
Introduction

Optic neuritis is a term used to refer to inflammation of the optic nerve. When it is associated with a swollen optic disc, it is called papillitis or anterior optic neuritis. When the optic disc appears normal, the terms retrobulbar optic neuritis or retrobulbar neuritis are used. Acute optic neuritis is by far the most common type of optic neuritis that occurs throughout the world and is the most frequent cause of optic nerve dysfunction in young adults. Much of our knowledge regarding this form of optic neuritis was obtained from the Optic Neuritis Treatment Trial (ONTT). The investigators in this trial enrolled 455 patients with acute unilateral optic neuritis and followed them for 15 years. Although the primary objective of the trial was the assessment of the efficacy of corticosteroids in the treatment of optic neuritis, the results have also provided information about the clinical profile of optic neuritis, its natural history, and its relationship to multiple sclerosis (MS). This article reviews much of what we have learned from the ONTT and other sources in regard to the diagnosis and treatment of optic neuritis as well as the visual and neurologic prognosis following an attack of optic neuritis.

Demographics

The annual incidence of acute optic neuritis is estimated in population-based studies to be between 1 and 5 per 100,000.^[1] In Olmstead County, Minnesota, where the Mayo Clinic is located, the incidence rate is estimated to be 5.1 per 100,000 person-years and the prevalence rate 115 per 100,000.^[2] The majority of patients with acute optic neuritis are between the ages of 20 and 50 years, with a mean age of 30 to 35 years; however, optic neuritis can occur at any age.^[3] Females are affected more commonly than males by a ratio of approximately 3:1.^[3]

Which of the following is *not* typically a feature of acute optic neuritis?

- Sudden loss of central vision
- A central or peripheral visual field defect
- Normal pupillary responses to light stimulation



Pain on movement of the eye

Clinical Presentation

The 2 major symptoms in patients with acute optic neuritis are loss of central vision and pain in and around the affected eye.^[3,4]

Loss of central visual acuity is reported by over 90% of patients. Vision loss is typically abrupt, occurring over several hours to several days. Progression over a longer time can occur but should make the clinician suspicious of an alternative disorder. The degree of visual loss varies widely from minimal reduction to complete blindness with no perception of light. The majority of patients describe diffuse blurred vision, although some recognize that the blurring is predominantly central. Occasionally, patients complain of a loss of a portion of peripheral field, such as the inferior or superior region, often to 1 side. The visual loss is monocular in most cases, but in a small percentage, particularly in children, both eyes are simultaneously affected.

Pain in or around the eye is present in more than 90% of patients with acute optic neuritis.^[3-5] It is usually mild, but it may be extremely severe and may even be more debilitating to the patient than the loss of vision. It may precede or occur concurrently with visual loss, usually is exacerbated by eye movement, and generally lasts no more than a few days. The presence of pain is a helpful differentiating feature from other causes of optic neuropathies such as anterior ischemic optic neuropathy, which typically produces painless visual loss.^[6]

Up to 30% of patients with optic neuritis experience positive visual phenomena, called photopsias, both at the onset of their visual symptoms and during the course of the disorder.^[3] These phenomena are spontaneous flashing black squares, flashes of light, or showers of sparks, sometimes precipitated by eye movement or certain sounds.

Examination of a patient with acute optic neuritis reveals evidence of optic nerve dysfunction. Visual acuity is reduced in most cases, but varies from a mild reduction to no light perception. Contrast sensitivity and color vision are impaired in almost all cases. The reduction in contrast sensitivity often parallels the reduction in visual acuity, although in some cases, it is much worse. The reduction in color vision is often much worse than would be expected from the level of visual acuity.^[7] Visual field loss can vary from mild to severe, may be diffuse or focal, and can involve the central or peripheral field. Indeed, almost any type of field defect can occur in an eye with optic neuritis, including central and cecocentral scotomas, altitudinal and arcuate defects, diffuse field loss, and even hemianopic defects.^[8]

A relative afferent pupillary defect is demonstrable with the swinging flashlight test in all unilateral cases of optic neuritis.^[9] When such a defect is not present, there is either a coexisting optic neuropathy in the fellow eye (eg, from previous or concurrent asymptomatic optic neuritis) or the visual loss in the affected eye is not caused by optic neuritis or any other form of optic neuropathy.

Patients with optic neuritis also can be shown to have a reduced sensation of brightness in the affected eye. This state can be ascertained either by simply asking them to compare the brightness of a light shined in one eye and then the other, or by more complex tests using polarized lenses or flickering lights of varying frequencies.

About one third of patients with acute optic neuritis have some degree of disc swelling (Figure 1).^[3,4] The optic disc may be slightly or markedly blurred; however, the degree of disc swelling does not correlate with the severity of either visual acuity or visual field loss.

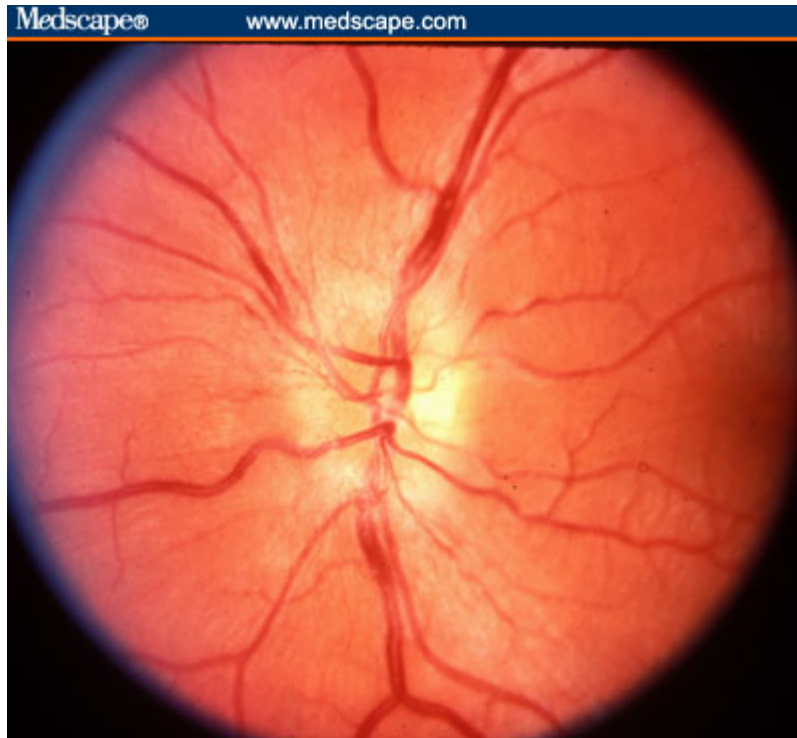


Figure 1. Color photograph of a patient with acute anterior optic neuritis (papillitis). Note swelling of the optic disc, unassociated with peripapillary hemorrhages. Disc or peripapillary hemorrhages and segmental disc swelling are less common in eyes with acute optic neuritis than in eyes with anterior ischemic optic neuropathy. The majority of patients with acute optic neuritis have a normal optic disc in the affected eye unless they have had a previous attack of acute or asymptomatic optic neuritis. Over approximately 4 to 6 weeks, the optic disc in an eye with acute optic neuritis may become or remain normal or become pale, even as the visual acuity and other parameters of vision improve. The pallor may be diffuse or located to a particular portion of the disc, most often the temporal region (Figure 2).



Figure 2. Color photograph of a patient 3 months after an attack of acute optic neuritis. Note pallor of the temporal aspect of the optic disc.

What is the most important diagnostic study to perform in a patient with presumed acute optic neuritis?

- Computed tomography
- Magnetic resonance imaging
- Lumbar puncture
- Serologic test for syphilis

Diagnostic Studies

Studies in patients with presumed acute optic neuritis are usually performed for 1 of 3 reasons: (1) to determine if the cause of the optic neuropathy is something other than inflammation, particularly a compressive lesion; (2) to determine if a cause other than demyelination is responsible for inflammation of the optic nerve; or (3) to determine the visual and neurologic prognosis of optic neuritis.

With the widespread availability of magnetic resonance imaging (MRI), computed tomography (CT) has little or no role in the evaluation of patients with presumed optic neuritis. MRI can reveal demyelinating lesions of the optic nerve, manifesting as foci of T2-bright signal, areas of enhancement, and even optic nerve enlargement. These lesions are nonspecific, and a similar appearance can be observed in patients with infectious and other inflammatory optic neuropathies. The most important application of MRI in patients with optic neuritis, however, is the identification of signal abnormalities in the white matter of the brain, usually in the periventricular region, consistent with demyelination (Figure 3).^[10] MRI is the strongest predictor of the eventual development of MS in patients with acute isolated optic neuritis.^[11]

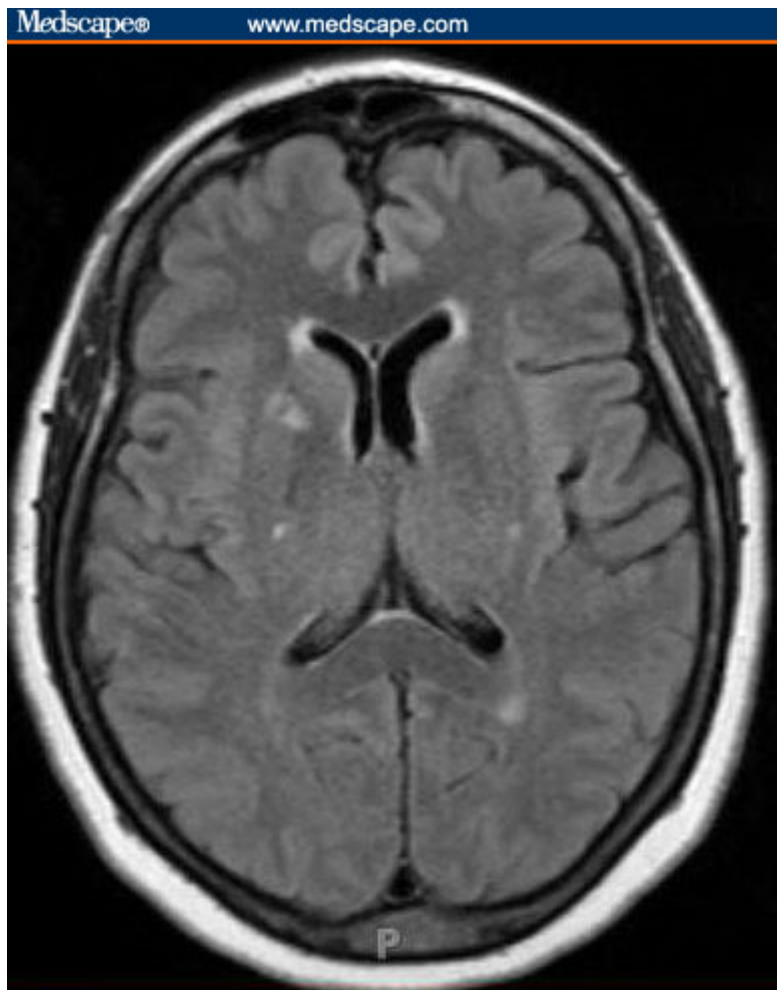


Figure 3. Magnetic resonance imaging (T2-weighted axial cut) shows multiple white-matter lesions in both cerebral hemispheres, including the periventricular regions. Other than MRI, most diagnostic tests are unhelpful in differentiating acute demyelinating optic neuritis from the less common systemic and local infectious and inflammatory optic neuropathies. The vast majority of patients with optic neuritis caused by these latter disorders can be identified

(or at least suspected) simply by performing a thorough history. Therefore, diagnostic testing should be performed on a case-by-case basis to detect disorders such as syphilis, sarcoidosis, cat-scratch disease, Lyme disease, or systemic lupus erythematosus.

The role of cerebrospinal fluid (CSF) analysis in the evaluation of patients with acute optic neuritis is not clear. Although the presence of oligoclonal banding in the CSF is associated with the development of MS, the powerful predictive value of brain MRI for MS has reduced the role of lumbar puncture in the evaluation of patients with optic neuritis. Lumbar puncture can help define a very low-risk population for MS if both CSF and MRI are normal.^[12] CSF studies in patients with optic neuritis are mostly useful to detect another inflammatory or infectious disorder.

After an attack of acute optic neuritis, most patients:

- Recover completely
- Complain that they still have visual difficulties
- Are blind in the affected eye
- Develop multiple sclerosis

Visual Prognosis

The natural history of acute idiopathic optic neuritis is to worsen over several days to 2 weeks and then to improve.^[13] The improvement initially is fairly rapid. It then levels off, but further improvement can continue to occur up to 1 year after the onset of visual symptoms. The mean visual acuity 1 year after an attack of otherwise uncomplicated optic neuritis is 20/15, and less than 10% of patients have permanent visual acuity less than 20/40. Other parameters of visual function, including contrast sensitivity, color perception, and visual field, improve in conjunction with improvement in visual acuity.^[13] Most patients, even those who experience another attack of optic neuritis, retain excellent vision for at least 15 years after their first attack of optic neuritis.^[14]

Although the overall prognosis for visual acuity after an attack of acute optic neuritis is extremely good, some patients have persistent severe visual loss after a single episode.^[13] Furthermore, even patients with improvement in visual function to "normal" may complain of movement-induced photopsias or transient loss of vision with overheating or exercise (Uhthoff symptom).^[3,15] Two major hypotheses regarding Uhthoff symptom are that (1) elevation of body temperature

interferes directly with axon conduction, and (2) exercise or a rise in body temperature changes the metabolic environment of the axon which, in turn, interferes with conduction.^[15]

It is important to reassure a patient who has Uhthoff symptom that the symptom never results in permanent visual loss. Thus, if Uhthoff symptom occurs in a patient during exercise, the patient should be told that she or he can continue to exercise without fear of experiencing permanent visual loss as a result. Such a patient may, however, wish to keep a bottle of cold (or ice) water handy while exercising, because drinking it may result in immediate restoration of vision.

Subjectively, patients with recovered optic neuritis frequently complain that their vision in the affected eye is "not right" or "remains fuzzy," or colors are "washed out."^[16] One cause of these symptoms is probably related to subtle abnormalities in the visual field in which patients experience abnormally rapid disappearance of focal visual stimuli and abnormally rapid fatigue in sensitivity. These patients typically complain that when they look at something, it appears as if they have "holes" in their vision.^[17]

About 25% of patients who experience an attack of acute optic neuritis will experience a second attack in that eye or a new attack in the previously unaffected eye.^[3] The risk of a recurrence or a new attack is substantially higher in patients treated with low-dose oral prednisone as opposed to patients who receive no treatment or who are treated with a 3-day course of high-dose (1 g/ day) intravenous methylprednisolone followed by a 2-week course of low-dose (1 mg/kg/day) prednisone.^[18]

Neurologic Prognosis

The risk of developing MS in a patient who experiences an attack of acute optic neuritis is about 75% in women and 34% in men over the subsequent 15-20 years, with the risk being greatest in the first 5 years after the attack.^[19-21] Without question, the most highly predictive baseline factor is the presence of at least 1 lesion in the periventricular white matter of the brain MRI.^[21,22] Other risk factors for the development of MS are white race, a family history of MS, a history of previously ill-defined neurologic complaints, and a previous episode of acute optic neuritis.^[21] However, none of these factors affect the risk of developing MS as much as the results of MRI. Some investigators have found that the younger the age of onset of optic neuritis, the greater the subsequent risk for MS.^[23] Winter onset of optic neuritis may also be a risk factor. Conversely, patients with acute optic neuritis who have a normal brain MRI, severe disc swelling, a macular star, or disc hemorrhages have a very low risk of developing MS, findings that emphasize the role of the ophthalmologist in defining the prognosis of optic neuritis.^[21]

Patients in whom MS develops after an attack of acute optic neuritis nevertheless have an excellent long-term neurologic prognosis. Validated neurologic methods of assessment have demonstrated that the majority of such patients have minimal or no significant neurologic dysfunction as long as 15-17 years following the development of MS.^[22]

Treatment of a patient with acute optic neuritis with oral prednisone in a dose of 1 mg/kg/day should be avoided because:

- It increases the risk of the development of multiple sclerosis
- It prevents recovery of vision
- It causes severe side effects
- It increases the risk of recurrent attacks of optic neuritis

Treatment of Optic Neuritis

Although corticosteroids are the main treatment option for patients with acute idiopathic optic neuritis, the prognosis for visual recovery after an attack of acute optic neuritis is excellent without treatment.^[14,18] If corticosteroids are used, treatment should be delivered first with 3 days of intravenous methylprednisolone in a dose of 1 g/day followed by a 2-week course of oral prednisone at a dose of 1 mg/kg/day with a taper over 3 days. This regimen does not affect the ultimate visual outcome of a patient, but it does speed recovery of vision compared with no treatment.^[18] It should also be emphasized that patients who experience an attack of acute optic neuritis should not be treated with low-dose oral prednisone alone. This mode of treatment does not result in a better visual outcome or a faster recovery than no treatment. Moreover, it is associated with an increased rate of recurrent attacks of optic neuritis in the previously affected eye and an increased rate of new attacks of optic neuritis in the fellow eye, compared with patients who are not treated or patients who are treated with the IV/oral regimen.^[18]

Another important aspect of treatment for acute optic neuritis is whether it may have an impact on the development of MS. Of note, patients in the ONTT who were treated with the intravenous followed by oral corticosteroid regimen had a reduced rate of development of clinically definite MS during the first 2 years following treatment.^[24] This benefit of treatment was seen only in patients who had abnormal brain MRI at the time of onset of the optic neuritis, and the clinical benefit of the intravenous treatment lessened over time such that by 3 years of follow-up, there was no significant difference in the rate of development of MS among treatment groups. These findings suggest that a patient with acute optic neuritis who has an abnormal brain MRI may benefit in the short term from treatment with the IV/oral steroid regimen.

A number of agents other than or in addition to systemic corticosteroids have been found to reduce the risk of the development of MS following an attack of acute optic neuritis over a longer period of time than corticosteroids alone. The Controlled High-Risk Avonex MS Prevention Study (CHAMPS)^[25,26] was a randomized, double-blind, placebo-controlled trial that enrolled patients with a first demyelinating event (eg, optic neuritis which was present in about 50% of the study population) and 2 or more white-matter lesions on a brain MRI. All patients received the intravenous/oral steroid regimen per the ONTT protocol. They were then randomized to treatment with either interferon-beta-1a or placebo. The group of patients receiving interferon beta-1a had a 44% reduction in the 3-year risk of developing MS compared with those receiving placebo.^[25,26] In addition, patients in the interferon group had fewer new and enhancing brain MRI lesions. The

effects of continued treatment were sustained for up to 5 years following initiation of treatment.^[27] A second prospective study, the Early Treatment of Multiple Sclerosis Study (ETOMS), also found that interferon beta-1a was associated with a reduction in the development of MS.^[28] In view of these findings, it is appropriate for all patients with acute optic neuritis who have white-matter lesions on MRI to be referred to a neurologist for consideration of treatment with interferon beta-1a.

Summary of Management Recommendations

In a patient with typical features of optic neuritis, a clinical diagnosis can be made with a high degree of certainty without the need for ancillary testing. Patients who have a single attack of acute optic neuritis, particularly those with an abnormal brain MRI, are at increased risk for the development of MS. Such patients may be considered for a course of intravenous steroids followed by oral steroids, a regimen that may accelerate visual recovery and delay the onset of MS, but that does not alter the long-term visual prognosis. Long-term treatment with interferon beta-1a should be considered in high-risk patients (ie, patients with abnormal brain MRI) even though, as noted above, the neurologic prognosis in patients in whom MS develops after an attack of optic neuritis is extremely good. Such patients should be referred to a neurologist for assessment.