Diagnosis and Monitoring of Patients With Multiple Sclerosis

From the 2017 guidelines to newest modalities.

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Multiple sclerosis (MS) is a demyelinating disorder affecting the central nervous system, primarily diagnosed in young adults, and with a higher prevalence in women than in men.[1] During the last 25 years, enormous scientific advances have increased successes in diagnosis and disease-modifying treatments (DMTs), with measurable improvement in outcomes. With the success of new treatments have come concerns about the safety of long-term immunomodulation or immunosuppression, making the correct diagnosis of MS all the more important.

The criteria for diagnosis of MS have changed multiple times over the years, with the most recent change titled *2017 McDonald Criteria* being published.[2] The goal of the revised criteria is to minimize the misdiagnosis of MS while allowing for early intervention in confirmed cases. Although the MS diagnosis may be based purely on clinical criteria, the use of MRI and cerebrospinal fluid (CSF) findings increase the accuracy of diagnosing MS and identifying the MS mimics that may lead to incorrect treatment decisions.

When a health care provider initially evaluates a patient with neurologic symptoms concerning for demyelinating disease, certain questions are vitally important for successful communication. If all of these questions are answered satisfactorily, it is much more likely that a shared decision-making strategy can be developed and followed (Box).

Box. The 5 Questions all Persons With Multiple Sclerosis Want Answered

1. Do I have multipe sclerosis?
2. What kind of multiple sclerosis do I have?
3. What is my prognosis?
4. Is there a best treatment for me?
5. How will we know if this medication is working?

Do I Have Multiple Sclerosis?

Most patients consulting neurology for possible MS have had a clinical event that precipitated a medical evaluation. The most common presentations include optic neuritis, transverse myelitis, or a brainstem syndrome, although other focal neurologic signs can also lead to a diagnostic evaluation, such as sensory, motor, or cerebellar dysfunction; bladder symptoms; or cranial nerve involvement (eg, trigeminal neuralgia).

The proper work-up of MS includes an MRI scan of the brain and spinal cord with and without contrast, with special sequences for the brain MRI (eg, sagittal fluid–attenuated inversion recovery [FLAIR]). The historical definition of MS has included the concepts of *dissemination in space and time* to indicate the necessity of multiple events in order to move from the concept of a *clinically isolated syndrome* to confirmed disease. The 2017 McDonald Criteria have made important changes to assist in the proper early diagnosis of MS (Table 1). In patients with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination in space, the presence of CSF-specific oligoclonal bands and the presence of enhancing and nonenhancing lesions on a single brain MRI fulfils the criteria for dissemination in time, thus allowing a diagnosis of MS. Symptomatic or asymptomatic lesions can be used to demonstrate dissemination in space or time in patients with supratentorial, infratentorial, or spinal cord syndrome; and cortical lesions can be used to demonstrate dissemination in space.[2]

The value of the changes in the MS diagnostic criteria involves the discrete process of attempting to counterbalance 2 crucial and inextricably linked constructs: precision and accuracy. The application of highly sensitive detection methods comes with the challenge of associating a particular lesion with a pathologic cause. Sensitivity and specificity of MS diagnosis based on MRI findings has been an issue, especially

TABLE 1. MCDONALD CRITERIA FOR DIAGNOSIS OF MULTIPLE SCLEROSIS	
Typical attack or clinically isolated syndrome at onset	≥2 attacks and objective clinical evidence of ≥2 lesions
	≥2 attacks and objective clinical evidence of 1 lesion AND history of prior attack
	≥2 attacks and objective clinical evidence of 1 lesion **AND** history of prior attack implicating different lesion site **OR** ≥1 MS-typical T2-enhancing lesion that is perientricular, juxtacortical, infratentorial, or in spinal cord
	1 attack and objective clinical evidence of ≥2 lesions **AND** history of prior attack implicating different lesion site **OR** simultaneous presence of BOTH enhancing and nonenhancing MS-typical lesions (symptomatic or asymptomatic) **OR** new T2 or enhancing MS-typical lesion compared to previous MRI findings **OR** presence of oligoclonal bands in CSF (not serum)
	1 attack and objective clinical evidence of 1 lesion **AND** history of prior attack implicating different lesion site **OR** ≥1 MS-typical T2-enhancing lesion in ≥2 periventricular, juxtacortical, infratentorial, or spinal cord sites **AND** history of prior attack implicating different lesion site **OR** simultaneous presence of BOTH enhancing and nonenhancing MS-typical lesions (symptomatic or asymptomatic) **OR** new T2 or enhancing MS-typical lesion compared to previous MRI findings **OR** presence of oligoclonal bands in CSF (not serum)
Progression of disability from onset	1 year of disability progression **AND** 2 of the following: **OR** ≥1 MS-typical T2-enhancing lesion in ≥2 periventricular, juxtacortical, infratentorial, or spinal cord sites **OR** ≥2 T2 spinal cord lesions **OR** presence of oligoclonal bands in CSF (not serum)

Abbreviation: CSF, cerebrospinal fluid.

with the increased use of MRI for identifying causes of various neurologic symptoms. Radiologists frequently include demyelinating disease in the diagnostic differential of small subcortical white matter lesions to minimize risk of failure to diagnose a treatable condition with significant sequela. However, a radiologist report stating that the findings "do not meet McDonald Criteria" should not override a clear clinical diagnosis, especially if backed by additional paraclinical data such as CSF markers or evoked potential testing.

In all, the most important question to ask at first evaluation is whether the true criteria have been met for the diagnosis of MS—the requirement for accurate diagnosis is paramount, and it is of the utmost importance to follow established guidelines before committing to long-term DMT.

What Kind of Multiple Sclerosis do I have?

Classification of MS has evolved as well.[3] The most important questions to ask during initial evaluation will determine whether a relapsing course, a progressive course, or both, apply to the patient (Table 2). It is also relevant to determine whether the course is active or inactive. Patients can be very confused about the concept of progressive MS, and the distinction between primary progressive (PP) and secondary progressive courses can have therapeutic implications. An important question to ask patients is whether they have experienced any changes in function within the last year, which can be stated as, "Compared to this time last year, is there anything that you can't do or have more difficulty doing?" The answer to this question may be complicated but often leads to much more powerful documentation of true disability.

Neurologic symptoms that are residuals of previous relapses vary depending on multiple factors (eg, general fitness, comorbid conditions, or worsening due to core overheating [Uthoff's phenomenon]).[4] It is very important to distinguish these potentially reversible conditions from true progression of MS, defined as progression without MS relapses lasting more than a year.

TABLE 2. TYPES OF MULTIPLE SCLEROSIS DEFINED AND FURTHER CHARACTERIZED[3]

Type	Definition	Further Characterizations			
		Not Active	Active	Stable	Worsening
Relapsing-remitting	Total or partial recovery with no apparent disease progression in between episodes of acute worsening of neurologic function (new symptoms or worsening of previous symptoms)	NEDA	New relapses, new Gd-enhancing lesions, or new or enlarging T2 lesions over specific time period	NEDA over a specific time frame after a relapse	Increased disability over a specific time period after a relapse
				Without Progression[a]	**With Progression[a]**
Primary progressive[b]	Steadily worsening neurologic function from onset without initial relapse or remission			No evidence of worsening on objective measure of change[c] over a specified time period.	Evidence of worsening on objective measure of change[c] over a specified period of time with or without relapses.
Secondary progressive	Initially relapsing-remitting course becomes more steadily progressive with or without relapses				

[a] Only the progressive forms can be characterized as without or with progression; only the relapsing-remitting form, stable or worsening.
[b] The formerly termed progressive relapsing type is now considered primary progressive.
[c] As an example, the Expanded Disability Status Scale (EDSS) is considered an objective measure.

Abbreviations: Gd, gadolinium; NEDA, no evidence of disease activity.

Another type of MS that is important to distinguish is radiographic isolated syndrome (RIS), which is the presence of lesions on MRI that are characteristic of MS in a patient who has not had any clinical events consistent with MS. These patients should be followed carefully for evidence of clinical findings consistent with MS but should not receive DMT until a diagnosis is confirmed using the McDonald criteria.[5] Any development of abnormalities on neurologic exam would certainly increase the risk of conversion from RIS to MS. Additional testing such as evoked potentials, optical coherence tomography (OCT), or CSF studies should be considered in these cases to determine if a relapsing or progressive course can be established.

What Is My Prognosis?

MS is an unpredictable and heterogeneous disease making accurate prognosis over time challenging. Certain presenting signs and symptoms portend a worsened prognosis, and these factors should be considered in prognosticating disease course.[6] Several studies have indicated that a poor prognosis is correlated with male gender; late age at onset; presentation with motor, cerebellar, and sphincter involvement or a progressive course; a short inter-attack interval; a high number of early attacks; and relevant early residual disability. Using additional parameters, including MRI and CSF findings, can aid in prognostication.[7] Positive CSF oligoclonal bands and baseline MRI findings of high lesion number, presence of global atrophy or T1-hyperintense lesions indicate more aggressive disease that has caused more injury to the central nervous system (CNS), portending a higher likelihood of earlier disability progression. Patients should be clearly informed about the good and bad prognostic factors for disease progression, as shared decision making requires not only discussion of risk of treatment, but the true risk of the disease itself.

Is There a Best Medication for Me?

The choice of initial therapy has been made increasingly complicated by the varied choices of DMTs. Multiple products with unique mechanisms of action and a lack of biomarkers to determine the best strategy for treatment result in variable choices of therapy among health care providers. Because there is no universal algorithm for choosing a therapy, patients can often feel overwhelmed with the available choices and may require long discussions with health care providers to arrive at a decision. If these conversations seem unsatisfactory, it can lead to increased stress experienced by patients and become a challenge to the provider-patient relationship.

Tailoring the treatment to the individual is of vital importance. Patients have different tolerances of risk and benefit for

treatment, and nonadherence to treatment is a major obstacle to successful outcomes.[8,9] Proper education of patients should start with defining goals, the subject of the last section. Once the reasons for treatment are fully established, it is much easier for the patient to understand that control of the autoimmune condition must optimally coexist with maintenance of immunocompetence. If the treatment of choice increases the risk of infection, either common or opportunistic, the patient must be clearly informed about the importance of safety monitoring. Missing an opportunity for a more effective therapy because of a resistance to any therapy that carries risk of opportunistic infection is placing the patient at risk of irreversible neurological compromise from MS itself. Treatments have risks and considerable costs, but inadequately treating MS is also expensive and dangerous. Inadequate response to medication must be identified with attentive clinical follow-up and MRI monitoring. The exact criteria for treatment failure" is difficult to define, but the presence of new or enhancing lesions on MRI or a clinically significant relapse or progression of symptoms is a reason to reevaluate the choice of DMT. The most recent Consortium of Multiple Sclerosis Center (CMSC) guidelines state routine brain MRI should be considered every 6 months to 2 years for all patients with relapsing MS.[10]

Multiple variables characterize the different DMTs (eg, mode of administration, frequency of dosing, mechanism of action, and amount of time since drug launch). Medications can also be differentiated by the available research and postmarketing data on efficacy, safety, and tolerability. The complexity of this choice can intimidate patients, and attempts to fully cover all of the possible choices of DMT in 1 appointment may be impractical. Lumping medications together into categories can be an effective strategy as a discussion guide. Choices for such categorization have previously been described as "platform" versus "second-line" medications, but this has been blurred to the point of being inaccurate and impractical. Immunomodulator versus immunosuppressor nomenclature is also very ambiguous, as any medication that increases the risk of an infection of any kind could legitimately be considered immunosuppressive. In practice, dividing the conversation into a simpler concept, such as injectable immunomodulators, oral medications, and biologic infusible products can improve communication. It is rare for a single DMT to be the only choice a patient has, but such issues as family planning, access to laboratory testing, and other factors can sway the decision. It may be helpful to ask patients early in the process whether they know someone with MS and whether medication has also been a subject of conversation. Preconceived notions, both positive or negative, influence opinions and can lead to a more streamlined and productive conversation.

Newer agents are continuing to come to market, with several in late-stage clinical trials. Some of these are modifications of older medications, such as sphingosine-1-phosphate (S1P) agonists (the mechanism of action of fingolimod) and B-cell depletion (the mechanism of action of rituximab and ocrelizumab). Treatment of the progressive forms of MS has been an unmet need, but approval of ocrelizumab for PPMS and recent positive trial results for siponimod[11] have improved the outlook for patients with these types of MS.

How Will We Know if This Medication Is Working?

Even before initiating a DMT, it is vital to discuss the goals of treatment:

- No clinical relapses or exacerbations
- Mitigation of attack severity
- No gadolinium-enhancing (active) lesions and/or no new or newly enlarging T2 lesions
- No change in the neurological exam or confirmed disability progression

This is the basis for the concept of no evidence of disease activity (NEDA).[12] Although different clinical trials do not allow for all DMT to be compared head-to-head, many of the recent trials have used NEDA as an endpoint, allowing us to advise patients on how a prospective treatment has fared in that regard. Even in the trials of highly effective DMT, NEDA cannot be achieved in the majority of cases. Nevertheless, it is not unreasonable to provide this as a guideline for successful control of disease activity. Advancing research into brain atrophy has led to the concept of expanded definitions of NEDA, and additional clinical components such as cognition, ambulation, and other outcome measures can also be used to define disease stability. The bar for successful treatment for MS has been raised repeatedly, and communication of this progress is now an integral part of all treatment strategies.

Conclusion

The clinical management of persons with MS is often thought to be highly complex, and given the unpredictable clinical course and the wide variety of presentations and progression of the disease, this reputation is well earned. However, consensus on the diagnosis has been updated with the 2017 McDonalds criteria. Furthermore, attempts to generate comprehensive practice guidelines on DMTs have now been published.[13] Although beyond the scope of this article, it is important to remember that following the confirmation of a working diagnosis of MS and the initiation of DMT, formidable work remains for most patients; how to live with MS, to expertly manage symptoms, and how to live in such a way so as to optimize health and wellness (eg, I have MS, but MS does NOT have me). Although many questions continue to exist, the ability to change the natural history of the disease has been advanced to the extent that reasonable (and more positive than ever) expectations can be given to a newly diagnosed patient. The questions posed by people with MS have not changed in the last 25 years, but the answers certainly have. ■

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