ABSTRACT
Clinically isolated syndrome (CIS) is the first symptomatic neurologic episode consistent with multiple sclerosis (MS). Because the majority of individuals with CIS and demyelinating lesions go on to develop clinically definite MS (CDMS), early detection and treatment is recommended to delay disability progression. This article reviews diagnostic criteria for CDMS, as well as various predictors of disease conversion; it concludes with a discussion of drug therapy for the management of CIS.

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CASE STUDY
RE is a 17-year-old white female who presents with visual disturbances in her right eye. Her aunt has had multiple sclerosis (MS) for the past 15 years, but this is the first time RE has experienced any neurologic symptoms. What is the best course of action at this time?

CLINICALLY ISOLATED SYNDROME
With increasing evidence that permanent tissue damage occurs early in the course of MS, and that timely treatment delays disease progression and disability, it is important that drug therapy be considered for patients with early stage disease. Clinically isolated syndrome (CIS), defined as a single, symptomatic neurologic episode that is consistent with MS, is typically the first clinical event to take place among patients with MS; symptoms may include optic neuritis, ocular motor syndromes, ataxia, dysarthria, sensory or motor signs, partial myelitis, and bladder or bowel dysfunction. Notably, up to 80% of those who experience CIS already have lesions at the time of this first attack. Furthermore, 60% to 80% of patients with CIS who have demyelinating lesions on magnetic resonance imaging (MRI) eventually develop clinically definite MS (CDMS; ie, a second event), as do 20% of those with normal MRIs. As such, the ultimate goal is to delay disease progression to CDMS, through the use of early therapeutic intervention.

DIAGNOSTIC CRITERIA FOR CDMS
Because no single clinical feature or diagnostic test is sufficient for the diagnosis of CDMS, diagnostic criteria have been developed based on the demonstration of lesions disseminated in space (DIS) and time (DIT), after exclusion of alternate causes. The diagnosis of CDMS according to the Poser criteria, developed in 1983, required the occurrence of at least 2 attacks and clinical evidence of 2 separate lesions, or 2 attacks with clinical evidence of 1 lesion and paraclinical evidence of another separate lesion. These criteria have become obsolete, however, as they have been recently replaced by the McDonald criteria. Originally developed in 2001 and revised in 2005, the McDonald criteria incorporate new diagnostic techniques (ie,
MRI guidelines) to provide evidence for DIS and DIT (Table 1).6,8,9 These criteria require at least 2 scans to be performed on most patients with CIS; the first scan detects lesions suggesting demyelination (and hence, a relatively high likelihood of MS), while the second scan is used to demonstrate DIT. Although it is occasionally possible for DIS and DIT to be fulfilled on a single scan, it must be performed at least 3 months after the onset of CIS.6,8,9 Given the importance of early and accurate diagnosis of CDMS, this delay in diagnosis is undesirable; instead, the ability to determine DIS and DIT with a single MRI performed within the first weeks of CIS onset would be ideal.

Fortunately, practical experience and research have revealed potential ways to simplify these diagnostic requirements without relaxing their accuracy (Table 1). Specifically, the Swanton criteria allow a second scan denoting DIT to be performed at any time, so long as a new T2 lesion is detected.9 Moreover, according to the recently proposed MAGNIMS (Magnetic Imaging in MS) criteria, a single scan done at any time may be sufficient to diagnose CDMS, provided that it demonstrates DIS and shows 1 or more asymptomatic, gadolinium-enhancing and nonenhancing lesion. The combination of enhancing and nonenhancing lesions likely reflects lesions in different stages of evolution, thereby indicating DIT.6 If this proposal is approved and implemented, it may enable patients with CIS who develop CDMS to be evaluated and treated in a more timely manner.

In addition to radiologic assessment, laboratory analysis of cerebrospinal fluid (CSF) and visual evoked potentials (VEPs; ie, electrical potentials related to visual stimulation) may be used to diagnose MS. Although radiologic imaging provides the most sensitive and specific information, a CSF analysis, which offers information regarding inflammation and immunologic disturbances, may be useful in the face of an atypical clinical presentation. Similarly, VEP, which is often abnormal in patients with MS, may be used to supplement a clinical examination.10

**CASE STUDY (cont’d)**

RE is evaluated for the presence of central nervous system (CNS) lesions. The MRI reveals 1 gadolinium-enhancing lesion, 2 juxtacortical lesions, and 1 infratentorial lesion in her brain; a second scan performed 1 month later shows 2 additional lesions. Does RE have CDMS? If so, how should she be treated?

**CIS to CDMS: Predictors of Conversion**

Baseline MRI findings can help to predict the risk of conversion from CIS to CDMS. Patients with scans revealing either T2 or gadolinium-enhancing lesions

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**Table 1. MRI Criteria for CDMS**

<table>
<thead>
<tr>
<th></th>
<th>McDonald Criteria6</th>
<th>Swanton Criteria9</th>
<th>MAGNIMS Proposal6</th>
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<tbody>
<tr>
<td><strong>DIS</strong></td>
<td>≥3 of the 4 Barkhof Criteria:</td>
<td>≥1 lesion in each of ≥2 characteristic locations:</td>
<td>≥1 lesion in each of ≥2 characteristic locations:</td>
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<tr>
<td></td>
<td>- 9 T2 lesions or 1 gadolinium-enhancing lesion</td>
<td>- Periventricular</td>
<td>- Periventricular</td>
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<tr>
<td></td>
<td>- ≥3 periventricular lesions</td>
<td>- Juxtacortical</td>
<td>- Juxtacortical</td>
</tr>
<tr>
<td></td>
<td>- ≥1 juxtacortical lesion</td>
<td>- Posterior fossa</td>
<td>- Posterior fossa</td>
</tr>
<tr>
<td></td>
<td>- ≥1 posterior fossa (infratentorial) lesion or spinal cord lesion</td>
<td>- Spinal cord</td>
<td>- Spinal cord</td>
</tr>
<tr>
<td><strong>DIT</strong></td>
<td>A gadolinium-enhancing lesion ≥3 mo after CIS onset</td>
<td>A new T2 lesion on follow-up MRI, irrespective of baseline scan timing</td>
<td>Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time</td>
</tr>
<tr>
<td></td>
<td>A new T2 lesion with reference to a baseline scan obtained ≥30 d after CIS onset</td>
<td>- A new T2 and/or gadolinium-enhancing lesion on follow-up MRI, irrespective of baseline scan timing</td>
<td>-</td>
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<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>Sensitivity</th>
</tr>
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<tbody>
<tr>
<td><strong>McDonald</strong></td>
<td>88%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Swanton</strong></td>
<td>87%</td>
<td>72%</td>
</tr>
<tr>
<td><strong>MAGNIMS</strong></td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

CDMS = clinically definite multiple sclerosis; CIS = clinically isolated syndrome; DIS = disseminated in space; DIT = disseminated in time; MAGNIMS = Magnetic Imaging in Multiple Sclerosis; MRI = magnetic resonance imaging.

Data from Montalban et al6; Polman et al8; and Swanton et al9.
are at increased risk of experiencing a second clinical attack compared to those with normal baseline MRIs.\textsuperscript{11,12} Furthermore, T2 disease burden (ie, number of T2 lesions present at CIS onset) correlates with the risk and time to development of CDMS,\textsuperscript{6} as well as with future disability progression.\textsuperscript{3} Indeed, one study assessing the impact of initial lesion load on patients with CIS revealed that all patients with a high lesion load at presentation progressed to CDMS within 10 years, compared to only 78% of those with a low lesion load. Moreover, 45% of patients with a high initial lesion load, versus only 18% of those with a low lesion load, ultimately had an Expanded Disability Status Scale score greater than 6 (on a scale of 0 to 10),\textsuperscript{13} signifying a need for ambulatory assistance.\textsuperscript{14}

Another potential prognostic factor for disease conversion is the presence of serum antibodies targeting myelin basic protein (MBP) and/or myelin oligodendrocyte glycoprotein (MOG). A recent study investigating the role of these antibodies in patients with CIS found that their presence was associated with early disease conversion, whereas their absence suggested that patients would remain disease-free for several years. Specifically, 83% of patients who were seropositive for anti-MOG antibodies and 95% of those who were seropositive for both anti-MOG and anti-MBP antibodies had a first relapse during the 1-year follow-up period; conversely, 77% of patients who were seronegative for both classes of antibodies remained relapse-free during this time. This indicates that antibody-mediated demyelination may be, at least in part, responsible for MS disease progression.\textsuperscript{15}

Another potential mechanism for disease conversion is epitope spreading, or the development of immune responses against endogenous epitopes, secondary to the release of self-antigen during the first clinical episode.\textsuperscript{16}

**Lifestyle Factors**

Lifestyle factors such as vitamin D deficiency, smoking, and obesity may place patients at an increased risk for developing MS. Epidemiologic and experimental evidence suggests that vitamin D, a potent immunomodulator, may play a protective role in reducing the risk of MS; indeed, research indicates that a high serum vitamin D level significantly decreases disease risk, particularly among Caucasians. Because it is unclear whether increased vitamin D intake is of any benefit to patients who have already been diagnosed with CDMS, vitamin D supplementation may be prudent for high-risk individuals who have not yet developed MS.\textsuperscript{17} Because obese individuals tend to have lower circulating vitamin D levels, increased body mass is another factor that may contribute to disease development. Additionally, obesity among adolescents is associated with a low-grade chronic inflammatory state, which also may heighten the risk for MS. Because weight reduction among patients with MS may not change the course of disease, adolescents at risk for disease should be advised to maintain a healthy weight.\textsuperscript{18}

Smoking is another important lifestyle factor that must be considered. Not only is it involved in the development and progression of MS, but it also promotes conversion of CIS to CDMS.\textsuperscript{19} In fact, one study found that 75% of smokers, compared to 51% of nonsmokers, experienced disease conversion within 3 years of developing CIS.\textsuperscript{20} As such, behavioral modification may help to reduce the risk of disease progression among individuals with CIS.

**Radiologically Isolated Syndrome**

Radiologically isolated syndrome (RIS), or subclinical MS, refers to early stage disease that occurs prior to the initial demyelinating event. Unlike CIS, RIS presents without overt clinical symptoms; instead, it is defined by incidental MRI findings suggestive of MS in asymptomatic patients lacking any history, signs, or symptoms of disease.\textsuperscript{21} As with CIS, the probability of conversion to CDMS, as well as disease prognosis, correlates with the number and location of CNS lesions.

In a study designed to determine the rate of disease conversion in patients with subclinical MS (based on incidental MRI findings), 70 patients with RIS were prospectively evaluated over a 5-year period. Twenty-three (33%) patients developed CIS, with a mean time to conversion of 2.3 years; VEP abnormalities, young age, infratentorial lesions, and gadolinium enhancement were independently predictive of conversion to CIS. It may be prudent to consider early intervention in patients with subclinical MS, given that it may evolve into CIS, and eventually, into CDMS.\textsuperscript{22}

**Dr Miravalle:** Although early intervention is beneficial, treatment of patients unlikely to develop CDMS is both costly and unnecessary. A thorough assessment of risk factors can help determine whether treatment is warranted; in many cases, it may be wise to hold off therapy until a more accurate diagnosis can
be made because the likelihood of developing significant disability within the first year of CIS is slim.

**THE ROLE OF TREATMENT IN CIS**

Four large-scale, phase III, randomized, placebo-controlled clinical trials were conducted to determine whether early treatment in patients with CIS helps to delay the second clinical event, and therefore, the diagnosis of CDMS (Table 2). All these studies demonstrated statistically significant reductions in the risk of CDMS, as well as delays in disability progression, and reductions in brain lesion number and/or volume. Based on these findings, the US Food and Drug Administration has extended the product labeling of subcutaneous (SC) interferon (IFN) β-1b, intramuscular (IM) IFNβ-1a, and SC glatiramer acetate to include CIS as an approved indication, and it is recommended that these patients be treated at the time of diagnosis or first clinical episode.

**Table 2. Treatment of CIS: Clinical Studies**

<table>
<thead>
<tr>
<th>Name</th>
<th>Agents/Dosing</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>PreCISe&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Glatiramer acetate 20 mg SC daily vs placebo</td>
<td>Compared to placebo, glatiramer acetate reduced risk of CDMS by 45% at 3 years and prolonged conversion time by 115%</td>
</tr>
<tr>
<td>BENEFIT&lt;sup&gt;24&lt;/sup&gt;</td>
<td>IFNβ-1b 250 µg SC every other day vs placebo</td>
<td>Compared to placebo, IFNβ reduced risk of CDMS by 17% at 2 years and prolonged conversion time by 142%</td>
</tr>
<tr>
<td>CHAMPS&lt;sup&gt;25&lt;/sup&gt;</td>
<td>IFNβ-1a 30 µg IM once weekly vs placebo</td>
<td>Compared to placebo, IFNβ patients had a relative reduction in brain lesion volume, fewer new or enhancing lesions, and fewer gadolinium-enhancing lesions at 18 months</td>
</tr>
<tr>
<td>ETOMS&lt;sup&gt;26&lt;/sup&gt;</td>
<td>IFNβ-1a 22 µg SC once weekly vs placebo</td>
<td>Compared to placebo, IFNβ reduced risk of CDMS by 11% at 2 years and prolonged time to CDMS by 126%</td>
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</table>

**PROGNOSIS IN THE ABSENCE OF DRUG THERAPY**

In the absence of drug therapy, patients with CIS who have converted to CDMS experience significant disability. Left untreated, 50% of patients with MS require ambulatory support within 15 years of disease onset and 30% eventually become wheelchair- or bed-bound. Moreover, approximately 5% of patients develop “malignant” (ie, rapidly progressive) MS, and may become wheelchair- or bed-bound within only 5 to 10 years. Although 10% to 20% of individuals develop “benign” MS and experience little disability, the majority of patients fall in between these 2 extremes. This further substantiates the need for drug therapy among these individuals.

**CASE STUDY (cont’d)**

RE’s MRI revealed lesions disseminated in both time and space, which is consistent with CDMS. Therapy (ie, IFNβ-1b, IFNβ-1a IM/SC, or glatiramer acetate) should be initiated as soon as possible in order to delay disability progression.

**CONCLUSIONS**

Clinically isolated syndrome is a single, sympto-
matic neurologic episode consistent with MS. Given that the vast majority of patients who have CIS and present with CNS lesions go on to develop CDMS, this condition warrants medical awareness. Early detection and management is crucial to prevent disability progression, which is commonly seen among the MS population. Currently approved medications for the treatment of CIS include IFNβ-1b SC, IFNβ-1a IM, IFNβ-1a SC, and glatiramer acetate SC. Based on the information provided, drug therapy should be administered at the time of the first clinical episode.

REFERENCES