Diagnostic criteria for multiple sclerosis (MS) have evolved considerably—ranging from the early, clinically oriented Poser criteria introduced in 1983 to the comprehensive, revised McDonald criteria published in 2005.1,2 This year, a new consensus document was released on the differential diagnosis of MS.3 In addition, new magnetic resonance imaging (MRI) guidelines are anticipated from a Consortium of Multiple Sclerosis Centers (CMSC) consensus meeting held in Vancouver, Canada.

Working with an MS patient to arrive at an accurate diagnosis involves much more than checking off a list of criteria. There are many “real world” factors to consider, such as the variability of MRI results among centers, patients whose presentation does not fit neatly into the diagnostic criteria, and the emotional upheaval that this diagnosis brings for patients and their families.

For this issue of MS Counseling Points™, a panel was convened to discuss how to apply the latest MS diagnostic criteria in the clinical setting, with consideration for these and other important challenges.

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Dear Colleague,

Arriving at a diagnosis of multiple sclerosis (MS) is one of the most challenging aspects of our practice. We must confirm clinical and magnetic resonance imaging (MRI) findings to prevent a false-positive diagnosis, but balance this with the desire to get patients started on a disease-modifying therapy that we hope will slow the progression of the disease. At the same time, we must counsel and support patients through this frightening, confusing, and often overwhelming part of their lives.

MS diagnostic criteria have evolved over time and continue to be evaluated and updated. Using these criteria involves much more than checking off a list of signs and symptoms—it requires clinical judgment and comprehension of the differential diagnosis, a thorough knowledge of the clinical presentations of this disease, and an ability to put MRI findings into the proper perspective.

In this edition of *MS Counseling Points™*, we discuss how to apply the current diagnostic criteria in the “real world” clinical setting, including a discussion of patient counseling issues. We hope that your practice benefits from this overview, and that you will continue to remain abreast of this important issue as new diagnostic guidelines are introduced.
**Evolution of Diagnostic Criteria**

Due to more refined diagnostic criteria and advanced imaging techniques, MS can be diagnosed much earlier in most patients. In the past, it was not uncommon for patients to wait as many as 10 years before receiving a definite diagnosis of MS. There is evidence that the delay from symptom onset to diagnosis is steadily decreasing and thus many more patients have mild disease at the time of initial diagnosis than in the past.\(^4\)

*It is important to note that as MS diagnostic criteria have changed, they have not replaced the previous criteria per se, but have built upon and updated the relevant portions.*

It is important to note that as MS diagnostic criteria have changed, they have not replaced the previous criteria per se, but have built upon and updated the relevant portions. An example is the Barkhof criteria, which were published in 1997 to demonstrate the dissemination in space of MS lesions.\(^5\)

These criteria helped assess the risk of conversion from clinically isolated syndrome (CIS) to clinically definite MS (CDMS), concepts that were encompassed in the 2005 update to the McDonald criteria.\(^2,6\)

Diagnostic criteria in MS will continue to evolve in an effort to further refine potentially confusing concepts and incorporate new technology and findings about the disease. Newer criteria may address technology, such as high-field MRI and other advanced MRI-based imaging techniques, that did not exist when these earlier criteria were developed. In the meantime, the challenge remains for the clinician to apply the available tools as well as possible in the clinical setting.

**Pitfalls in the Diagnosis of MS**

A common pitfall, especially outside of MS centers, is the tendency to “stick with the familiar” by using outdated diagnostic criteria. Just as failure to use the most recent criteria can create diagnostic pitfalls, so can over-reliance on imaging technology without consideration of the clinical findings.\(^7\) The authors of the revised McDonald criteria mention in their discussion that these criteria “appear to have been incorrectly interpreted by some as mainly relying on MRI for making a diagnosis of MS.”\(^2\) In fact, the authors stress, “The McDonald criteria cannot even be applied without careful clinical evaluation of the patient.”\(^2\) They add: “A purely clinical diagnosis remains appropriate when MRI and other paraclinical examinations are not possible.”\(^2\)

While MRI plays a critical role in the diagnosis of MS, lesions on these scans can be nonspecific. A number of other conditions, both demyelinating and non-demyelinating, can produce lesions on MRI that may confound the diagnosis. These include infectious, neoplastic, congenital, metabolic, or vascular disease, or non-MS demyelinating conditions. The latter may include neuromyelitis optica (NMO), opto-spinal MS (seen in Asian populations), or acute disseminated encephalomyelitis (ADEM). An algorithm for separating MS from these conditions was developed by a large international panel and presented in a differential diagnosis consensus document released earlier this year (Figure 1).\(^3\)

According to the panel, previous diagnostic guidelines have not adequately addressed how to differentiate patients with clinical presentations of central nervous system (CNS) disease that may not develop into MS.\(^3\)

*A recent study of medical records from almost 9,000 MS patients showed that the presence of co-morbid conditions may delay the diagnosis of MS anywhere from 1 to 10 years.*

Other diagnostic pitfalls may arise in patients with co-morbidities. A recent study of medical records from almost 9,000 MS patients showed that the presence of co-morbid conditions—including vascular, autoimmune, musculoskeletal, gastrointestinal, visual, or mental co-morbidities—may delay the diagnosis of MS anywhere from 1 to 10 years.\(^8\) Notably, obesity was one of the conditions found to delay diagnosis. MS symptoms are often nonspecific and thus could be attributed to a pre-existing condition rather than being explored further, the authors of this study noted. Patients with co-morbidities were also found to have a greater level of disability at the time of diagnosis than those who did not.\(^8\)
Symptoms Consistent with Inflammatory Demyelinating Disease (Monofocal or Multifocal Syndromes)

Exclude Non-demyelinating Syndrome
(as appropriate based on demographics, specific symptoms and signs, clinical course, radiology, laboratory tests)

Classify Idiopathic Inflammatory Demyelinating Disease
(based on demographics, clinical course, specific symptoms and signs, radiology, laboratory tests)

Determine Diagnosis of Non-inflammatory Demyelinating Disease
(recognize red flags to suggest specific diagnosis or comprehensive evaluation if diagnosis not apparent)

Not MS
(NMO, ADEM, Unclassified)

Consistent with Prototypic MS
(includes CIS)

MS Established
Dissemination in Time and Space (McDonald criteria)

MS Not Yet Established

Figure 1. Steps in MS differential diagnosis.³

ADEC=acute disseminated encephalomyelitis; CIS=clinically isolated syndrome; MS=multiple sclerosis; NMO=neuromyelitis optica.

The complexities of MS differential diagnosis underscore the importance of having the patient evaluated at an MS center, where clinical judgment and experience in reading radiographic results can help place MRI findings in the proper context.\(^9\)

**Updates in MRI Guidelines**

The 2003 CMSC guidelines for MRI in MS are currently under revision, with the published report anticipated some time in 2009.\(^{10}\) What are clinicians looking for in updates of the MRI guidelines? While the original guidelines cover the use of MRI in the diagnosis of MS, a consensus is lacking about the use of MRI in the follow-up of MS patients. In addition, use of nonconventional imaging techniques such as magnetic resonance spectroscopy (\(^1\)H-MRS) and better standardization of MRI techniques among centers are areas that need to be addressed.

Several nonconventional MRI techniques can provide insight into changes occurring in normal-appearing tissue that are not visible on standard or lower-field (1.5 Tesla) MRI.\(^{11}\)

Some MS centers provide a copy of the guidelines (Table 1, full guidelines available at [www.mscare.org/cmsc/images/pdf/MRIprotocol2003.pdf](http://www.mscare.org/cmsc/images/pdf/MRIprotocol2003.pdf)) to patients before they undergo an MRI to make sure an appropriate protocol for MS is followed.\(^{10}\) Many MRIs are conducted outside of major academic hospitals or MS centers, so having the patient bring the protocol to the imaging visit may help to ensure greater consistency between scans and that gadolinium is dosed and timed appropriately.

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**Table 1. Consortium of Multiple Sclerosis Centers MRI Guidelines for Diagnosis and Follow-up of MS\(^{10}\)**

<table>
<thead>
<tr>
<th>When MS is suspected:</th>
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<tbody>
<tr>
<td><strong>Baseline Evaluation</strong></td>
</tr>
<tr>
<td>• A brain MRI with use of the contrast agent gadolinium is recommended</td>
</tr>
<tr>
<td>• A spinal cord MRI is also advised if a patient has on-going symptoms that suggest there is spinal cord involvement or if a brain MRI doesn’t give enough information for clinicians to make a diagnosis</td>
</tr>
<tr>
<td><strong>Follow-up Evaluation</strong></td>
</tr>
<tr>
<td>• A follow-up brain MRI is recommended to determine if a patient has new disease activity</td>
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<table>
<thead>
<tr>
<th>When MS has been diagnosed already:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Evaluation</strong></td>
</tr>
<tr>
<td>• A brain MRI is advised with or without gadolinium enhancement</td>
</tr>
<tr>
<td><strong>Follow-up Evaluation</strong></td>
</tr>
<tr>
<td>• Follow-up MRIs should be performed if a patient has a relapse, if he or she is starting or changing therapy (to reassess the number and size of lesions in the brain), and/or if clinicians suspect the patient has another disease besides MS</td>
</tr>
</tbody>
</table>

MRI=magnetic resonance imaging; MS=multiple sclerosis.

When the Presentation Doesn’t Fit the Diagnostic Criteria

Although current diagnostic criteria are broad enough to address typical presentations of MS, there are some patients for whom the diagnostic criteria and clinical picture don’t match.

One scenario is the patient who presents with neurologic signs that are reproducible and appear to be caused by MS, but occur in conjunction with a normal MRI, normal cerebrospinal fluid (CSF), and/or other laboratory parameters. This situation can be very frustrating for the patient, who may feel that he or she is accused of “making up” or imagining the symptoms. These patients should be followed closely and may wish to seek another medical opinion. Differential diagnosis to rule out other conditions that mimic the clinical signs of MS is an important step in the management of these patients.

An increasingly common scenario is that of a patient who has a normal clinical presentation but has an MRI consistent with MS. This may occur in clinical trials among control subjects, or among patients who have undergone MRI studies to evaluate other conditions such as headache. These cases of “subclinical” MS have been described in the literature and may be seen more often with the increased use of diagnostic brain MRI. Such patients should be followed closely to detect any changes in MRI findings (dissemination in space and/or time), but the decision of whether to treat patients who have a normal neurologic history or exam with disease-modifying therapy (DMT) usually depends upon the judgment of the clinician and the specific circumstances of the case, as well as the patient’s openness to treatment. Patient education should focus on documenting any signs or symptoms of MS, although there is a high margin for error as some patients tend to ignore many symptoms and others may misinterpret normal sensations.

Using Diagnostic Criteria in CIS

Nowhere are current diagnostic criteria more important than in the population of patients with CIS. Compared with earlier criteria, the revised McDonald criteria speed diagnosis of MS by allowing for:

- two separate MRI scans (rather than three) to evaluate disease progression; and
- one clinical attack (rather than two) if lesions on MRI demonstrate dissemination in time and/or space.

By removing the requirement for dissemination in time and/or a second clinical event, the updated McDonald criteria speed the time to diagnosis and resolve the difficult “limbo” period for patients much more quickly.

By removing the requirement for dissemination in time and/or a second clinical event, the updated McDonald criteria speed the time to diagnosis and resolve the difficult “limbo” period for patients much more quickly. Under the original guidelines, patients whose condition did not meet McDonald criteria for CDMS may not have had a full evaluation until they experienced another set of clinical symptoms.

However, authors of the recently released consensus statement on differential diagnosis of MS have argued that the current definition of CIS leaves much to be desired. This international panel of MS experts noted that the term CIS “ignores first presentations that may not be clinical but may be detected by paraclinical and laboratory findings.”

Table 2. Suggested Subcategories for Clinically Isolated Syndrome (CIS)

| Type 1 | Clinically monofocal; at least one asymptomatic MRI lesion |
| Type 2 | Clinically multifocal; at least one asymptomatic MRI lesion |
| Type 3 | Clinically monofocal; MRI may appear normal; no asymptomatic MRI lesions |
| Type 4 | Clinically multifocal; MRI may appear normal; no asymptomatic MRI lesions |
| Type 5 | No clinical presentation to suggest demyelinating disease, but MRI is suggestive |

MRI=magnetic resonance imaging.
currently defined, “does not discriminate between patients who have a single clinical presentation with or without additional symptoms on MRI—two entities that have different prognoses,” they add. The consensus panel recommends a more specific breakdown of CIS subcategories (Table 2) to better describe the clinical and radiologic findings at the earliest stages of MS. Patients with at least one asymptomatic MRI lesion characteristic of demyelination (Types 1 and 2) have a higher probability of later meeting criteria for MS, and this prognosis correlates with the number and location of these lesions. In contrast, patients with monofocal presentation and no lesions on MRI (Type 3) have a low risk for developing MS. The authors add that the Type 4 scenario (multifocal clinical presentation with no MRI lesions) is probably rare and would suggest the need for a thorough differential diagnosis.

**Patient Steps and Actions**

The interval of CIS when the diagnosis of MS is not certain may present an opportunity to encourage patients to check into life insurance, health insurance, and any other loose ends that may become more difficult down the road. Not all patients are open to hearing this message, but the nurse can suggest these steps are important and necessary regardless of the ultimate diagnosis.

Patients can be encouraged to purchase a binder with plastic envelopes to hold discs containing MRI records, and pages to record medication history, addresses, and dates of procedures. While they needn’t keep a complete diary, such a system is a good way for patients to have everything in one place as they journey through the evaluation and treatment process.

**Benefits of Early Treatment**

In addition to the inflammation occurring early in the course of MS, we now know that axonal loss also starts in the early or even preclinical stages. A landmark study by Trapp and colleagues showed that transected axons could be seen as early as 2 weeks after the onset of disease activity. In these early stages, normal-appearing white matter and gray matter are likely to be undergoing damage that is not visible on standard imaging equipment, but which can be identified with more advanced imaging methods such as higher Tesla-strength MRI.

The current evidence clearly demonstrates that DMT works best when initiated as early as possible in the MS disease course, before significant neurodegeneration has occurred. In the CHAMPS trial, patients with CIS who were treated with intramuscular interferon beta-1a (IM IFNβ-1a) had a 44% lower probability of developing CDMS after 18 months than placebo-treated CIS patients.
also had 71% fewer gadolinium-enhancing lesions versus those on placebo. Another early treatment trial, BENEFIT, showed a significant delay in the development of CDMS in patients treated with IFNβ-1b.\textsuperscript{19}

Newer data continue to establish the benefits of treating patients with CIS. Data from the recent PRECISE Trial presented at the 2008 American Academy of Neurology meeting compared the time to CDMS in patients with CIS (one clinical event and at least two T2-weighted brain lesions) receiving glatiramer acetate and placebo.\textsuperscript{20} Treatment with glatiramer acetate reduced the patient’s risk of developing CDMS by 45% versus placebo and prolonged the time to CDMS by 115% (722 days versus 336 days). After this interim analysis, all patients were moved into the active treatment group for ethical reasons.\textsuperscript{21}

**Discussing the MS Diagnosis with the Patient**

Despite the evidence supporting early treatment, some medical practitioners still subscribe to a “wait and see” approach in the management of patients with CIS. Furthermore, while it’s difficult for patients to comprehend and come to terms with a diagnosis of CDMS, this difficulty may be amplified in cases of CIS. Communicating the advantages of early treatment to patients whose clinical signs are minimal presents a significant challenge. Some patients who are open to treatment may want to wait for the availability of oral therapies. While many oral therapies for MS are in the pipeline, these treatments do not have the long-term safety records of established DMTs and thus carry many question marks for a new MS patient who may be receiving treatment for many years.\textsuperscript{22}

When educating patients with CIS or early MS, comparing the natural history of the disease to the clinical course typically seen with long-term DMT may offer encouragement and hope for patients.

If the patient is truly not ready to start treatment, his or her wishes should be respected, as the most important goal is not to “lose” the patient. By giving the person some time, a role in the decision-making process, and “open door” access to the MS center or clinic, the CIS patient is less likely to be lost to follow-up. The diagnosis of MS can be enormously stressful to comprehend. Trying to force a patient into a treat-

Researching the disease on the Internet can be another source of fear and misunderstanding for new MS or CIS patients. Nurse educators who are counseling these patients might caution them to avoid the Internet altogether as they absorb what is happening, to avoid the stress and anxiety that accompany information overload. Instead, face-to-face or telephone discussion with nurse specialists will give patients a clearer concept of how MS is affecting them individually.
ment decision too quickly may reduce the adherence rate to therapy in the near term as well as over time.

Surveys of people with MS indicate the majority of patients feel they received insufficient support in understanding and making sense of their diagnosis. One survey revealed that many patients were given insufficient information about their illness and thus were forced to seek out information and answers on their own. In another survey, people diagnosed with MS described the experience as “powerfully evocative and unforgettable.” Although approaches to delivering the diagnosis have improved as clinicians have been better educated, there is still room for further improvement. Patient feedback has indicated that an appropriate setting (privacy, no interruptions), sufficient time for discussion, and information tailored to the individual are among the recommended improvements.

Try framing force a patient into a treatment decision too quickly may reduce the adherence rate to therapy in the near term as well as over time.

Clinicians must recognize that working with a newly diagnosed MS patient often requires more time than working with patients with other diagnoses. If patients are rushed through appointments, they are likely to require much more phone support. If the clinician is not prepared to take the time or does not feel comfortable presenting information about the disease, it is advisable to refer these patients to an MS center where they can receive appropriate counseling to cope with their diagnosis and begin early treatment.

References

Current multiple sclerosis (MS) diagnostic criteria include the 2005 revision to the McDonald Criteria, the Consortium of Multiple Sclerosis Centers (CMSC) MRI guidelines (currently in revision), and the newly released differential diagnosis consensus published in 2008.

Diagnosis of MS involves a combination of clinical findings and magnetic resonance imaging (MRI) results, including evidence that lesions on MRI are changing (dissemination in time and/or space).

In the evaluation of patients with clinically isolated syndrome (CIS), new guidelines suggest breaking down the CIS definition further based on whether signs/symptoms are clinical or based on MRI results.

Some patients’ presentations do not fit neatly into existing diagnostic criteria. These include patients who have normal MRI results but clinical signs similar to MS, and patients who have a diagnostic MRI showing signs of MS in the absence of clinical signs.

Co-morbidities have been shown to delay the diagnosis of MS.

There is growing evidence that neurodegenerative changes in MS occur very early in the disease process and likely precede clinical symptoms. Thus, early treatment during the CIS stage is considered to offer the best chance of delaying conversion to clinically definite MS and reducing long-term disability.

Counseling patients during the CIS and early diagnostic stages is a particular challenge. It requires time, patience, education, and emphasis of treatment benefits versus the natural history of the disease.

Future updates to diagnostic guidelines may further clarify the use of MRI in the follow-up of MS patients; the role of nonconventional imaging techniques such as magnetic resonance spectroscopy (1H-MRS); and better standardization of MRI techniques among centers.
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