Acute demyelinating optic neuritis

Rod Foroozan, MD, Lawrence M. Buono, MD, Peter J. Savino, MD, and Robert C. Sergott, MD

Acute demyelinating optic neuritis associated with multiple sclerosis (MS) is the most common cause of inflammation of the optic nerve. The Optic Neuritis Treatment Trial (ONTT) has provided important clinical data on the use of corticosteroids, and demonstrated that patients with characteristic inflammatory lesions within the brain on magnetic resonance imaging had a greater chance of developing clinically definite MS (CDMS).

The current approach to patients with optic neuritis has been modified by the results of the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS). Patients with an initial clinical episode of demyelination (optic neuritis, incomplete transverse myelitis, or brain-stem/cerebellar syndrome) and at least two characteristic demyelinating lesions within the brain were randomized to receive interferon β-1a or placebo after initial treatment with intravenous corticosteroids. At the 3-year point patients treated with interferon β-1a showed a 50% less risk of CDMS. The results of this study have set the standard for patients with a first bout of demyelinating optic neuritis.

Optic neuritis is, with the exception of glaucoma, the most frequent optic neuropathy encountered in general ophthalmic practice. Although the term optic neuritis literally means inflammation of the optic nerve from any cause, by convention it has come to mean optic nerve affliction due to demyelination.

Other conditions (syphilis, sarcoidosis, Lyme disease, sinusitis) can produce inflammation of the optic nerve, but this review deals exclusively with demyelinating optic neuritis.

Incidence

The annual incidence of demyelinating optic neuritis in a population-based study from Olmstead County, Minnesota is approximately 5:100,000 person-years, with a prevalence of 115:100,000 [1]. This incidence compares with that estimated for anterior ischemic optic neuropathy, which is 0.3% of patients older than 50 years of age, and for glaucoma, approximately 0.5% to 1% of the population.

Optic neuritis treatment trial

The most reliable information we have concerning optic neuritis comes from the Optic Neuritis Treatment Trial (ONTT), a study that began in 1988 [2]. This prospective, multicentered, National Eye Institute–sponsored study remains the gold standard in defining the clinical disorder of optic neuritis. In the ONTT, 15 clinical centers in the United States enrolled 457 patients between July 1, 1988 and June 30, 1991. Nine of these patients were ultimately found to be ineligible for the study, so that the data from the remaining 448 patients provide the basis for much of our current knowledge regarding optic neuritis.

Patients were admitted to the ONTT if they had the following eligibility criteria:

- The presence of acute unilateral optic neuritis of unknown or demyelinating origin
- Visual symptoms lasting 8 days or less
- Ages between 18 and 46 years
- A relative afferent pupillary defect (RAPD) and visual field defect in the affected eye

Each patient underwent a series of visual function and laboratory tests (antinuclear antibodies, fluorescent tre-
ponemal antibody absorption titers, chest radiograph) and a magnetic resonance imaging (MRI) scan. A clinical neurologic evaluation was performed on each enrollee to determine whether the patient had “no,” “possible,” “probable,” or “definite” multiple sclerosis. The data collected at the 6-month visit were the major measurements of outcome [3].

Patients who satisfied the inclusion criteria were then randomized to one of three treatment regimens:

- Intravenous methylprednisolone 250 mg every 6 hours for 3 days, followed by oral prednisone 1 mg/kg of body weight per day rounded out to the nearest 10 mg for 11 days
- Oral prednisone (1 mg/kg/d for 14 days)
- Oral placebo received on the same schedule as the oral prednisone group

**Visual acuity**
Loss of visual acuity occurred in approximately 90% of patients with optic neuritis [2]. The level of acuity loss ranged from minimal to no light perception. The visual loss was usually accompanied by ocular discomfort or pain (see later) and often progressed over 7 to 10 days after the onset of symptoms. Progressive deterioration of acuity after approximately 2 weeks is highly uncharacteristic of optic neuritis, and if this occurs, the diagnosis of optic neuritis must be viewed with suspicion. A minority of patients retained excellent central acuity but had other signs of optic neuritis, including a RAPD and visual field defect.

Improvement in visual acuity usually began within the first month of enrollment. The best predictor of the prognosis for visual recovery was the baseline acuity at enrollment in the study. More than 90% of all patients enrolled in the study achieved a final visual acuity of 20/40 or better, whereas 64% of patients with light perception or no light perception at the time of study enrollment achieved the same visual outcome.

**Color vision**
Color vision is usually abnormal in patients with optic neuritis. In fact, color perception may be affected disproportionately compared with visual acuity in some patients. It is distinctly unusual to have poor acuity from optic neuritis and to maintain normal color vision. In the ONTT, the Ishihara pseudoisochromatic color plate test findings were abnormal in 88% of the affected eyes. Even when vision was 20/20 or better, abnormal results of color plate testing were noted in approximately 51% of eyes.

**Contrast sensitivity**
Contrast sensitivity was a very sensitive marker for optic neuritis. Abnormal contrast sensitivity was encountered in 99% of the patients with visual acuity less than 20/20 and in 87.2% of patients with acuity of 20/20 or better [2]. However, abnormal contrast sensitivity can be seen in other disorders (amblyopia and cataract) and is not specific for optic neuritis.

**Pupillary testing**
It is a good general rule that patients suspected of having optic neuritis must have an RAPD on the affected side. Patients with bilateral symmetrical optic nerve disease would be an exception to this rule. The absence of an RAPD in a patient with unilateral or asymmetric visual acuity or field loss makes the diagnosis of optic neuritis untenable.

The RAPD can be measured with neutral density filters over the unaffected eye. This provides a quantitative measure that can be followed to determine whether the optic neuropathy is stable, improving, or worsening.

**Pain**
Orbital or ocular pain with eye movement is a typical finding in optic neuritis. This pain precedes the onset of visual loss or may appear concomitant with it. Ocular pain was present in approximately 90% of patients in the ONTT. Pain on eye movement, however, is not specific for optic neuritis, but also may be seen in other optic neuropathies such as anterior ischemic optic neuropathy [4].

**Visual field abnormalities**
Prior to the ONTT, the central scotoma was presumed to be typical of optic neuritis. The ONTT documented that a variety of visual field abnormalities may be seen in patients with optic neuritis [5]. The visual field defects found in the 448 patients enrolled in the ONTT were characterized as being “diffuse” or having specific patterns of visual field loss. The main patterns of visual field abnormality are as follows:

- Diffuse: 48.2%
- Localized defects, including altitudinal or other nerve fiber bundle defects: 20.1%
- Central or cecocentral scotomas: 8.3%
- Other: 23.2%

Interestingly, visual field abnormalities were seen in 308 (68.8%) of fellow eyes of the 448 patients enrolled. Many of these visual field defects in the contralateral eye resolved during the follow-up period, indicating that they were not remnants of previous subclinical attacks of optic neuritis [6]. The visual field deficits usually recover, and at the 1-year follow-up visit of the ONTT, 55.9% of previously abnormal visual fields were normal [7].
Fundus appearance

Patients with optic neuritis may have an optic disc that is normal (retrobulbar optic neuritis), or the optic disc may be swollen (papillitis). The presence of a pale optic disc indicates a remote event and is not a valid disc appearance in the patient with optic neuritis causing recent visual loss.

In the ONTT, approximately two thirds of the patients had normal optic discs and one third had papillitis. Para-papillary hemorrhages and retinal exudates were uncommon findings. Exudate in the pattern of a macular star (neuroretinitis) should prompt an evaluation for other causes of optic neuritis and is distinctly uncommon in cases of demyelinating optic neuritis.

Treatment of optic neuritis

Prior to the publication of the ONTT, a survey of general ophthalmologists indicated that 65% of these physicians treated patients with optic neuritis with some form of systemic corticosteroids. Approximately 35% recommended no treatment [8]. In addition, patients were being treated with different regimens of corticosteroids; some patients were being treated with high doses of intravenous corticosteroids, (so-called pulse therapy) whereas others were treated primarily with oral corticosteroids.

The ONTT evaluated the efficacy of the high-dose intravenous treatment as well as the oral prednisone therapy against an oral placebo. The questions that were posed in the study were the following:

Does treatment of optic neuritis with either form of steroid reduce permanent optic nerve damage? Does either treatment speed recovery? Are the complications of steroid treatment insignificant in relation to the magnitude of the treatment effect? [8]

The results of the three “treatment” regimens were reported at 6 months [3] and at 1 year [9]. The findings were as follows:

Visual acuity at 1 year was 20/40 or better in 95% of the placebo group, 94% of the intravenous methylprednisolone group, and 91% of the oral prednisone group. There was no statistically significant difference between these groups. Therefore it was concluded that treatment of optic neuritis with corticosteroids does not improve the ultimate visual outcome. It was noted that patients who were treated with the intravenous methylprednisolone followed by an oral corticosteroid taper recovered vision at a more rapid rate, but the end visual acuities were the same in all three groups.

Patients who were treated with oral prednisone alone, while not achieving any improved beneficial effect in final visual recovery, did experience a higher rate of new attacks of optic neuritis in the initially affected and fellow eyes. It was therefore recommended that oral prednisone alone should not be used as a treatment for optic neuritis [3].

Associated illnesses

As part of the ONTT, testing was done in an attempt to detect nondemyelinating causes of optic neuritis, including collagen vascular disease, syphilis, and sarcoidosis. Lumbar puncture with examination of the cerebrospinal fluid was optional and was performed in 141 patients. The laboratory tests performed included antinuclear antibodies, chest radiographs, and syphilis serology. The laboratory data indicated that in the presence of “typical” optic neuritis, these additional tests are not necessary [3].

Association of multiple sclerosis and optic neuritis

One of the most important questions when dealing with a patient with optic neuritis has been “Does this represent the first attack of multiple sclerosis?” The ONTT and subsequently the Longitudinal Optic Neuritis Study (LONS) [10,11] addressed this issue.

On admission to the ONTT, patients were evaluated by a neurologist for the presence of multiple sclerosis. During the follow-up periods, they were re-examined to determine whether their neurologic status had changed and whether subsequent attacks of neurologic dysfunction could be identified to document the presence of multiple sclerosis.

The advent of MRI has dramatically changed the approach to the diagnosis of multiple sclerosis. It has long been known that patients with multiple sclerosis have characteristic lesions in the cerebral white matter (Fig. 1). It has also been recognized that patients with isolated optic neuritis and no other signs or symptoms of multiple sclerosis can have identical white matter lesions. All patients enrolled in the ONTT underwent initial unenhanced MRI scanning to identify the presence or absence of these lesions. Although the lesions were graded into five categories, from no lesions to four or more lesions, the overall significant difference was between a “normal” (no lesions) MRI scan and an “abnormal” MRI scan (showing four or more lesions). Forty-one percent of the scans were normal. This is a much higher percentage of normal scanning than in previous studies and may be the result of the ONTT patients being enrolled relatively early in the course of their disease, within 8 days of the appearance of their initial visual symptom [12]. Subsequent follow-up of the ONTT patients in the LONS further defined the association between optic neuritis and the eventual development of multiple sclerosis.
An unsuspected and important finding of the ONTT concerned the subsequent development of clinically definite multiple sclerosis (CDMS) in the enrolled patients. The patients with abnormal MRI scans who were treated with intravenous methylprednisolone developed CDMS at a much lower rate than similar patients in the other two treatment groups [13]. This protective value of intravenous methylprednisolone did not last beyond the 2-year period. After 2 years, the rate at which the patients developed CDMS was statistically the same in all three treatment groups.

The only prognostic indicator of the development of CDMS was the number of lesions seen on the MRI scan (lesion load) performed on enrollment. At the 5-year point, 16% of patients with normal MRI scans at study entry had developed CDMS. In contrast, 51% of patients with three or more lesions on their entry MRI scan had developed CDMS.

Cerebrospinal fluid analysis
Examination of the cerebrospinal fluid in patients with optic neuritis to detect further indications of risk factors for developing CDMS (oligoclonal banding, immunoglobulin G, and myelin basic protein) remains controversial. Because patients with normal lumbar puncture findings may develop CDMS, and likewise patients with abnormal lumbar puncture findings may not develop the disease, it does not appear necessary to perform a lumbar puncture on patients with typical optic neuritis.

Recurrence of optic neuritis
At the 5-year follow-up point, the rates of recurrent optic neuritis were as follows:

- 19% for the affected eye
- 17% for the fellow eye
- 30% for either eye

Recurrences were higher in the group treated with oral prednisone and in those patients who had been diagnosed with CDMS by the 5-year follow-up point.

Recommendations for treatment and investigation of optic neuritis
Using the guidelines of the ONTT and the LONS, a scenario was constructed by which a patient with typical optic neuritis (unilateral visual loss, in the appropriate age range, accompanied by pain on eye movement, with an RAPD, a visual field abnormality, and a normal or swollen optic nerve) should undergo MRI scanning. MRI in typical optic neuritis is not for confirmation of the diagnosis but rather is to be used as a prognosticator, because patients with a high lesion load are at greater risk to develop CDMS over a 5-year period. Patients with a high lesion load are offered intravenous methylprednisolone for 3 days followed by an oral taper to lower their risk of developing CDMS over the subsequent 2 years. This intravenous treatment regimen has become the standard and was actually used as the baseline treatment in a subsequent study that provides further information about the treatment of optic neuritis and the subsequent development of CDMS [14].

Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study
Interferon-β1a has been shown to be beneficial in patients with established multiple sclerosis [15]. The Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) was a multicenter study designed to determine whether weekly injections of interferon-β1a (Avonex; Biogen) could reduce the risk of CDMS. This study examined a cohort of 383 patients who presented with the first acute clinical demyelinating event (optic neuritis, incomplete transverse myelitis, or brain-stem/cerebellar syndrome) and two or more characteristic lesions on MRI. Optic neuritis was the presenting event in 50% of these patients. This subgroup was reported separately (see later) [16]. The patients reported in the CHAMPS were randomized, within
27 days after the onset of symptoms, into one of two treatments groups:

Initial treatment with intravenous methylprednisolone and an oral taper followed by weekly intramuscular injections of 30 µg of interferon-β1a. Same initial treatment followed by weekly injections of a placebo.

At 3 years after the onset of treatment, the cumulative probability of CDMS was 35% in the interferon-β1a group and 50% in the placebo group (Fig. 2). Patients in the interferon-β1a group also had fewer MRI lesions and fewer new or enlarging lesions at 18 months. There was also a decrease in the number of gadolinium enhancing lesions at the 18-month follow-up [16].

These data have had a significant impact on how patients with optic neuritis are treated. Many physicians at this juncture, when presented with a patient with optic neuritis, will obtain an MRI scan and, if this shows two or more white matter lesions characteristic of demyelinating disease, go on to step two. In step two, the patient is placed on intravenous methylprednisolone (a total of 1 gm/day) for 3 days followed by an oral taper similar to the ONTT. During this period of time, the patient is offered treatment with interferon-β1a.

There is controversy about this approach to patients with typical optic neuritis, but one characteristic MRI lesion. There are side effects of the medication, especially a flu-like syndrome, which developed in 50% of patients in the CHAMPS. Additionally, the relatively high cost of the drug may prevent the widespread adoption of the treatment. Some practitioners have suggested that, in the absence of additional clinical deficits, these patients should undergo repeat neuroimaging to attempt to document the onset or progression of demyelinating lesions. The timing and frequency of additional neuroimaging has yet to be defined.

References


