Optic Neuritis and Multiple Sclerosis

The investment of the National Eye Institute in the Optic Neuritis Treatment Trial continues to pay dividends. In this issue of the ARCHIVES, the Optic Neuritis Study Group reports on the risk of developing multiple sclerosis (MS) after an attack of isolated optic neuritis. This issue is of great importance to patients and physicians and, as the authors acknowledge, has been addressed in prior studies, some of which yielded similar results. However, with its impressive number of subjects, high retention rate, prospective design, standardized procedures, and well-defined criteria, the Optic Neuritis Treatment Trial has produced results that will likely be influential.

The Optic Neuritis Study Group provides 10- to 13-year follow-up on a cohort of patients who had experienced an attack of acute optic neuritis unaccompanied by other clinical evidence of MS. Follow-up was available on 87% of the original 388 patients, a remarkable achievement in itself. The risk of developing MS by clinical criteria was 38% at 10 years and 40% at 12 years. Magnetic resonance imaging (MRI) findings at the time of the acute optic neuritis episode correlated with the risk. Patients with at least 1 brain lesion had a 10-year risk of 56%, whereas 22% of those with normal brain MRI results developed clinical MS during that interval.

See also page 944

Important and accurate as these data are, some caveats seem appropriate. With a chronic disease such as MS, which can smolder for decades, a 10- to 13-year follow-up period cannot be considered definitive. Despite the diminishing likelihood of conversion to MS with time (Figure 1 of original), one can safely predict that some seemingly MS-free subjects at 10 to 13 years will subsequently develop clinical MS.

In the absence of a definitive test to establish the diagnosis of a disease, physicians must depend on criteria that are in the final analysis somewhat arbitrary. This is the case with regard to the diagnosis of MS. The Optic Neuritis Treatment Trial based its diagnoses of MS strictly on clinical signs and symptoms. However, alternate techniques for diagnosing MS incorporate the results of MRI, cerebrospinal fluid analysis, and electrophysiological studies; these methods are currently used by physicians and investigators. It is likely that the risk of MS would have been much higher in the patients in the Optic Neuritis Treatment Trial if these paraclinical findings had also been considered, although we cannot answer the more important question of whether the results of the subgroup analyses would change. Presumably, future reports from the Optic Neuritis Study Group will illuminate this issue.

During follow-up of this large cohort, the investigators found no unusual occurrence of any disease other than MS. The patients without brain lesions on MRI scans had a low risk of developing clinical MS during the study interval, and no doubt some patients with optic neuritis will never develop clinical findings of MS. For many of the latter patients, their attack of optic neuritis could represent either a one-time demyelinating lesion or a portent of MS that might be diagnosed only with paraclinical investigation. However, the presence of Optic Neuritis Treatment Trial subgroups with a very low likelihood of developing MS also raises the possibility that some of these patients may not even have optic neuritis. The clinical symptoms and signs of optic neuritis overlap with those of disorders such as nonarteritic anterior ischemic optic neuropathy, neuroretinitis, and papillophlebitis, among others. Even experienced neuro-ophthalmologists can misdiagnose optic neuritis.

The questions of how to diagnose MS and when the disease begins would be merely of academic interest were it not for 2 rather recent developments. First, there is excellent evidence that following the initial demyelinating attack, even asymptomatic patients experience a progressive subclinical decline. Neurologists now recognize that MS is not only a demyelinating disease, as it was considered for decades, but also a disease of axons; that is, a neurodegeneration. Seminal articles in the British and American literature have described biochemical and anatomical alterations in the axons within MS lesions. This axonal degeneration would explain the irreversible nature of the clinical impairment seen in the later stages of relapsing-remitting MS as well as the downhill course of progressive MS. It has also become clear that although most patients with relapsing-remitting MS retain good neurological function early in their disease course, there is concomitant hidden damage manifested by progressive loss of cerebral volume on MRI scans. In most cases MS appears to be a drama with acts and intermissions, but in reality the tragedy continues even when the house lights are up.

The second development is in the pharmacological arena. New treatments for suppressing inflammation by modulating the immune system have been shown to decrease the relapse rate and in some cases to retard neurological disability. These include the interferon drugs (interferon beta-1a and interferon beta-1b) as
well as glatiramer acetate, an amino acid copolymer, and are self-administered by injection on a daily to weekly basis depending on the drug. Although ineffective in stroke and head trauma, neuroprotection, or treatment to prevent neuronal loss associated with neurodegeneration, has proved effective for chronic disorders such as amyotrophic lateral sclerosis\textsuperscript{9} and Alzheimer disease.\textsuperscript{10}

With neurodegeneration progressing even in asymptomatic patients who have MS and with treatments becoming available, it becomes critical to make the diagnosis as accurately and early as possible. According to the results of the Optic Neuritis Treatment Trial, we would advise the following. First, immunomodulatory treatments should be deferred in a patient with monosymptomatic optic neuritis who has a normal MRI result and marked optic disc swelling, retinal edema or exudates, or lack of pain. Because the fundus findings are important, it would be advisable for all patients suspected of having optic neuritis to undergo a dilated fundus examination by an opthalmologist. Second, even a single brain lesion on a T2-weighted MRI scan is sufficient to consider initiating immunomodulatory treatment in a patient with typical optic neuritis.

Despite the foregoing, we still have not determined the best treatment for patients with optic neuritis. Even if immunomodulatory agents are used, we do not know the long-term outcome in terms of disability, either visual or systemic. We do not have the data to prove that early treatment is superior to late even though this would be expected from studies showing subclinical progression and axonal loss in MS. Finally, although we now have ways of identifying patients at relatively low risk for developing MS, we do not have a good decision-analytic framework to decide who else would not benefit sufficiently from treatment. Only once these questions are answered, with data from the Optic Neuritis Treatment Trial and other randomized clinical trials, will we best be able to treat our patients and thus sustain them to the final curtain.

Leonard A. Levin, MD, PhD
Madison, Wis

Simmons Lessell, MD
Boston, Mass

Dr Levin has served as a consultant on neuroprotection to several pharmaceutical companies.

Corresponding author: Leonard A. Levin, MD, PhD, University of Wisconsin Medical School, 600 Highland Ave, Room K6/456 CSC, Madison, WI 53792-4673.

REFERENCES