corroborate symptoms
- Objective evidence specific for central nervous system 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 Dissemination in Space and Dissemination in Time

- In patients with monophasic syndrome of a single symptomatic brainstem or spinal cord lesion where only one additional MRI dissemination in space region is satisfied, consider awaiting appearance of an additional MRI lesion or additional clinical event to meet dissemination in space criteria, especially when comorbidities are present

CSF Evaluation

- CSF evaluation is recommended before finalizing a diagnosis of primary progressive MS
- Oligoclonal bands restricted to the CSF should be used with caution in the presence of high numbers of polymorphonuclear cells or highly elevated protein
- Positive oligoclonal bands should be used to substitute for dissemination in time 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 central nervous system condition
- If CSF is negative for findings typical of MS, a diagnosis of MS should be made with caution

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.
[a] Reprinted with permission from Solomon AJ, et al, Neurology.[40] © 2018 American Academy of Neurology.

if remote and subsequently resolved symptoms (eg, a history of visual disturbance, vertigo or diplopia, or sensory and motor impairment in an extremity) are indeed typical of MS-related demyelination can be especially difficult. Without corroborating objective CNS findings on neurologic examination, visual evoked potentials, or MRI, consideration of such historical symptoms for the demonstration of dissemination in time warrants caution given its association with misdiagnosis. In some cases, waiting to confirm a diagnosis of MS until interval imaging demonstrates MRI dissemination in time may be prudent. In the majority of patients who do not demonstrate clinical or MRI dissemination in time but have a high likelihood of developing MS, evaluation for the presence of CSF-restricted oligoclonal bands may now provide fulfillment of dissemination in time according to the 2017 criteria.[4]

In the absence of a highly specific biomarker for MS, misdiagnosis may not always be avoidable. In some cases, the passage of time after an initial diagnosis may be necessary to reveal subsequent red flags for clinical features atypical for MS and raise suspicion for alternative diagnoses. For this reason, it is necessary to continue to reassess any diagnosis of MS. Yet, as detailed above, many causes of MS misdiagnosis reflect inappropriate application of MS diagnostic criteria. Although the McDonald criteria necessitate clinical assessments that, by definition, may be susceptible to error, a detailed knowledge of the criteria and their various caveats and strict adherence to their application would likely prevent many cases of MS misdiagnosis. The 2017 McDonald criteria now provide detailed discussion of MS misdiagnosis and its avoidance and a helpful glossary defining the fundamental clinical, paraclinical, and radiologic terms necessary for its correct application.[3] TABLE 2-7 summarizes recommendations for the prevention of MS misdiagnosis in the application of 2017 McDonald criteria.[40]

CONCLUSION

The skilled confirmation of a syndrome typical for MS demyelination is required to maintain accuracy for the initial clinical assessment for a diagnosis of MS. Meticulous knowledge of MS diagnostic criteria and their careful application is necessary to confirm demonstration of dissemination in space and time suggestive of MS. Vigilance for clinical, paraclinical, and radiographic red flags and an understanding of the causes of MS misdiagnosis ensures that no better explanation exists other than a diagnosis MS.

KEY POINTS

- The McDonald criteria have not been evaluated in patients presenting with atypical syndromes or typical syndromes with red flags, and additional clinical, paraclinical, or radiographic evaluation and monitoring is necessary to confirm a diagnosis of multiple sclerosis.
- In patients presenting to establish care with a preexisting diagnosis of multiple sclerosis, reassessment of the accuracy of multiple sclerosis diagnosis is prudent.
- The diagnosis of primary progressive multiple sclerosis and its mimics differs from that of relapsing-remitting multiple sclerosis and requires a thorough understanding of the assessment of clinical progression.
- Misdiagnosis of multiple sclerosis is often caused by misapplication of the McDonald criteria in patients with atypical syndromes, overreliance on or misunderstanding of MRI dissemination in space, or consideration of historical episodes of symptoms without objective evidence of a central nervous system lesion for demonstration of dissemination in time.

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