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Chapter 3

Visual Loss in Neuro-Ophthalmology

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Abstract

Optic neuropathy is damage to the optic nerve from any cause. Damage and death of these nerve cells lead to characteristic features of optic neuropathy. The main symptom is loss of vision (visual acuity and visual field damages), with colors appearing subtly washed out in the affected eye. The diagnosis is made on clinical examination. The history often points to the possible etiology of the optic neuropathy. In most of the cases, one eye is affected but it could be both. A rapid onset is typical of demyelinating, inflammatory, ischemic, and traumatic causes. A gradual course points to compressive, toxic/nutritional, and hereditary causes. The classic clinical signs of optic neuropathy are visual acuity and field defects, dyschromatopsia, and abnormal pupillary response. There are ancillary investigations that can support the diagnosis of optic neuropathy. Visual field testing, neuroimaging of the brain and orbit are essential in many optic neuropathies including demyelinating and compressive. In the last decade, increase of use new technology for optic neuropathies evaluation including multifocal visual evoked potentials and optic coherence tomography. Long standing of optic neuropathy is described by pale optic disk or optic atrophy, which means damage and death of these nerve cells or neurons.

Keywords: optic neuropathy, optic neuritis, non-arteritic anterior ischemic optic neuropathy (NAION), arteritic anterior ischemic optic neuropathy (AION), traumatic optic neuropathy

1. Introduction

Accurate medical history is very important information, helping to evaluate the etiology of visual loss. Rapid onset is characteristic of optic neuritis, ischemic optic neuropathy, inflammatory (non-demyelinating), and traumatic optic neuropathy. On the other hand, gradual onset over months or even years is typical of compressive toxic/nutritional optic neuropathy. A history over years is seen in compressive and hereditary optic neuropathies. The

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ophthalmologist or neurologist can make the differential diagnosis according the symptoms, the age of onset, and the gender. Young age group (15–45 years) for optic neuritis women gender and pain on eye movement are more typical for optic neuritis versus. Elderly patients (older than 50 years), painless loss of vision without gender predisposition are typical for ischemic optic neuropathy. Additionally, in a young patient, history of neurological symptoms such as parenthesis, limb weakness, and ataxia is suggestive of demyelinating optic neuritis.

In an elderly patient (more than 60 years mostly 70–80 years) with signs of severe optic neuropathy and the presence of preceding transient visual loss, temporal pain, jaw claudication, fatigue, fever, anemia, weight loss and myalgia, an arteritic ischemic optic neuropathy (AION) due to giant cell arteritis (GCA) should be suspected.

In children, a history of recent flu-like illness or vaccination days or weeks before vision loss points to a para-infectious or postvaccinia optic neuritis, respectively.

Transient visual obscurations, transient diplopia, and headache should raise the suspicion of increased intra-cranial pressure.

The use of any medications should be carefully noted, since some are either directly or indirectly toxic to the optic nerve. These include drugs as ethambutol, methanol, isoniazid, tobacco alcohol, and more. History of diabetes mellitus, systemic hypertension, hypercholesterolemia, coagulation deficit, and smoking is more common in patients with nonarteritic ischemic optic neuropathy (NAION). Patients who have history of malignancy may have infiltrative or para-neoplastic optic neuropathy. It is important to inquire into the patient's general health, eating, and social habits (drinking and smoking) in suspected nutritional optic neuropathy (complex B–vitamins). In addition, a detailed family history is inquired in diagnosing hereditary autosomal and mitochondrial optic neuropathies.

This chapter addresses the major diseases neuropathies accompanied by rapid visual loss: nonarteritic and arteritic optic neuropathy, traumatic optic neuropathy, and optic neuritis.

2. Anterior ischemic optic neuropathy (AION)

Anterior ischemic optic neuropathy (AION) is a medical condition involving insufficient blood supply of the pial vessels originating from the choroidal vessels to the optic disk. AION is generally divided into two types: arteritic AION (or AAION) and nonarteritic AION (NAION) [1, 2].

We have to differentiate between two different etiologies, and therefore, workout prognosis and treatment possibilities are different.

2.1. Nonarteritic ischemic optic neuropathy (NAION)

NAION is the most common cause of sudden optic nerve-related vision loss. It is estimated that the incidence of NAION is about 8000/year in the USA and encountered for 90% of the optic neuropathies. NAION is mostly unilateral [3] and rare bilaterally. NAION is more

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frequent in Caucasians, no gender predisposition, and mean age at onset in most studies is from 57 to 65 years. No clinically effective treatment exists because little is known about its pathophysiology, and there are only few histopathological studies of the acute condition.

NAION [1, 2] typically presents suddenly upon awakening the painless patient notes seeing poorly in one eye. Vision in that eye is obscured by a dark shadow, often involving just the upper or lower half of vision. On examination, the patient is found with visual acuity reduction from 20/25 down to hand movement only, relative afferent pupillary defect (RAPD), swollen disk (segmental or diffuse) with splinter hemorrhages (see **Figure 1**), absent of large cup, and contralateral disk is small and crowded in 20–40% of the patents [4]. In approximately 6 months following the infarct visual acuity improves by 3 or more lines of vision on the Snellen chart in 42.7% of patients. In addition, vision had worsened by 3 lines or more in 12.4% of patients; some clinicians use the term "progressive ischemic optic neuropathy". Second eye involvement occurs in approximately 20% of patients with NAION within 5 years. Furthermore, most cases of NAION involve the loss of an altitudinal hemifield (**Figure 2**) (either the upper or mostly lower half of the visual field, but not both), and visual acuity remains almost normal or slightly reduced.

Figure 2 shows a few cases of NAION, which involve almost total loss of vision. The mechanism of injury for NAION is used to be controversial. Experts have come to a consensus that most cases involve two main risk factors. The first is a predisposition in the form of a type of optic disk shape named crowded disk [4, 5] or "disk at risk," where the cup/disk ratio is low (0.0–0.1), and secondly, cardiovascular risk factors as diabetes mellitus, hypertension, hypercholesterolemia, and coagulation deficits. Laboratory examinations at the presentation to differentiate between NAION and AAION include (erythrocyte sedimentation rate [ESR] that should be less than 40 mm/h) and C-reactive protein (CRP). It is advised to draw complete blood count and serum chemistry especially glucose, serum cholesterol and triglycerides, coagulophatic state, antitrombin III antiphospholipid antibody, and serum fibrinogen. Analysis of brain MRI suggests an increasing number of ischemic white matter lesions.

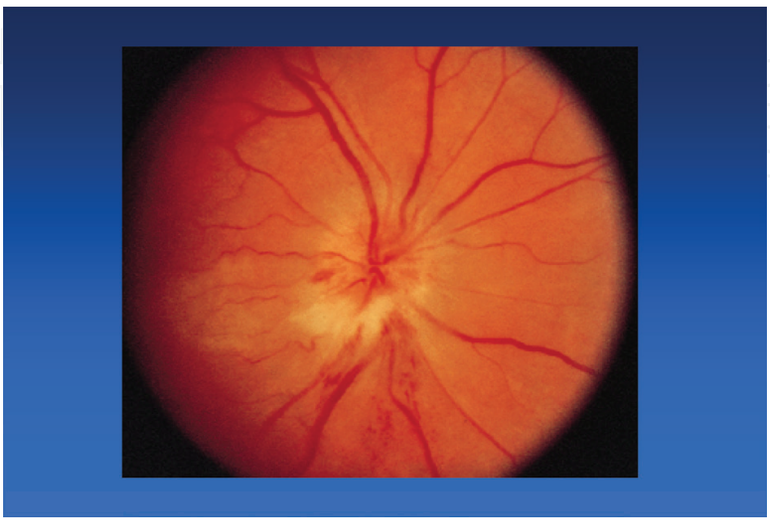


Figure 1. Disk appearance in nonarteritic ischemic optic neuropathy.

Additional risk factor such as obstructive sleep apnea, migraine, and hyperhomocysteinemia, smoking and optic disk drusen [6]. Ipsilateral carotid disease does not seem to be a risk factor for NAION. Association between cerebral and cardiac vascular disease seems to be very circumstantial. Drugs associated with NAION are amiodarone, phosphodiesterase-5 inhibitors such as sildenafil [7], and interferon-a.

Most experts throughout the world believe that there is no accepted treatment to reverse the damage. However, a recent large study by Hayreh has shown that if patients are treated with large doses of corticosteroid therapy during the early stages of NAION, in eyes with initial visual acuity of 20/70 or worse, seen within 2 weeks of onset, there was visual acuity improvement in 70% in the treated group compared to 41% in the untreated group [8]. Hayreh and Zimmerman performed a nonrandomized, open-label trial of systemic corticosteroids for acute NAION, and the untreated group had more vascular risk factors than the treated group, and therefore, this study was very criticized and not accepted by most neuro-ophthalmologists worldwide.

2.2. NAION treatments attempted with no specific success to improve vision

- Medical [9–11]
- Diphenylhydantoin
- Systemic: aspirin [12], corticosteroids [8]
- Intravitreal: anti-VEGF agents (e.g., Bevacizumab), (see more information)
- Erythropoietin/erythropoietin receptor agonists
- Surgical: optic nerve sheath fenestration, optic neurotomy (see more information)
- Hyperbaric oxygen [13]

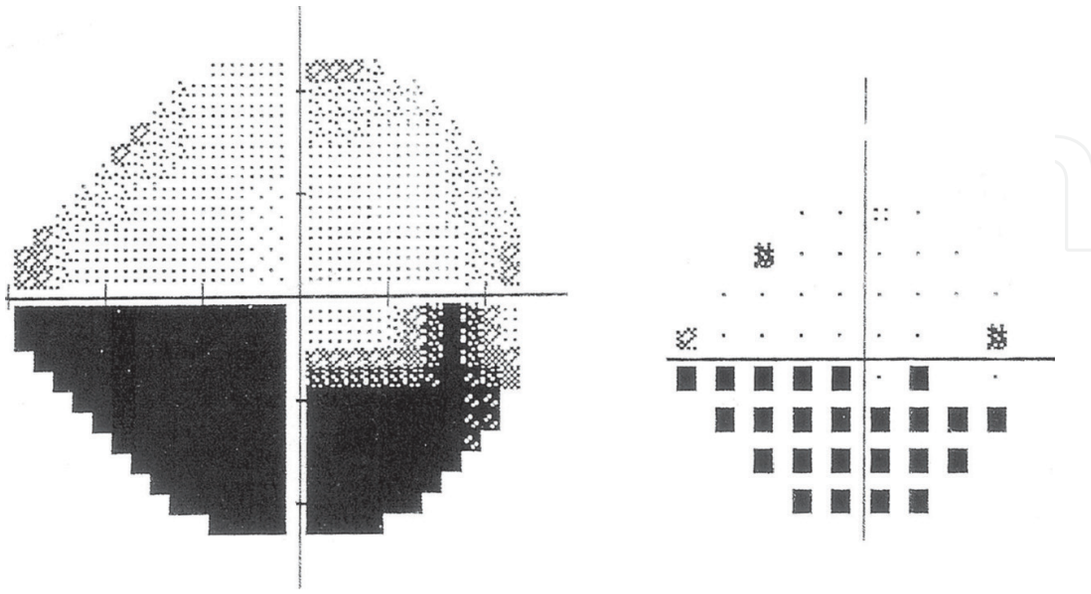


Figure 2. Visual field in NAION and lower altitudinal hemianopia.

2.2.1. Ischemic optic neuropathy decompression trial (IONDT)

The trial was done to assess the safety and efficacy of optic nerve decompression surgery compared with careful follow-up alone in patients with nonarteritic anterior ischemic optic neuropathy (NAION). The ischemic optic neuropathy decompression trial (IONDT) is a randomized, single-masked, multicenter trial and was carried out in 1994. Study was done by 244 patients with NAION and visual acuity of 20/64 or worse.

First group of 125 patients had been randomized to careful follow-up, and second group with 119 patients had been randomized to surgery, with 6 months of follow-up.

Patients in the surgery group received optic nerve decompression surgery and follow-up ophthalmologic examinations; those in the careful follow-up group received ophthalmologic examinations at the same times as the surgery group. A parameter of gain and loss of three or more lines of visual acuity on the New York Lighthouse chart at 6 months after randomization was used by the research group and measured by technicians.

Results showed that patients assigned to surgery did no better when compared with patients assigned to careful follow-up regarding improved visual acuity of three or more lines at 6 months: 32.6% of the surgery group improved compared with 42.7% of the careful follow-up group. According to the results, IONDT indicates that optic nerve decompression surgery for NAION is not effective and may be harmful [14].

2.2.2. Bevacizumab (Avastin®) trial

Intravitreal bevacizumab for the treatment of NAION neuropathy: a prospective trial [15].

2.2.2.1. Methods

In this non-randomized controlled clinical trial, 1.25-mg intravitreal Bevacizumab was compared with natural history [15]. Twenty-five patients were enrolled (17 with treatment and 8 controls). Patients were examined at baseline, 1, 3, and 6 months with a full neuro-ophthalmic exam, automated perimetry, and optic nerve optical coherence tomography (OCT) measurements. The primary outcome measure was change in mean deviation on Humphrey visual field testing. Secondary outcome measures were changed in visual acuity and optic nerve OCT thickness.

2.2.2.2. Results

(A) There was no significant effect of treatment on the primary outcome measure of mean deviation score ($P = 0.4$). (B) There was no effect of group assignment on the secondary outcome measures of change in mean Early Treatment Diabetic Retinopathy Study (ETDRS) letters ($P = 0.33$). (C) No change in nerve fiber layer thickness on OCT ($P = 0.11$).

Results show optic disc in NAION the results, there was no difference between Bevacizumab and natural history for change in visual acuity, visual field, or optic nerve OCT thickness [15].

2.3. New treatment opportunities (ongoing studies)

NAION is still an enigma regarding pathogenesis and treatment. The current therapeutically efforts are to preserve vision and minimize the damage from the primary insult. QPI-1007 is a small interfering ribonucleic acid (siRNA) designed to temporarily block cells from making Caspase 2 (controls cell apoptosis). Quark pharmaceuticals and NORDIC collaborated in a study that uses the possible effect of this drug as a possible neuroprotection therapy for NAION.

2.4. Arteritic anterior ischemic optic neuropathy (AAION)

Distinction between AAION and different etiologies of anterior ischemic optic neuropathy. will be discussed. AAION is due to temporal arteritis (also called giant cell arteritis (GCA)), an inflammatory disease of medium-sized blood vessels that occurs especially with advancing age (more than 60 years, mostly 70–80 years). Annual incidence rate in population age 50 years or older is estimated as 15–30/10,000. Female-to-male preponderance of 3.5:1 is prevalent in white population of European origin. GCA is associated with polymyalgia rheumatica. About 50% of the GCA patients have polymyalgia rheumatica, and 10–20% of the patients with polymyalgia rheumatica have GCA. Polymyalgia rheumatica may precede GCA or can occur simultaneously.

The symptoms and signs of severe optic neuropathy [16] include the presence of preceding transient visual loss, temporal pain, jaw claudications, fatigue, fever, anemia, weight loss, and myalgias are strongly suggestive of arteritic ischemic optic neuropathy (AAION). In contrast, NAION results from the coincidence of cardiovascular risk factors in a patient with "crowded" optic discs. Nonarteritic AION occurs in a slightly younger group and is much more common than AAION. Most cases of AAION involve nearly complete vision loss (light perception to no light perception), while only a few cases of NAION result in near total loss of vision (**Figure 3**). Swollen disk, elevated CRP, and ESR (60–120 mm/h) are highly suggestive of temporal arteritis (arteritic AION) [3, 17]. At times, the optic disk in AAION is characterized

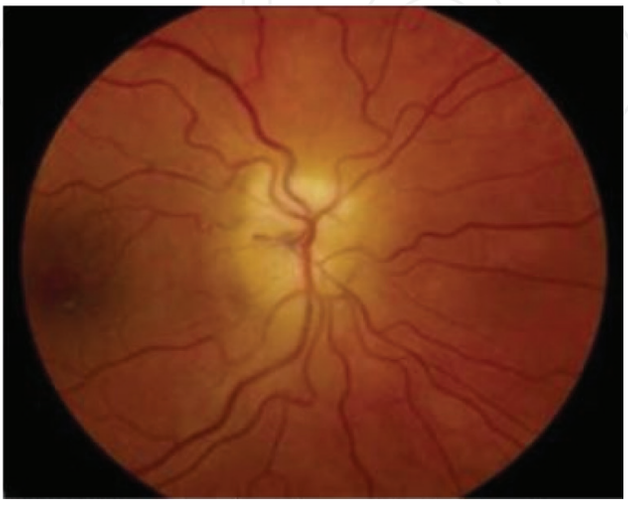


Figure 3. Shock white disk in arteritic anterior ischemic optic neuropathy.Ó 2018 American Academy of Ophthalmology.

by a milk-pale edema that may extend to the retina. In some cases, even central retinal occlusion with "cherry -red spot" may occur. Diagnosis is confirmed by temporal biopsy, and if the histological result is negative, it is necessary to biopsy the other side. Biopsy is taken from several segments along the temporal artery because the inflammation is segmental and may be missed by one site biopsy. Another possibility for diagnosis is ultrasound of the temporal artery but it is less accurate compared to biopsy.

Neuroimaging is not usually required in patients with typical presentations of giant cell arteritis (GCA) and when performance is generally normal [18]. However, some patients have already undergone imaging before neuro-ophthalmic evaluation, and these studies may be abnormal. They report four main imaging findings described in the literature:

1. Nonspecific orbital enhancement.
2. Optic nerve parenchymal enhancement.
3. Perineural sheath enhancement.
4. Optic chasmal enhancement.

Other important MRI findings in GCA include those involving the vascular supply not only extracranially but also intracranial, particularly vessel wall enhancement of the intramural ICA. MRI findings may hold some diagnostic value in distinguishing between A-AION as in GCA and in nonarteritic AION, in which they are typically normal. Differential diagnosis for these MRI findings can lead to inappropriate testing and delay diagnosis and treatment [18].

2.4.1. Summary of AAION

1. GCA is a vascular disorder that may result in devastating visual loss if not treated promptly.
2. Biopsy is the gold standard for diagnosing, and neuroimaging plays a role only in atypical presentations.
3. Neuroimaging findings in GCA are often nonspecific and can lead to delay in diagnosis and treatment.

Patients are hospitalized for evaluation and intravenous corticosteroid treatment with at least 1 g/day (3–5 days) of methylprednisolone followed by prednisone 1 g/kg for 10 days and then tapering down. The dosage is decreased to 20–40 mg/day in 3 weeks, and treatment is continued for 12–18 months. A steroid sparing agent is tocilizumab, a monoclonal humanized antibody against interleukin 6 receptor. The dosage is 1 g/day for 12–24 months, and it is not given in the first trimester of pregnancy. It can be combined with corticosteroids, and this allows decreasing the dosage of the later. During the follow-up period, the inflammatory parameters including sedimentation rate, CPR, platelets, etc. is monitored, and if they increase, the dosage is accordingly increased. Treatment is very urgent to avoid AAION in the fellow eye, as it can happen even within days or weeks after the first eye was affected. Treatment generally does not improve the vision of the affected eye.

3. Optic neuritis

Optic neuritis is a condition that produces abnormal vision loss without causing ocular abnormalities and we have to differentiate between typical and atypical optic neuritis.

1. **Typical optic neuritis:** Condition of visual loss caused by inflammatory demyelization of the optic nerve either idiopathic or associated with multiple sclerosis (MS). The myelin sheath is the target of attack.
2. **Atypical optic neuritis:** The nerve becomes inflamed as a part of uveitis or systemic inflammation treatment can help to improve vision.

3.1. Typical optic neuritis

Optic neuritis is a term used to refer to inflammation of the optic nerve, and it appears in two forms: (1) when associated with a swollen optic disk, it is called papillitis or anterior optic neuritis. (2) When the optic disk appears normal, the term retro bulbar optic neuritis is used. Acute optic neuritis is 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 mostly women. In this chapter, we will provide information about the clinical profile of optic neuritis, its natural history, its relationship to multiple sclerosis (MS), and the efficacy of corticosteroid treatment according the Optic Neuritis Treatment Trial (ONTT) [19–22].

3.2. Demographics

The annual incidence of acute optic neuritis is estimated in population-based studies to be between 1 and 5 per 100,000 people in the general population [23]. The majority of patients with acute optic neuritis are aged between 18 and 46 years, with a mean age of 30–35 years. However, optic neuritis can occur at any age, and females are affected more commonly than males by a ratio of 3:1 to 4:1.

3.3. Clinical presentation

Clinically, there are three major symptoms in patients with acute optic neuritis: (A) central visual loss in 90% of the patients. (B) Pain especially is exacerbated by eye movement around the affected eye in more than 90% of patients. (C) Relative afferent pupillary defect (RAPD) in all patients with unilateral optic neuritis [24].

Loss of central visual acuity occurs within few hours to several days, and the degree of visual loss varies from very minimal reduction to counting fingers (in rare cases, complete blindness can be observed). The majority of patients describe central vision loss predominately, and some of them complain of peripheral field defects. The visual loss is monocular in most cases, but particularly in children, both eyes are simultaneously affected.

The presence of pain is a very helpful, differentiating optic neuritis from other causes of optic neuropathies such as anterior ischemic optic neuropathy, which produces painless visual loss.

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Examination of a patient with acute optic neuritis reveals evidence of optic nerve dysfunction [24]. In addition, color vision (especially red color) is typically impaired in almost all cases and is helpful to differentiate from other optic neuropathies.

A relative afferent pupillary defect (RAPD) is demonstrable with the swinging flashlight test in all unilateral cases of optic neuritis. Patients with optic neuritis may also have a reduced sensation of brightness and contrast sensitivity in the affected eye.

Visual field (VF) scotomas involve many forms of central or peripheral field disturbances such as ceco-central scotoma, inferior or superior altitudinal hemianopia, central scotoma, Bejerrum scotoma, hemianoptic defects, and more, almost any type of visual field defect (see **Figure 4**).

Presentation of optic disk in the acute phase is mostly normal with sharp disk margins and reddish color. Some of the patients with acute optic neuritis have minor degree of disk swelling with no correlation to visual acuity or visual field loss [25]. Over approximately 4–6 weeks, the optic disk in an eye with acute optic neuritis may become or remain normal or become pale, and most parameters of vision improve. In the chronic phase, the pallor of the optic disk may be diffuse or sectorial from my personal experience often the temporal part (42%) because the papillo-macular bundle is damaged in many patients with optic neuritis [26].

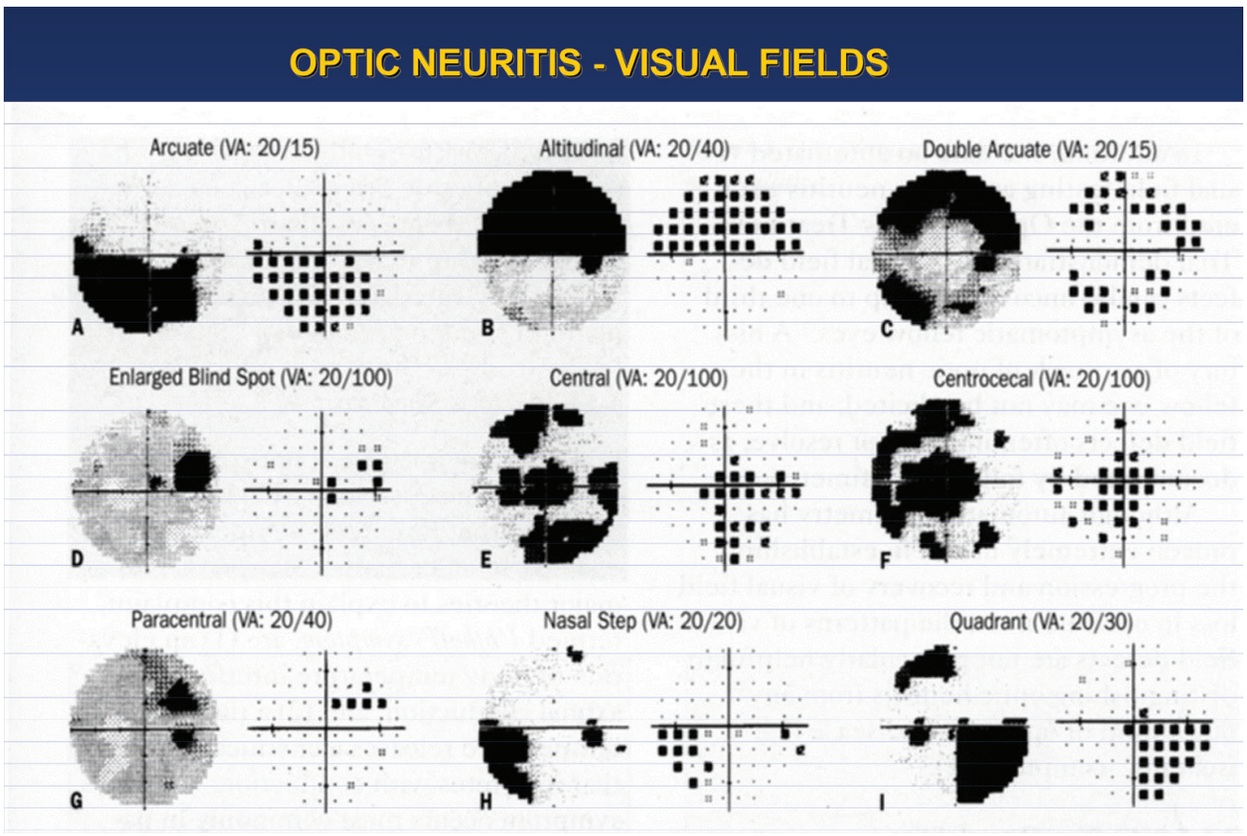


Figure 4. Visual field possibilities in optic neuritis.

3.4. Diagnostic studies

Imaging studies in patients with presumed acute optic neuritis are usually performed for the following reasons: (A) to rule out particularly a compressive lesion; (B) to determine if a cause other than demyelization is responsible for inflammation of the optic nerve; or (C) to determine the visual and neurologic prognosis of optic neuritis.

The best imaging study can be done by magnetic resonance imaging (MRI), it can reveal demyelization 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 is the identification of signal abnormalities in the white matter of the brain, usually in the periventricular region, consistent with demyelization. MRI is the strongest predictor of the eventual development of MS in patients with acute isolated optic neuritis. It can show multiple white-matter lesions in both cerebral hemispheres, including the periventricular regions.

Cerebrospinal fluid (CSF) analysis in the evaluation of patients with acute optic neuritis is not any more a strong predictor for MS. The presence of oligoclonal banding in the CSF is associated with the development of MS, but it can show false positive results. The powerful predictive value of brain MRI for MS is increased also because the Lumbar puncture examination is invasive. Therefore, CSF examination in the evaluation of patients with optic neuritis has been reduced. CSF studies in patients with optic neuritis are mostly useful to detect another inflammatory or infectious disorder.

3.5. Associated neurologic disorder

3.5.1. Risk factors for developing MS

The presence of at least 1 lesion in the periventricular white matter of the brain MRI is highly predictive, family history of MS, white race, old neurologic complains, winter onset, and younger age of optic neuritis. Conversely, patients with acute optic neuritis who have a normal brain MRI, severe disk swelling, a macular star, or disk hemorrhages or older age of onset have a low risk of developing MS.

The risk of developing MS [27–29] 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 first attack.

3.6. MRI diagnostic criteria for multiple sclerosis

Multiple sclerosis can be diagnosed when the MRI [30–32] in a patient with optic neuritis reveals two or more typical lesions of multiple sclerosis, at least one of which is contrast enhancing. The demyelization foci in the brain commonly appear in the corpus callosum and periventricular white matter and are best seen on T2-flair images.

The number of inactive typical white-matter lesions is the most important criterion for estimating the risk that the patient will develop multiple sclerosis [31]. Optic neuritis with two or

more noncontrast enhancing lesions typical of multiple sclerosis on MRI is called a "clinically isolated syndrome" and is associated with a high risk of MS. Multiple sclerosis arises in only 25% of patients in whom MRI reveals no foci of demyelination in the brain. If one or two such foci are initially present, the risk is 65%; if three or more are present, it is 78% [31].

3.7. Treatment

Many studies have shown that there are no data to support the efficacy in any treatment to alter the final visual outcome during a period of a year after optic neuritis. Treatment with corticosteroids is the main treatment option for patients with acute idiopathic optic neuritis. The prognosis for visual recovery after acute optic neuritis is very good also without treatment. According the ONTT (IV regimen of corticosteroids) [19–21, 32], steroid treatment should be delivered in acute optic neuritis if symptoms of 8 days duration or less. Begin with 3 days of intravenous Methylprednisolone in a dose of 1 g/day followed by 11 days course of oral prednisone at a dose of 1 mg/kg/day with a taper over 3 days. The ONTT was done in randomizing 457 patients with acute optic neuritis, comparing a group of patients following the IV steroid regimen versus a group of patients receiving placebo. The results of the trial showed that this regimen does not affect the final visual outcome of a patient, but it accelerates the recovery of vision compared with no treatment in the first 2 years. In addition, patients who experience an attack of acute optic neuritis should not be treated with low-dose oral prednisone alone because it provide no effect of visual outcome and may double the recurrence rate for optic neuritis.

The ONTT [19] results had another important aspect of treatment for acute optic neuritis regarding the possibility of having impact on the development of MS. Patients who were treated with the intravenous followed by oral corticosteroid regimen had a reduced rate of developing clinically definite MS during the first 2 years following treatment. MS developed in only 8% of patients who were treated according the corticosteroid regimen versus 17% of patients in the placebo group. This benefit of treatment was seen only in patients who had abnormal brain MRI at the time of onset of the optic neuritis. The protective effect was short and by 3 years after optic neuritis groups treated with ONTT IV regimen versus placebo groups had equal incidence to develop MS. These findings suggest that a patient with acute optic neuritis who has an abnormal brain MRI may benefit in the short term (2 years) 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 [33] Prevention Study (CHAMPS), a randomized, double-blind, placebo-controlled trial that enrolled patients with a first demyelinating event, offer some help. Weekly intramuscular injection with 30 ug of beta interferon 1a (Avonex) to patients who had 2 or more white-matter lesions of at least 3 mm on a brain MRI together with a 14-day course of Methylprednisolone followed by prednisone lowered the probability for MS. 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. In addition, patients in the interferon group had fewer new and enhancing brain MRI lesions.

To conclude, a clinician should discuss with a patient having acute optic neuritis the treatment benefits comparing to no treatment emphasizing that there is a good chance (more than 80%) that visual acuity will recover to 20/20 within a year without treatment. It is important to explain the patient the relation between optic neuritis and the chances of developing MS. No treatment affects the final outcome of visual acuity.

3.8. Visual prognosis

The natural history of acute idiopathic optic neuritis is to worsen over several days to 2 weeks and then to improve mostly rapidly. Improvement can continue to occur up to 1 year after the onset of visual symptoms. I had some patients of which improvement started only after 2 months but it is uncommon. The mean visual acuity 1 year after an attack of otherwise uncomplicated optic neuritis is 20/20, and less than 10% of patients have permanent visual acuity less than 20/40. Most parameters of visual function, including contrast sensitivity, color perception, and visual field, improve in conjunction with improvement in visual acuity. According to some investigators, most patients retain excellent vision for at least 15 years after their first attack [24].

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. Furthermore, even patients with improvement in visual function to "normal" may complain of movement-induced photopias or transient loss of vision with overheating or exercise (Uhthoff symptom). The ONTT since 1992 has made it clear that 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 according the ONTT [19]. 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.

3.9. Atypical optic neuritis

Optic neuritis that develops before the age of 15 years or after the age of 50 years may be atypical. Many of these cases have no periocular pain, and visual decline is over few weeks. Atypical optic neuritis should be divided to three categories: infectious, immune, and Sarcoid. Most of them appear with disk edema.

3.10. Infectious optic neuritis

This may occur in meningitis/encephalitis [34] and is treatable. The pathogens could be bacteria (Homophiles, Streptococcus, Staphylococcus, spirochetes, or mycobacteria), protozoa as Toxoplasmosis, fungi as Cryptococcus or Aspergillus, or herpes viruses [35, 36]. Syphilitic optic neuritis can develop very rapidly from every stage of the disease. Tuberculosis causes meningitis. Lyme optic neuritis is rare and mostly associated with those who visited near New Haven, Conn, USA.

Another type of optic neuritis is called Leber's stellate neuro retinitis caused by *Bartonella henselae* responsible for cat-scratch disease. States with disk edema and within weeks, we can find star shape collection of hard micro-exudates (star-shape) at the macula called neuroretinitis [37].

3.11. Immune optic neuritis

Optic neuritis can appear within days or weeks after systemic influenza illness [34] or vaccination [38]; often binocular with good vision recovery [32]. Atypical optic neuritis is also associated with acute disseminated encephalomyelitis (ADEM), a condition in which multiple CNS manifestations occur at once; in most cases, patients recover and never recur. Some authors recommend high dose of corticosteroid treatment.

In optic neuritis, if an underling cause is found, it should be treated with either corticosteroid or immunosuppressive medications.

Optic neuritis is rare in Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, behest's disease, Wegener's granulomatosis, and lupus erythematosus.

3.12. Sarcoidosis

When the optic nerve is involved, the vision declines and the optic disk might be swollen, with or without systemic signs. Vision recovers with corticosteroid therapy. Relapses are common [39].

- Recommended laboratory tests mostly for atypical cases
  - C-reactive protein
  - Complete blood count
  - Serum chemistry
  - Blood sugar
  - Vitamin B_{12}
  - Rheumatoid factor
  - Antinuclear antibodies
  - Anti-phospholipids antibodies
  - Anti-ds-DNA antibodies
  - Lupus anticoagulant
  - Serum angiotensin-converting enzyme test
  - *Borrelia* serology
  - Urinalysis
- Additional tests in case of "clinically possible differential diagnosis"
  - Anti-neutrophilic cytoplasmic antibodies (ANCA)
  - Extractable nuclear antibody (ENA) profile

- Auto antibodies against aquaporin-4
- HIV serology
- Human T-lymphotropic virus type 1 (HTLV-1) serology
- *Treponema pallidum* hemagglutination assay (TPHA), long-chained fatty acids
- *Mycoplasma* serology
- Urinary methylmalonate excretion

4. Anterior versus posterior traumatic optic neuropathy

Traumatic optic neuropathy is the name given to the syndrome of an optic neuropathy after head or ocular trauma in the absence of other causes [40]. Like any other optic neuropathy, there are variable degrees of visual acuity and visual field loss and an afferent pupillary defect if unilateral or significantly asymmetric.

Traumatic optic neuropathy is either anterior or posterior and within each category can either be direct or indirect. Trauma to the anterior optic nerve usually injures the central retinal artery and vein, which enter or exit the nerve approximately 10 mm posterior to the globe. This vascular injury often results in retinal infarct. Hemorrhages are usually the result of severing the pial vessels with or without disk edema and rarely manifestations of central retinal or branch artery occlusion, central retinal vein occlusion, or anterior ischemic optic neuropathy. Axonal injury in the posterior optic nerve does not cause any acute effects on the disk, nerve fiber layer, or retinal ganglion cell layers. Axonal transport abnormalities posteriorly do not affect the more anterior nerve fibers, and so disk edema is not seen in posterior traumatic optic neuropathy. For these reasons, isolated posterior traumatic optic neuropathy is associated with a normal fundus examination at presentation. Only after a few weeks, we can see the structural signs of optic neuropathy evident, namely disk pallor and thinning of the retinal nerve fiber layer. A particular type of posterior traumatic optic neuropathy is when there is injury to the chiasm, in which case, there may be unilateral or bilateral temporal visual field defects respecting the vertical meridian. Rare chiasmal injury can be seen with posterior avulsion of the optic nerve, for example, traumatic enucleation, or penetration from a foreign body.

4.1. Direct anterior traumatic optic neuropathy

Direct anterior traumatic optic neuropathy is defined when there is penetration of the optic nerve by a foreign body or projectile. Anterior direct optic nerve injuries result from medial penetrating orbital trauma that damages the anterior optic nerve, for example, a knife transecting the optic nerve just posterior to the globe. This is because the optic nerve course transverses the medical part of the deep orbit and is not protected there by the bones or the eye. Posterior direct optic nerve injuries result from penetrating orbital or head trauma more posteriorly, for example, a bullet that passes just anterior to the chiasm. Direct injuries tend to produce severe and immediate visual loss, with little likelihood of recovery. The reason

for this presumably is that a major element in these injuries is transection injury to retinal ganglion cell axons, which causes instantaneous loss of axonal conduction and an inability to regenerate axons later.

4.2. Indirect anterior traumatic optic neuropathy

This is diagnosed when traumatic optic neuropathy occurs without a history of foreign body. It occurs in anterior indirect injuries, which associated with sudden rotation of the globe from blunt trauma. Examples include a digit trauma to the globe or falling and hitting the eye on the corner of a table. Anterior indirect traumatic optic neuropathy can cause partial or total avulsion of the optic nerve, with associated peripapillary hemorrhage.

4.3. Posterior indirect traumatic optic neuropathy

Posterior indirect injury is the most common cause of traumatic optic neuropathy. It results from blunt head trauma that transmits a concussive force to the optic nerve, resulting in contusion at the optic canal. There may be little or no evidence of significant head trauma; a fall from a bicycle may suffice. In other cases, there is multisystem trauma or significant brain injury. Loss of consciousness occurs in 40–72% of patients with traumatic optic neuropathy. Motor vehicle and bicycle accidents are the most frequent causes of traumatic optic neuropathy, accounting for 17–63% of cases. Traumatic optic neuropathy may be iatrogenic, especially after maxillofacial or endoscopic surgery as a result of inadvertent direct injury to the optic nerve or transmitted force fracturing the optic canal. The common site of posterior indirect optic nerve injury is at the optic canal; the intracranial optic nerve is the next most common site of injury. There may or may not be bone fractures. Despite being most common, posterior indirect traumatic optic neuropathies fortunately occasionally have the most favorable prognosis, its spontaneous visual recovery sometimes occurring at variable times after injury. Presumably, the injury causes concussion and focal blockade of axonal conduction without loss of its structural integrity. Once there is healing of the edema or other molecular events blocking conduction, axonal function can return. The severity of initial visual loss in patients with traumatic optic neuropathy varies from no light perception to 20/20, with sometimes only a visual field defect as functional evidence of disease. An afferent pupillary defect is always present and is the major clue for the diagnosis in the presence of otherwise normal eye. Patients with very poor vision (e.g., light perception only or no light perception) are less likely to improve, regardless of therapy, than patients with vision better than light perception. The reason is likely that severe injury causes axonal transection, membrane disruption, or cytoskeletal disorganization, any of which can lead to axonal dissolution and irreversible loss of conduction of visual information. In some cases, the visual loss only begins several hours to days after the injury. If this happens, the possibility of an intrasheath hemorrhage should be entertained, and neuroimaging should be repeated.

4.4. Neuroimaging

The diagnosis is radiological. It is essential in the evaluation of a patient with traumatic optic neuropathy not only for demonstrating correlative signs of injury but also detection of pre-existing

structural lesions and coincident intracranial effects of trauma, e.g., hematomas or carotid cavernous fistulas. CT scanning is superior to magnetic resonance imaging (MRI) in delineating fractures of bone. It is critical that CT be performed with very thin sections that are aimed to the optic canal, and reconstructions performed, particularly in the coronal plane. About 20 to 50% of patients with posterior traumatic optic neuropathy have evidence of an optic canal fracture by neuroimaging, and sometimes, the clue is a small loss of contour of bone. Although the displacement on neuroimaging may be small, it is possible that at the time of injury, there was a much larger displacement of the bone into the canal. Even in the absence of a fracture, blood in the sphenoid sinus should raise suspicion for optic nerve injury. MRI is better for imaging soft tissue, particularly the intracranial optic nerve and chiasm, and may be useful for delineating intrasheath hemorrhage that occurs at the orbital portion from penetrating injury (anterior direct TON). It is critical that MRI only be performed after a metallic intracranial, intraorbital, or intraocular foreign body has been ruled out by CT scanning or conventional radiography. If CT is used for screening, care should be taken to use thin slices and no interslice skip.

4.5. Treatment of traumatic optic neuropathy

In anterior and direct traumatic optic neuropathy, there is no evidence that treatment of anterior optic injuries or direct optic nerve injuries is efficacious. In the former, the concurrent vascular injuries cause direct ischemia and infarction to the neural retina and/or optic nerve head, and the time until irreversible neuronal death is measured in minutes to hours. In the latter, there is often sufficient direct axonal trauma to disrupt the integrity of the axon, up to and including its transection, and in the central nervous system of mammals, this is a point of no return for neuronal function. An exception is anterior traumatic optic neuropathy associated with neuroimaging evidence of an enlarged optic nerve sheath. In these cases, an optic nerve sheath fenestration should be performed in the hopes of evacuating an intrasheath hematoma.

4.6. Treatment of posterior indirect traumatic optic neuropathy

With respect to posterior indirect traumatic optic neuropathy, the three commonly used approaches that have been used are very high doses ("mega doses") of corticosteroids [41], decompression of the optic canal, and observation alone; there is insufficient evidence from good quality randomized trials to guide decision-making on how to treat traumatic optic neuropathy. Because visual function often spontaneously improves in this disease, clinical trials are particularly necessary for physicians to select therapies based on evidence. Mega-dose corticosteroids experimental models of white matter trauma in animals showed that doses of 15–30 milligrams per kilogram of intravenous methylprednisolone are protective for injured neurons [41]. The NASCIS 2 and 3 studies found that patients treated within 8 hours of spinal cord injury with a loading dose of 30 milligrams per kilogram of intravenous methylprednisolone load followed by 5.4 ml/kg/hr continuous infusion for 48 hours had a better outcome than control patients [42, 43]. Extrapolating these results to traumatic optic nerve injury, it was thought reasonable to believe that similar doses should be used for injury to this comparable central nervous system white matter structure. However, over the years, there has been controversy about interpretation of the NASCIS data [44, 45], and its application

to the treatment of spinal cord injury is not uniform [46, 47]. Furthermore, animal and cell culture data suggest that high doses of methylprednisolone may actually be toxic for the retinal ganglion cell and/or its axon [48–50]. Finally, the Corticosteroid Randomization After Significant Head Injury (CRASH) trial demonstrated that 48 hours of mega-dose methylprednisolone significantly increased the risk of death after head injury [51], with a hazard ratio at 6 months of 1.15 (95% CI 1.07–1.24) [52].

The authors concluded that "These final results still provide clear evidence that treatment with corticosteroids following head injury affords no material benefit."

4.7. Optic canal decompression

Decompression of the optic canal is usually achieved through the transethmoidal route, most commonly via an external ethmoidectomy or endonasally [53]. The canal is then decompressed inferomedially from the superior lateral wall of the sphenoid sinus, with care taken to avoid the carotid artery. Although the canal can also be decompressed through an intracranial approach, the former is less invasive. However, if surgery in the area is being performed for other reasons necessitating unroofing of the canal, then an argument can be made that decompression of the canal should be done through this approach. However, there is also no evidence that optic canal decompression is efficacious. A recent Cochrane review concluded that there is no conclusive evidence that any particular form of surgical decompression improves the visual outcome in TON. The decision to proceed with surgery in TON remains controversial and each case needs to be assessed on its own merits. The final decision will inevitably reflect a combination of clinical judgment, the availability of local surgical expertise, and the patient's perception of the possible risks and benefits. If surgery is to be considered, it should only be performed in centers with experience with the procedure. Because of the possibility that the carotid may be iatrogenic injured, there should be informed consent regarding the risk of death or stroke. Surgery should not be performed on an unconscious patient because of the difficulty in assessing visual function. Observation of traumatic optic neuropathy may improve without any treatment. There are no convincing randomized control trials to show a treatment benefit in traumatic optic neuropathy, and a nonrandomized concurrent comparative study did not demonstrate clear differences between treatments and observation. Therefore, when a patient cannot give informed consent for corticosteroid or surgical therapy, some neuro-ophthalmologists may simply observe the patient as none of these treatments have been proved to be superior.

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