Multiple Sclerosis Misdiagnosis

Accurate diagnosis requires correspondence to typical clinical syndromes, correct interpretation of radiologic and CSF data, and thorough evaluation for mimics.

By Alexandra Galati, MD and Marwa Kaisey, MD

Accurate diagnosis of multiple sclerosis (MS) hinges on correct interpretation of a patient’s clinical history and radiologic studies.1 Because there is no single highly specific biomarker for MS, misdiagnosis—when a patient without MS receives an incorrect diagnosis of MS—is unfortunately common. In a study of 2 independent MS referral centers, 18% of new patients referred with an established diagnosis of MS were deemed misdiagnosed.2 Those who are misdiagnosed often carry the diagnosis for multiple years until being “undiagnosed,” some carrying the diagnosis for a decade or longer.3 Objective evidence of demyelinating disease and appropriate application of diagnostic criteria is necessary to prevent misdiagnosis.

**Misdiagnosis Ramifications**

Misdiagnosis of MS has physical, psychosocial, and financial ramifications. Misdiagnosed patients often receive MS disease-modifying therapy (DMT) associated with various risks and side effects,³ such as injection site or infusion reactions, flu-like symptoms, bradycardia, infection, and teratogenicity. In the above-mentioned misdiagnosis study, more than half of the misdiagnosed patients received Food and Drug Administration (FDA)-approved DMTs including glatiramer acetate, dimethyl fumarate, natalizumab, and fingolimod as well as off-label medications, such as cyclophosphamide and methotrexate. Almost half (48%) of the patients in the study received a DMT known to have the risk of progressive multifocal leukoencephalopathy (PML), a disabling and potentially fatal infection. Another contemporary study reported similar findings: In a group of 110 misdiagnosed patients, 70% had exposure to DMTs, and almost a quarter received a DMT with a known risk of PML.¹

Along with these physical risks, MS DMTs come at a significant cost. The cost of DMT is rising,⁵ with the median price in 2018 at $80,000.⁶ Furthermore, while misdiagnosed patients are receiving these unnecessary, potentially harmful, and costly medications, they are also going without treatment for their true diagnoses.

The psychologic burden and practical consequences of eventually going through an undiagnosis of MS can be significant.⁷ Many patients with a diagnosis of MS become involved with and seek support in their local and national MS communities. Often, MS is part of their personal identity, and in our experience, this can make the undiagnosis of MS a very difficult experience.

**Misdiagnosis Etiologies**

Misdiagnosis of MS typically occurs due to the misapplication of the McDonald Criteria.²,³ These criteria were designed to predict the risk of conversion from clinically isolated syndrome (CIS) to clinically definite MS, not necessarily to distinguish MS from its mimics. The criteria were developed in 2001⁹ and since then, they have undergone 3 revisions¹⁰,¹¹ to allow for earlier MS diagnosis.

There are 2 independent studies suggesting that more than two-thirds of patients misdiagnosed with MS presented with a clinical syndrome that was not typical of MS.²,³ The 2017 McDonald Criteria stress their use only with clinical syndromes typical of MS; these include optic neuritis, incomplete transverse myelitis, and brainstem syndromes such as internuclear ophthalmoplegia and trigeminal neuralgia. To be considered MS-typical, symptoms should last at least 24 hours in the absence of fever and infection. Changes on objective examination or paraclinical testing should also be seen.

Misdiagnosis of MS also stems from overreliance on radiographic signs, so physicians must be familiar with the MRI characteristics of both MS and its mimics.¹² The Table outlines atypical clinical presentations and radiographic findings that should raise suspicion of a diagnosis alternate to MS.”¹³,¹⁴
Objective findings are key to an accurate MS diagnosis, and a normal neurologic examination and brain MRI in a patient with suspected MS should raise a red flag. In a retrospective study of 143 patients with neurologic symptoms who did not have associated abnormalities on neurologic examination or brain MRI, none progressed to having MS.19

The most recent revision of the McDonald Criteria allows for a patient with CIS to fulfill criteria for dissemination in time if they have cerebrospinal fluid (CSF)-specific oligoclonal bands (OCBs).1 Patients with CSF-specific OCBs have a higher conversion rate from CIS to MS compared with those without OCBs20; however, this diagnostic tool lacks specificity, as other CNS inflammatory diseases, infections, vascular events, and tumors are associated with OCBs.21

Other diagnostic tools such as visual, brainstem-auditory, and somatosensory evoked potentials lack specificity for MS as well,22 highlighting the importance of using these tools as supportive evidence rather than the basis for a diagnosis of MS.

**Novel Biomarkers**

Given the increased sensitivity of the 2017 McDonald Criteria and the relatively high prevalence of MS misdiagnosis, there is a need for more specific MS biomarkers. Burgeoning serum and radiographic biomarkers may allow for increased diagnostic specificity.

One radiographic biomarker under investigation is the central vein sign. Autoregulatory T cells enter the CNS through the systemic circulation, leading to a perivenular distribution of white matter lesions that may be a helpful distinguishing characteristic of MS.23 In a prospective study of 29 patients with potential MS in whom the diagnosis could not be confirmed at initial evaluation, all patients who ultimately received a diagnosis of MS had central veins in over 40% of their brain lesions, whereas those who received an alternative diagnosis had central veins in less than 40% of brain lesions.24 Although promising, this study was completed at a field strength of 7 Tesla, far higher than what is presently available in clinical practice. Serum and CSF biomarkers may also help guide diagnosis of MS. Neurofilaments are proteins released into the extracellular space during axonal breakdown.25 Elevated levels of CSF neurofilament light chains (NFL) are associated with risk of progression from CIS to clinically definite MS.26 Elevated levels of NFL have also been shown to correlate with disease severity and progression in MS.27 Although this research is promising, elevated NFL levels are found in many neurodegenerative diseases, and increase with normal aging.28 Lack of specificity for elevated NFL levels may limit use for MS diagnosis, but further studies may delineate a use in the young and otherwise healthy patient presenting for evaluation. There are also data supporting the use of multiparametric assays assessing the expression of multiple genes or proteins. In contrast to a

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### TABLE. CLINICAL AND RADIOGRAPHIC SIGNS SUGGESTING AN ALTERNATIVE DIAGNOSIS TO MS

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Radiographic findings</th>
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<tbody>
<tr>
<td>Bilateral optic neuritis</td>
<td>Normal MRI</td>
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<tr>
<td>Complete transverse myelopathy</td>
<td>Symmetrically distributed lesions</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Poorly defined lesions</td>
</tr>
<tr>
<td>Subacute cognitive decline</td>
<td>Large lesion in center of corpus callosum</td>
</tr>
<tr>
<td>Headache/meningismus</td>
<td>Simultaneous enhancement of all lesions</td>
</tr>
<tr>
<td>Isolated fatigue</td>
<td>Infarcts</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>Isolated lesion with ring enhancement</td>
</tr>
<tr>
<td>Intractable nausea, vomiting, hiccups</td>
<td>Longitudinally extensive spinal cord lesion</td>
</tr>
</tbody>
</table>

*A Although these suggest an alternative diagnosis, a first attack or clinically isolated syndrome (CIS) can also occur with all lesions enhancing or a single lesion that is enhancing.*

Typical radiographic changes seen in MS lesions include juxtacortical, periventricular, and infratentorial brain regions (Figure 1) as well as the spinal cord. Typically, there will be multiple focal lesions, with intermediate to low signal on T1-weighted imaging and associated high signal on T2-weighted imaging. The lesions usually have distinct margins, though as the disease progresses, they can converge and appear more confluent (Figure 2). Lesions typically occur bilaterally but are not usually symmetrical. Subcortical lesions measuring less than 3 mm, often labeled nonspecific on MRI reports, are insufficient to make the diagnosis. If using a single MRI to prove dissemination in time, both enhancing and non-enhancing lesions are required.15

Other disease entities commonly misdiagnosed as MS include small vessel ischemic disease, fibromyalgia, neuro-myelitis optica spectrum disorder, clinically or radiographically isolated syndrome, and idiopathic transverse myelitis.1,2 Migraine is the most common true diagnosis in a patient misdiagnosed with MS,2,3 and one of the most common in patients referred for evaluation of a potential MS diagnosis.16,17 A history of migraine attacks, especially when associated with focal neurologic symptoms, is incorrectly dubbed a typical MS syndrome, and migraine-associated white matter lesions on MRI are used to satisfy imaging criteria. Small vessel ischemic disease is a common radiographic mimic of MS. Like MS, it can produce multiple focal lesions in the subcortical white matter; however, unlike MS, the lesions typically spare the U-fibers and do not involve the cerebellum or corpus callosum.18
Figure 1. Typical lesions of multiple sclerosis are found in the juxtacortical (A, arrow), periventricular (B), infratentorial (C) regions and the corpus callosum (D).
single biomarker, these assays aim to determine a pattern of expression of many genes or proteins at once to aid in diagnosis and prognosis. One such study investigated serum long noncoding RNA gene expression to identify clinically definite MS.28 This test reports a sensitivity of 91% and specificity of 98% for RNA gene expression tests against healthy controls, but a lower sensitivity of 79% and specificity of 87% when compared with patients with autoimmune and other chronic diseases.29 While early in development, these assays may provide a suitable biomarker to aid in diagnosis.

Conclusion

Accurate diagnosis of MS is challenging, and misdiagnosis occurs relatively frequently. This has wide-ranging implications including the risks and costs of MS treatment as well as psychologic stress. Though outside the scope of this article, underdiagnosis also occurs, with some patients presenting to numerous physicians prior to receiving a diagnosis of MS. To more accurately diagnose MS, we must be vigilant in our use of the McDonald Criteria, with careful consideration of whether symptoms correspond to a typical clinical syndrome, corroboration of symptoms with the neurologic examination, correct interpretation of radiologic and CSF data, and thorough evaluation for MS mimics. Identifying and validating novel biomarkers for more accurate MS diagnosis will decrease our reliance on radiographic findings and significantly enhance patient care and outcomes.


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