COMMENTARY

Confirming a Historical Diagnosis of Multiple Sclerosis

Challenges and Recommendations

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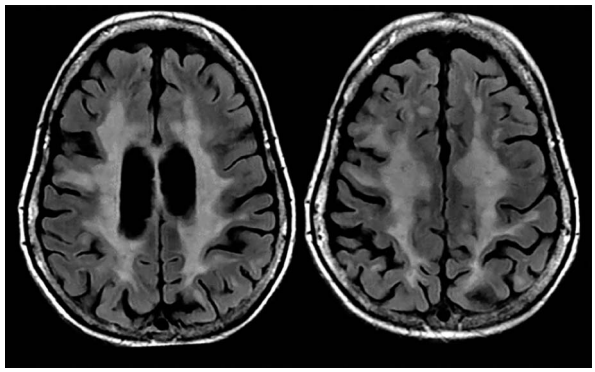
Abstract



Patients with a historical diagnosis of multiple sclerosis (MS)—a patient presenting with a diagnosis of MS made previously and by a different clinician—present specific diagnostic and therapeutic challenges in clinical practice. Application of the McDonald criteria is most straightforward when applied contemporaneously with a syndrome typical of an MS attack or relapse; however, retrospective application of the criteria in some patients with a historical diagnosis of MS can be problematic. Limited patient recollection of symptoms and evolution of neurologic examination and MRI findings complicate confirmation of an earlier MS diagnosis and assessment of subsequent disease activity or clinical progression. Adequate records for review of prior clinical examinations, laboratory results, and/or MRI scans obtained at the time of diagnosis or during ensuing care may be inadequate or unavailable. This article provides recommendations for a clinical approach to the evaluation of patients with a historical diagnosis of MS to aid diagnostic confirmation, avoid misdiagnosis, and inform therapeutic decision making.

Patients diagnosed with multiple sclerosis (MS) may transfer care to a new clinician for a variety of reasons. Such patients present with a historical diagnosis of MS—one made previously and by a different clinician. Application of the McDonald criteria[1] is often straightforward when applied contemporaneously with a clinical syndrome typical of an MS attack or relapse. Retrospective application of the criteria in routine care is feasible and has been successfully applied to longitudinal research cohorts. Yet in some patients, assessment of a previous diagnosis of MS can be challenging.

A clinical approach to historical diagnosis of MS should consider several interrelated clinical questions beyond reevaluation of a remote diagnosis. Have the clinical and imaging characteristics remained consistent with MS? What were the characteristics and frequency of disease activity over time? Are current symptoms and disability the result of MS or a comorbid condition? Were there disease-modifying therapy (DMT) changes in the past, and, if so, what was the rationale? Does available clinical and paraclinical information justify the risks and benefits of continuing DMT initiated by a previous clinician?

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Table 1 Common Challenges in Confirming a Historical Diagnosis of Multiple Sclerosis

Clinical	Laboratory or imaging	Health care system
Incomplete patient recollection of: • Disease onset • Relapses • DMT decision making • Progression Inability to verify by neurologic examination: • Objective evidence of relapse(s) • Disease progression	Testing never completed: • CSF • Spinal cord MRI • Orbit MRI • Evoked potentials • AQP4 and MOG-IgG Imaging: • Evolved since presentation • Does not corroborate relapses • Acquired on different MRI scanners and with different imaging parameters	Incomplete or inaccessible prior documentation: • Neurologic examinations • Relapses • Laboratory testing • Imaging • Initiation of DMT • Discontinuation or switching DMT

Abbreviations: AQP4 = aquaporin-4; DMT = disease-modifying therapy; MOG = myelin oligodendrocyte glycoprotein; IgG = immunoglobulin G.

Clinical, laboratory, imaging, or health care system barriers complicate the evaluation of a historical diagnosis (Table 1). This commentary highlights these common challenges and important red flags in patients presenting with a historical diagnosis of MS and provides recommendations for clinical approaches.

Challenges in the Evaluation of a Patient With Historical Diagnosis of MS

Confirming Relapse Onset Disease

The McDonald criteria for relapsing-remitting MS (RRMS) require a clinical syndrome typical for MS (e.g., unilateral optic neuritis, partial myelitis, and focal cerebral or brainstem syndromes)[1] with corroborating objective evidence by neurologic examination or paraclinical testing.[1] Recent data suggest that these concepts are sometimes neglected or misunderstood,[2,3] resulting in misapplication of the criteria in patients with atypical syndromes without objective evidence of a CNS lesion and ultimately misdiagnosis.[4] In some patients presenting with a historical diagnosis, it may be difficult to determine whether the criteria were previously applied correctly at the time of diagnosis. This situation should prompt reevaluation to prevent diagnosis momentum bias[5]—the tendency to accept a previous diagnosis that may perpetuate misdiagnosis.

Confirming a remote relapse associated with diagnosis can be challenging. Patients may imprecisely recollect symptoms that occurred years earlier, and contemporaneous health care records may be incomplete or unavailable. Nonspecific descriptions of prior symptoms such as blurry vision, dizziness, and numbness, while compatible with optic nerve, brainstem, or spinal cord demyelinating syndromes, can also occur in alternative disorders frequently referred for MS evaluation, such as migraine.[6] In some patients, abnormal neurologic examination findings may have resolved. Limited patient recollection and inadequate documentation are insufficient to conclude a diagnosis of MS is incorrect, but should prompt further investigation for objective evidence of a CNS lesion in a region typical for MS to corroborate a prior reported relapse (Table 2). The McDonald criteria for RRMS were validated in patients with presentations typical for MS—retrospective application in patients lacking convincing evidence of such a syndrome likely diminishes its specificity and raises the risk of misdiagnosis.[7]

Assessing Historical Disease Activity

Although a previous syndrome typical of MS and without clinical or radiologic red flags suggesting alternative disorders[8] can be confirmed in some patients with a historical diagnosis, an accurate determination of the accumulation and severity of clinical relapses or active (contrast-enhancing or new T2) MRI lesions in the years after diagnosis may also be difficult. Such information is important to inform shared decision making surrounding the risks and benefits of continuing DMT initiated by a prior clinician.

The challenges of MS relapse ascertainment are well recognized.[9] The number and characteristics of remote relapses in patients with longstanding MS may be difficult to recall. The term relapse is sometimes misunderstood and ascribed to fluctuating symptoms that are instead the sequelae of prior CNS inflammatory events or pseudorelapses[10]—reemergence of symptoms attributable to prior relapses in the setting of stressors such as infection. In some patients, these phenomena may have been misinterpreted as evidence of active disease, resulting in DMT escalation.[9] Several clinical approaches can be considered (Table 2) when historical disease activity is uncertain.

Evaluating Clinical Progression or Severe Disability

Confirming a progressive MS phenotype[11,12] by either patient report or clinical documentation of accumulating

Table 2 Recommendations for a Clinical Approach to a Historical Diagnosis of Multiple Sclerosis

Clinical challenges	Recommendations
Diagnostic reevaluation: confirming prior relapsing disease	1. When history is typical for MS relapse, obtain and assess contemporaneous documentation of objective clinical and/or paraclinical supporting evidence (MRI, VEP, and OCT) of a corresponding CNS lesion. If prior data are inadequate or unavailable, seek current objective evidence supporting the prior episode. 2. In absence of objective evidence confirming at least 1 relapse, consider full diagnostic reevaluation. 3. History of multiple reported episodes of neurologic symptoms that do not clearly localize to the CNS by description and that are without historical or contemporary clinical or paraclinical objective corroboration of a CNS lesion raise concern for a misdiagnosis.
Assessing historical disease activity	1. Prior DMT changes in response to clinical relapses lacking historical or contemporaneous objective clinical or paraclinical evidence of a CNS lesion raise concern for accuracy of reported historical disease activity, particularly if there has been minimal disability worsening and/or MRI lesion accumulation despite reported frequent relapses. 2. If evidence of prior reported active disease remains difficult to confirm, reconsideration of the risks and benefits of current DMT may be prudent 3. In patients presenting for enrollment in MS clinical trials requiring recent active disease, confirmation by contemporaneous or residual objective evidence of disease activity should be required, rather than history alone. 4. A history of recurrent stereotyped symptoms suggest pseudorelapses or should prompt consideration of alternative diagnoses including MOGAD, migraine, transient ischemic attacks, or epilepsy rather than MS relapses.
Evaluation of historical clinical progression and severe disability	1. Consider obtaining MRI to evaluate for evidence of active disease or alternative diagnoses contributing to disability progression, especially myelopathy, if not performed recently. 2. Severe optic neuritis or myelitis and residual static disability without progression should prompt consideration of alternative diagnoses such as NMOSD and MOGAD. 3. CSF evaluation, if not performed previously, might be an appropriate part of a diagnostic reevaluation if clinical or MRI features are atypical of progressive MS. 4. Clinical and radiologic follow-up might be necessary before introducing or escalating DMT if history and documentation are insufficient to confirm disability worsening or recent active disease. 5. In older and severely disabled patients with progressive MS and continued worsening, consider reassessment of the risks and benefits of continuing DMT.
MRI interpretation for diagnostic and disease activity reassessment	1. Peripherally located pontine lesions are more specific for MS. Centrally located pontine lesions are often associated with long-standing small-vessel ischemic disease.[28] 2. When brain MRI findings are compatible with both longstanding MS and age-related comorbidities, detection of spinal cord lesions and CSF findings may increase confidence in a prior MS diagnosis. 3. A greater number than the 1 periventricular lesion formally required for McDonald criteria DIS[1] may increase confidence in MS diagnosis in older patients or those with comorbidities associated with small-vessel ischemic disease.[29,30] 4. Acquisition of new imaging as well as interval 6- or 12-mo follow up may be required to assess recent disease activity to inform decisions regarding DMT.
Diagnostic approaches to adults with a history of pediatric-onset MS	1. Consider MOG-IgG testing, especially when historical clinical or paraclinical features are atypical for adult-onset MS. ADEM, focal cortical encephalitis, recurrent monocular or bilateral optic neuritis, or normal brain MRI and negative CSF oligoclonal bands may suggest MOGAD. 2. Severe myelitis, optic neuritis, or area postrema syndrome should prompt evaluation for NMOSD. 3. Evaluation for leukodystrophies, hereditary spastic paraparesis, or mitochondrial cytopathies should be considered in adults with a history of pediatric-onset MS with a progressive course at onset.[19,31]

Abbreviations: ADEM = acute disseminated encephalomyelitis; DIS = dissemination in space; DMT = disease-modifying treatment; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disorder; MS = multiple sclerosis; NMOSD = neuromyelitis optic spectrum disorder; OCT = optical coherence tomography; VEP = visual evoked potential.

disability can be difficult in some patients with a historical diagnosis. Patients may present with a vague history of worsening disability, mild or minimal disability on neurologic examination, and poor documentation of sustained clinical changes. Fluctuation of symptoms due to stressors such as infection, and effects of comorbidities and aging, can confound previous assessments for progression, influence patient perceptions of worsening symptoms, and may make interpretation of previous documentation challenging.

In patients with a history of progressive MS with severe longstanding disability, clinicians may be reluctant to reevaluate diagnosis, disease activity, or clinical progression. Such patients may not be receiving DMT or regular MRIs, with care instead focused on symptom management. In some patients, obtaining a new MRI may reveal MS disease activity that could prompt reconsideration of DMT or a comorbid condition amenable to treatment, such as compressive myelopathy[13] or a neoplastic disorder.[14] Clinical reassessment may also identify severe optic neuritis or myelitis with marked residual disability without evidence of progression—a phenotype more consistent with neuromyelitis optic spectrum disorder (NMOSD) where diagnosis may alter treatment even in patients with advanced disability.

In the era of DMT for primary progressive MS or secondary progressive MS with potential to result in serious adverse effects, particularly in those who are older and more disabled,[15,16] accurately establishing historical progressive disease (Table 2) is a particularly pressing concern.

Challenges With MRI Interpretation in Patients With Historical Diagnoses

MRI may aid or complicate the evaluation of patients with a longstanding diagnosis of MS. Accurate assessment for new T2 lesions from prior MRIs to either support DIT or interval disease activity may be limited by lack of availability of prior scans. Also, differences in pulse sequences, acquisition parameters (e.g., slice thickness), scanning planes, and magnetic field strengths between scanners may complicate comparison.

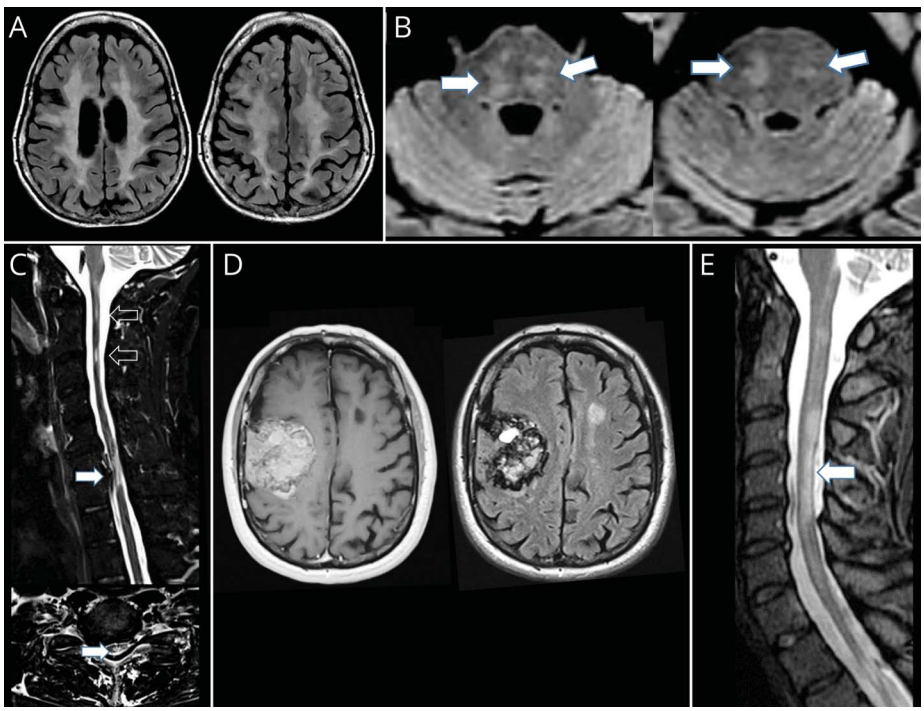
MRI scans acquired in patients with longstanding MS without the benefit of prior scans for review may also raise questions concerning the accuracy of diagnosis. Coalescence of discrete MS lesions over time may mimic small-vessel vascular disease, leukodystrophies, or toxic/metabolic injury.[17] Similarly, coalescence of multiple discrete spinal cord lesions in MS may mimic longitudinally extensive myelitis (LETM) and mistakenly suggest NMOSD or myelin oligodendrocyte glycoprotein antibody–associated disorder (MOGAD). MRI sequelae of age-related comorbidities may also confound retrospective brain MRI assessment for both diagnosis and disease activity. Hypertension and other causes of chronic vascular disease can simulate the appearance of Dawson fingers[18] or pontine demyelinating lesions.[17] The Figure demonstrates examples of these imaging findings, and Table 2 enumerates clinical approaches.

History of Pediatric-Onset MS

Patients with pediatric-onset MS usually eventually transition care to adult neurologists. These clinicians may at times be less aware of evolving data concerning the differential diagnosis of MS in children.[19] Pediatric-onset MS is ultimately diagnosed in only approximately 20% of children presenting with acquired demyelinating syndromes.[19]MS in children almost never exhibits a progressive course from onset and is associated with higher relapse rates[20] and better relapse recovery,[21] but earlier age at onset of secondary progression[22] compared with adult-onset MS. Contrary to previous literature, contemporary data suggest that pediatric presentations of demyelination with characteristics atypical for adult MS (e.g., severe/bilateral optic neuritis) are more likely to be other demyelinating disorders, rather than pediatric-onset MS.[19]

Pediatric NMOSD is diagnosed in less than 5% of children with demyelinating syndromes and exhibits clinical features similar to adult NMOSD.[19] MOG-IgG is detected in approximately one-third of children with acquired demyelinating syndromes such as optic neuritis and myelitis,[19] and MOGAD accounts for a much higher proportion of these syndromes in children (especially those aged <11 years) than in adults.[23] Diagnostic reevaluation in patients with a longstanding diagnosis of pediatric-onset MS is often warranted, particularly when either clinical presentation or MRI findings were atypical for adult-onset MS (Table 2).

Figure Imaging in Patients With Long-Standing MS: Effects of Comorbidity and Disease Duration and Mimics of Clinical Progression



(A) Periventricular and subcortical confluent MRI signal abnormalities mimicking chronic small vessel ischemic disease or leukodystrophy in a patient with longstanding MS without a history of, or risk factors for, vascular disease. (B) Central pontine lesions (solid arrows) suggestive of small vessel ischemic disease in a patient with both MS and vascular disease. (C) A patient with MS and progressive leg weakness due to compressive cervical myelopathy. Images show compression on the spinal cord exerted by intervertebral disc protrusion at the C6-C7 level, associated with central spinal cord signal changes (solid arrow), and lesions from MS seen superiorly (open arrows). (D) A patient with MS who presented with gradually progressive left arm and leg weakness due to an enlarging meningioma. (E) Formerly discrete lesions in a patient with MS, which over time have formed the appearance of longitudinally extensive myelitis (solid arrow). MS = multiple sclerosis.

Evaluation of a patient with a historical diagnosis of MS presents several challenges. The clinical and neuroradiologic evolution of MS with increasing disease duration and age, as well as health care system barriers, may complicate the reassessment of diagnosis, disease activity, and disability needed to guide optimal treatment decisions. Approaches that include retrospective consideration of core elements of the McDonald criteria and vigilance for specific red flags can aid clinicians in the care of such patients.

Even after thorough reevaluation, the diagnosis of MS may remain tentative. Sensitive and specific diagnostic and prognostic biomarkers would be helpful. Emerging neuroimaging biomarkers, such as the central vein sign,[24] have shown promise in differentiating of MS from common mimics even in longstanding disease and in the presence of comorbid conditions.[25] Accumulating data also suggest that serum neurofilament light chain may serve as a sensitive measure of active disease in MS.[26] Such progress is encouraging, but the utility of such advances in clinical practice remains to be determined.[27]

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Continued

Appendix *(continued)*

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