ABSTRACT

Clinically isolated demyelinating syndromes, such as optic neuritis, transverse myelitis, and brain-stem disorders, often require therapeutic intervention. At least 4 major studies have examined the management of these disorders, most often in the setting of an abnormal brain magnetic resonance image. Data from these and other investigations are presented here, along with what has been discovered in terms of risk factors for disease progression to clinically definite multiple sclerosis. Various treatment options are reviewed, including the use of corticosteroids and interferons. (Adv Stud Med. 2006;6(7D):S687-S693)

Clinically isolated syndromes (CIS) may herald the future development of multiple sclerosis (MS), and it is important to be able to try to determine which patients with CIS will progress and whether early intervention will make a difference in terms of their prognosis. Risk factors for disease progression to clinically definite multiple sclerosis (CDMS) and data from 4 major studies concerning the management of these disorders are reviewed, as are various treatment options, including the use of corticosteroids and interferons. Multiple sclerosis may first manifest with ocular, brain-stem, or spinal cord symptoms, as is illustrated by the following cases.

COMMON PRESENTATIONS OF CIS AS PRECURSORS TO MS: CASE STUDIES

OH is a 23-year-old woman who presents with the complaint of decreased vision in the left eye that has occurred over a 7-day period. In addition, the patient reports pain upon eye movements. On physical examination, her visual acuity is 20/20 OD and 20/80 OS, she has impaired color vision in the left eye, and visual field testing reveals a central scotoma OS. A left afferent pupilary defect is also noted. The funduscopic examination is normal. A magnetic resonance image (MRI) of the brain shows evidence of multiple high-signal abnormalities concentrated in the periventricular area, perpendicular to the ventricles and involving the corpus callosum (Figure 1). Two of these lesions enhance with gadolinium. Imaging also reveals an enlarged, enhancing optic nerve on the affected side (Figure 2).

Comment: This patient presents with the classical findings of optic neuritis and a positive brain MRI consistent with demyelination. On a historical basis, acute visual loss and pain upon eye movements should suggest the diagnosis.
of optic neuritis. This patient also has the hallmark features of an optic neuropathy, including decreased acuity, impaired color vision, a field defect, and an afferent pupil defect. When the optic nerve is normal in the acute presentation, we call the case "retrobulbar neuritis."

The following 2 cases illustrate individuals who, similar to in the case of OH, are at high risk for the development of MS:

BW is a 38-year-old previously asymptomatic, healthy female who presents with horizontal double vision. On examination she is noted to have a sixth nerve palsy on the left. MRI shows high-signal abnormalities consistent with demyelination (4 supratentorial T2 periventricular lesions and one brain-stem lesion at the sixth nerve exit site).

TC, a 36-year-old woman, with no prior neurological history, presents with new-onset quadriparesis, and a C7 sensory level. Serologic studies are negative. On spinal MRI, the sagittal T2 and postcontrast T1-weighted images show a lesion in the spinal cord typical of MS—short segmental involvement of the cervical spinal cord that enhances with gadolinium. The lesion is located at C6 and is oval-shaped and associated with swelling of the cord. MRI of the brain reveals larger lesions concentrated around the periventricular area. The lesion features are consistent with demyelination.

Comment: Both of these patients (1 with a brain-stem presentation and the other with a spinal cord syndrome) are also at high risk for the development of MS.

**Making the Diagnosis and Assessing Risk**

The patients described here are at high risk for the development of MS by virtue of their neurologic symptoms coupled with their positive brain MRI scan. As described in the prior article, there are a number of other conditions that may mimic MS and present with visual loss or other neurologic findings. For example, in young patients, migraine headaches may present with transient neurologic deficits that usually last less than 24 hours. On MRI scan, these individuals may have subcortical lesions, but they are usually not in a pattern typical for MS. In older patients, similar MR findings may be the result of small vessel ischemic disease. Again, the clinical symptoms of these patients are usually atypical for MS. By contrast, it can be difficult to distinguish between patients with collagen vascular disorders or infections and those who have MS because there is considerable overlap in their clinical presentations and MR scans. It is also possible that a
particular patient has a concomitant autoimmune disorder. For instance, Sjögren’s syndrome may occur in association with MS rather than be a distinct entity producing demyelination.

Aside from MRI imaging, how useful are routine diagnostic tests in recognizing MS versus other mimics? Blood tests, such as antinuclear antibody, rapid plasma reagin, angiotensin-converting enzyme, and Lyme titers, chest X rays, and lumbar punctures (LPs) have a low yield in the prototypical case of optic neuritis. However, it may be prudent to perform these tests before committing patients who potentially fall into the category of early or possible MS to long-term immunomodulatory therapy. Specifically with regard to LPs, in this patient population for whom we are trying to establish with some certainty whether they have a potentially recurring demyelinating process, LP may be important, particularly if they have an atypical history or MRI. Once other potential etiologies have been eliminated, the next question is how best to manage their care.

**MANAGEMENT OF THE HIGH-RISK MONOSYMPTOMATIC PATIENT**

There have been 4 class I studies that help clinicians to determine how to manage the monosymptomatic high-risk patient as described earlier in this article: the Optic Neuritis Treatment Trial (ONTT), Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS), Early Treatment of Multiple Sclerosis (ETOMS) trial, and the Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) study.

**CLINICAL TRIAL DATA**

**OPTIC NEURITIS TREATMENT TRIAL**

The investigators for this trial randomly assigned 457 patients with acute optic neuritis to receive oral prednisone for 14 days; intravenous (IV) methylprednisolone for 3 days, followed by oral prednisone for 11 days; or oral placebo for 14 days. During the subsequent 6 months, the investigators found that visual function recovered faster in the group receiving IV methylprednisolone than in the placebo group (especially with regard to the reversal of visual-field defects \( P <.001 \)). Although the differences between the groups decreased with time, the IV steroid group still had slightly better visual fields, contrast sensitivity, and color vision (although not better visual acuity) after 6 months. However, these visual outcome differences were not found at a 1-year evaluation of the data. Although the outcome in the oral-prednisone group did not differ from that in the placebo group, new episodes of optic neuritis were more common in the group receiving oral prednisone than among those receiving IV medication or placebo.

Results from the ONTT indicate that oral prednisone alone is not only an ineffective treatment, but may also increase the risk of new episodes of optic neuritis. The data also demonstrate that IV and oral corticosteroids have no effect on final visual outcome at 1 year, although they do hasten the recovery of visual function by a few weeks. Thus, the decision to use steroids in the setting of optic neuritis for visual recovery alone is an individual one made between clinician and patient. Furthermore, because there is potentially an increased risk of recurrent optic neuritis with oral steroids, it is prudent, if one is to use steroid medications, to administer them intravenously.

Of even further interest in the ONTT study was the finding that, after 2 years, there was a statistically significant reduction in the risk of developing MS among patients who received IV steroids when compared to the oral prednisone and placebo groups (8% vs 15% and 17%, respectively). Unfortunately, at 3 years, the arm receiving IV corticosteroids caught up to the risk of those who had taken placebo or oral prednisone (Figure 3). After 5 years, it was observed
that those patients who harbored high-signal abnormalities on their baseline MRI scan had a higher risk of developing MS than those who had a normal MRI scan—16% of patients who had a normal baseline MRI, 37% of patients who had 1 to 2 signal abnormalities, and 51% of patients with 3 or more signal abnormalities subsequently developed MS.4

Data from the ONTT trial indicate that patients followed for 10 years after an episode of optic neuritis, but with a normal baseline MRI, have an extremely low risk of developing MS if they have no light perception vision, no pain, severe disc edema, disc hemorrhage, or macular exudates at presentation (atypical features for optic neuritis).

Overall, among 388 patients, the 10-year risk of MS was 38% (95% confidence interval, 33%–43%). Patients who had 1 or more typical lesion on the baseline MRI scan of the brain had a 56% risk; those patients with 0 lesions had a 22% risk (P <.001). However, the authors note that, even when brain lesions are seen on MRI, more than 40% of the patients will not develop clinical MS after 10 years. This information is extremely important for patients like OH, in terms of weighing the risks versus the benefits of initiating prophylactic treatment when a patient presents with optic neuritis or other initial central nervous system demyelinating event.5 It should be pointed out that the ONTT enrolled a heterogenous group of patients that had normal and abnormal MR scans at baseline and thus may not represent a typical cohort of high-risk monosymptomatic patients. Furthermore, brain MR scans were done only at baseline and in approximately 70% of patients 10 years later. Because follow-up was done over the phone in years 6 to 9, it is possible that the conversion to MS could have been underestimated in this clinical study.

**CHAMPS Study**

The CHAMPS study evaluated the 3-year risk of developing CDMS following isolated optic neuritis, spinal cord, or brain-stem syndromes. Three hundred eighty-three monosymptomatic patients were followed prospectively for the development of definite MS.6

All patients in this study were treated with IV corticosteroids, and investigators examined whether initiating treatment with interferon beta-1a (Avonex, Biogen Idec, Cambridge, Mass) at the time of the first demyelinating event made a difference in terms of prognosis. Patients were candidates for the study if they had had a first acute clinical demyelinating event (optic neuritis, incomplete transverse myelitis, or brain-stem or cerebellar syndrome) and evidence of prior subclinical demyelination on brain MRI. After initial treatment with corticosteroids, 193 patients were randomly assigned to receive weekly intramuscular injections of Avonex (30 µg) and 190 were assigned to receive weekly injections of placebo. The study endpoints were the development of CDMS and changes in findings on brain MRI. The 3-year cumulative CDMS was significantly lower (P = .002) in the Avonex than in the placebo group. The risk of developing MS was reduced by 44% (Figure 4).

As compared to the patients in the placebo group, patients in the Avonex group had a relative reduction in the volume of brain lesions (P <.001), fewer new or enlarging lesions (P <.001), and fewer gadolinium-enhancing lesions (P <.001) at 18 months. In subgroup analyses, it was demonstrated that regardless of the patient’s initial presentation (optic neuritis, spinal cord disease, or brain-stem disease), patients derived clinical benefit from combination therapy with Avonex and IV corticosteroids. The clinical benefit was most evident in the group with spinal cord lesions. On the other hand, the MRI benefit was most appar-
ent in the group with optic neuritis (Figure 5). Tintore et al confirmed the findings of the CHAMPS study, following 320 patients with CIS prospectively for a median of 39 months. Conversion to CDMS was the same for all CIS—once their brain MRI is abnormal, approximately 70% of patients will develop MS in a 3-year time frame.

The next question investigators of the CHAMPS study evaluated was whether MRI criteria could be used to predict which patient groups would have the greatest treatment effect with a combination of IV steroids and Avonex. Those patients with gadolinium enhancement at baseline appeared to derive the greatest benefit. The other important question to address in terms of whether to treat patients with CIS that may or may not ultimately develop into CDMS is whether MRI can be used to identify the low-risk groups. In other words, given the potential adverse events and costs of therapy, are there patients with early signs or symptoms who should not be treated with interferon? From the CHAMPS cohort, we could not identify a subgroup with a very low risk of developing MS. Even patients with a low number of baseline lesions (2–8) and no gadolinium enhancement still have a 2-year risk of developing MS in the range of 60% to 70%.

The Controlled High-Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance (CHAMPIONS) study, which was an extension of the CHAMPS study, attempted to address the long-term benefits of early treatment. Investigators evaluated 203 patients comparing those who had received immediate treatment with Avonex with the group that received Avonex in a delayed fashion to determine if there would be a “penalty” for waiting an average of 2.5 years before initiating therapy. In the immediately treated group, there was a 43% reduction in CDMS and a 42% reduction in new or enlarging MR lesions as compared to the group that received delayed treatment at 5 years. The delayed treatment group also had double the relapse rate of the immediately treated group.

**EARLY TREATMENT OF MULTIPLE SCLEROSIS STUDY**

The ETOMS was another study that evaluated the use of interferon beta-1a in a lower dose formulation (Rebif, Serono, Geneva, Switzerland) to determine its effect on the subsequent development of CDMS. Patients with a first neurologic episode and an MRI scan suggestive of MS ($n = 241$) were randomized to receive Rebif (22 µg) or placebo subcutaneously once weekly for 2 years. The primary endpoint was the rate of development of CDMS, and there was a significant (24%; $P = .047$) difference in the conversion to CDMS (569 days in the interferon group and 252 in the placebo group; Figure 6). Fewer patients developed CDMS in the interferon group than in the placebo group (52/154 [34%] vs 69/154 [45%]; $P = .047$). The annual relapse rates were 0.33 and 0.43 ($P = .045$); the number of new T2-weighted MRI lesions

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**Figure 5. Comparative Outcomes for CDMS According to Initial Presentation and by Treatment Groups: Avonex Versus Placebo**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Avonex</th>
<th>Placebo</th>
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<tr>
<td>Optic Neuritis</td>
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<td>Brain-Stem</td>
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<td>Spinal Cord</td>
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<td>Cerebellar</td>
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*All patients were also receiving intravenous steroids. CDMS = clinically definite multiple sclerosis.

**Figure 6. ETOMS: Primary Outcomes for CDMS at 2 Years**

CDMS = clinically definite multiple sclerosis; ETOMS = Early Treatment of Multiple Sclerosis.
and the increase in lesion burden were significantly lower with active treatment (63%; \( P = .002 \)). Although there were important differences between the CHAMPS and ETOMS studies, both studies confirmed that early intervention with interferon beta-1a makes a difference in patient prognosis.

**BENEFIT STUDY**

The BENEFIT study was a double-blind, randomized, phase III investigation of 487 patients presenting with monofocal or multifocal symptoms and a screening MRI scan suggestive of MS to determine if early treatment would make an impact on disease progression. The patients were randomized to receive interferon beta-1b (Betaseron, Berlex, Montville, NJ) 250 \( \mu g \) or placebo subcutaneously every other day for up to 2 years. They were then evaluated to determine the effect of Betaseron in terms of the following endpoints: time to CDMS based on a relapse, Expanded Disability Status Scale (EDSS) progression of 1.5 points, or diagnosis of definite MS according to the McDonald criteria. Results from the study showed that treatment significantly delayed the development of CDMS. After 2 years, 45% of the placebo group compared to 28% in the Betaseron group \( (P < .0001) \) had developed CDMS, a relative risk reduction of 50% in the group treated with Betaseron. Utilizing the McDonald criteria, patients in the Betaseron group were less likely to develop MS, with 85% of placebo patients progressing to MS compared to 69% for Betaseron-treated patients \( (P < .0001) \).

**LONG-TERM FOLLOW-UP OF PATIENTS WITH CLINICALLY ISOLATED DEMYELINATING SYNDROME**

To ascertain what occurs with these patients over time, Brex et al studied 71 patients with clinically isolated demyelinating syndrome over 14 years via serial MRI scans.\(^9\) The authors concluded that the most important predictive test for these patients is their baseline brain MRI—the presence of lesions as determined by T2-weighted MRI increases the likelihood that MS will develop. Eighty-eight percent of patients with an abnormal baseline MRI went on to develop CDMS as compared to only 19% whose MRIs were normal at the onset. The authors found that the number of lesions did not predict the risk of CDMS. Furthermore, 98% of patients with an abnormal baseline had a new clinical or radiologic event.\(^9\)

**CONCLUSIONS**

As a result of research conducted by Trapp et al, we now recognize that axonal injury occurs quite prominently in MS, and it occurs in the very earliest stages.\(^14\) In a study published by Kuhlmann et al, it was demonstrated that the greatest amount of axonal loss in acute lesions was seen in those patients with disease duration of less than 1 year.\(^15\) In another study by Paolillo et al, those patients with the greatest amount of gadolinium activity on brain MRI also had the greatest amount of brain atrophy, suggesting that inflammation (as evidenced by gadolinium enhancement) correlates with atrophy.\(^16\) Of note, atrophy appeared only after a delay of months following acute inflammation, suggesting that gadolinium-enhancing lesions may be predictive of future brain atrophy.

As we continue to evaluate the role of early and aggressive intervention in patients with CIS, new technologies and measurement techniques will become increasingly important. For example, contrast sensitivity testing for vision and the Multiple Sclerosis Functional Composite scale for activity capture disease and disability data not adequately measured by standard evaluations, such as the EDSS. Optical coherence tomography now provides axonal information on the retinal nerve fiber layer revealing early subclinical pathology.\(^17\) Although not routinely done today, formal cognitive testing demonstrates that 66% of patients, even early on, may have cognitive dysfunction strengthening the position to treat early. Finally, improved MRI techniques, including perfusion imaging, diffusion tensor imaging, and determination of N-acetyl aspartate levels, show “silent” changes in normally appearing occipital white matter that all may help with earlier surveillance, diagnosis, and treatment of CIS before they convert to CDMS.

**REFERENCES**