

# Approach to Optic Neuropathies

## Clinical Update

Sashank Prasad, MD, Nicholas J. Volpe, MD, and Laura J. Balcer, MD, MSCE

**Abstract:** Visual loss is a common symptom brought to the attention of the practicing neurologist. In this circumstance, the proper identification of an optic neuropathy is critical. Recognition of key clinical clues will permit the clinician to construct a likely differential diagnosis and pursue appropriate testing. This review first addresses the elements of the history and examination which are most useful in evaluating a patient with visual loss, and then briefly discusses the main entities responsible for causing unilateral and bilateral optic neuropathies.

**Key Words:** optic neuropathy, visual loss, clinical history, clinical examination

(*The Neurologist* 2010;16: 23–34)

### RECOGNIZING AN OPTIC NEUROPATHY: HISTORY AND EXAMINATION

Visual loss is a common symptom in clinical neurology. It is therefore important for the clinician to be fluent with the diagnosis and management of disorders of the optic nerve. Often the general etiology for an optic neuropathy can be established on the basis of clinical history (ie, character/progression of vision loss) and examination (ie, pattern of visual field loss and optic disc appearance), without the need for extensive ancillary testing. In the appropriate setting, directed evaluation with imaging studies (including MRI, optical coherence tomography [OCT], and orbital ultrasound), electrophysiologic studies (such as visual evoked responses), serologies, and genetic testing are essential in establishing the correct diagnosis. This review presents a rational approach to the evaluation of an optic neuropathy, with a focus on conducting a history and examination, establishing a differential diagnosis, and pursuing appropriate additional testing.

*In patients with compressive lesions, vision loss may be slowly progressive; in patients with optic neuritis it may quickly evolve and then subsequently improve; and in ischemic optic neuropathy it may be sudden with less significant improvement.*

Optic neuropathy is suggested by visual loss in the affected eye, and confirmed by features of the history and examination which distinguish optic neuropathy from retinal and ocular pathology. The patient will typically recognize the onset of visual loss earlier when central vision is affected. With more insidious, peripheral visual loss, patients may be unaware of the deficit and do not seek prompt medical attention. Furthermore, vision loss in 1 eye may go unnoticed because binocular acuity, which has greater practical relevance, is unaffected. The tempo of vision loss gives important clues regarding the potential etiology of an optic neuropathy. For example, in patients with compressive lesions vision loss may be slowly progressive; in patients with optic neuritis it may quickly evolve and then subsequently improve; and in ischemic optic neuropathy it may be sudden with less significant improvement.

Key components of a detailed examination confirm an optic neuropathy, and distinguish it from other causes of vision loss. Defective color vision, a relative afferent pupillary defect (RAPD), and an abnormal optic disc appearance are the hallmarks of an optic neuropathy. In cases of monocular vision loss in which these features are absent, the diagnosis of optic neuropathy should be considered unlikely and other etiologies should be sought.

Although central visual acuity is often reduced in optic neuropathies, it is an insensitive measure that does not reliably correlate with the extent of optic nerve dysfunction.<sup>1,2</sup> Refractive errors should be excluded as the cause of acuity loss by testing acuity with the patient wearing corrective lenses, or using a 2-mm pinhole that effectively reduces optical distortion. Visual acuity testing is typically performed with the Snellen eye chart. The ability to correctly discern a letter depends upon the patient's minimal angle of resolution. In humans this is typically between 30 seconds and 1 minute of arc for high-contrast central vision, which forms the basis for the size of the 20/20 Snellen "E."<sup>2</sup> Another sensitive measure of optic nerve function is low-contrast acuity, which allows identification of subtle deficits which spare high-contrast acuity<sup>3,4</sup> (Fig. 1).

*Reduced color vision, particularly out of proportion to loss of acuity, is a very sensitive indicator of optic neuropathy.*

Reduced color vision, particularly out of proportion to loss of acuity, is a very sensitive indicator of optic neuropathy<sup>5</sup> (Fig. 2). Patients frequently notice the acquired deficit, describing color desaturation with the affected eye. Although the Ishihara and Hardy-Rand-Rittler color plates were designed to assess congenital dyschromatopsia, they are a useful screening tool for acquired defects as well. Although there is a tradition of specifically testing perception of red hues, the most severe color desaturation as a result of optic neuropathy may in fact be in the bluish-green to purple range.<sup>6</sup> The reason that color desaturation is a prominent feature of optic neuropathy may be that normal color processing

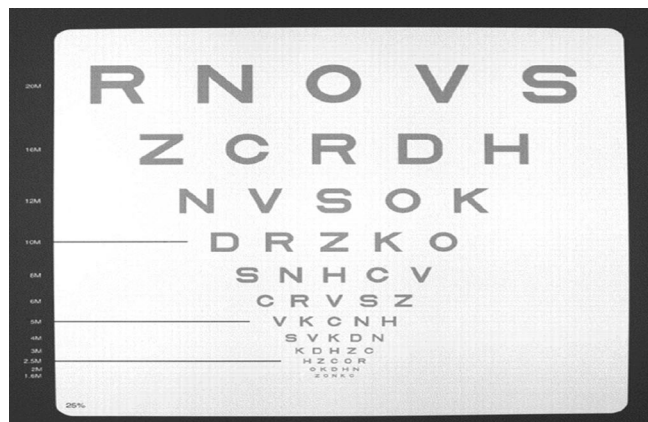
From the Division of Neuro-ophthalmology, Departments of Neurology and Ophthalmology; University of Pennsylvania School of Medicine, Philadelphia, PA.

Reprints: Sashank Prasad, MD, University of Pennsylvania School of Medicine, 3W Gates Bldg, 3400 Spruce St, Philadelphia, PA 19104. E-mail: sashank.prasad@uphs.upenn.edu.

Copyright © 2010 by Lippincott Williams & Wilkins

ISSN: 1074-7931/10/1601-0023

DOI: 10.1097/NRL.0b013e3181be6fad



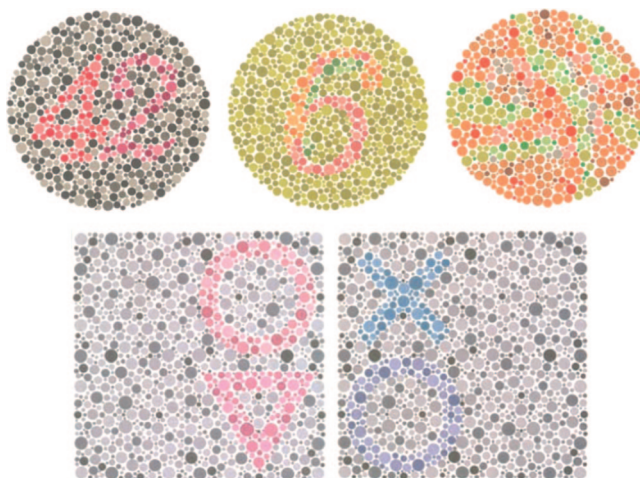
**FIGURE 1.** The Sloan low-contrast visual acuity chart, which is more sensitive than standard Snellen eye charts to subtle optic nerve dysfunction.

requires high-fidelity transmission, with a 1:1 relationship between color-sensitive cone photoreceptors and ganglion cells. These ganglion cell axons comprise a high proportion of the optic nerve, and their dysfunction is a reliable sign of optic nerve pathology.

Certain patterns of field loss may suggest particular etiologies of optic neuropathy, although considerable overlap prevents definitive conclusions on this basis alone. Both optic neuritis and compressive lesions generally produce central visual loss, while ischemic optic neuropathy typically produces a nerve fiber bundle field defect (originating from the physiologic blind spot and respecting the horizontal meridian, according to the arrangement of retinal fibers traveling to the optic disc) (Fig. 3).

The RAPD, as diagnosed by the swinging flashlight test, reliably identifies asymmetric optic nerve pathology.<sup>7,8</sup> Because an affected optic nerve contributes less to the consensual pupillary light response, a paradoxical dilation of both pupils will occur when light is received on that side (Fig. 4). The swinging flashlight test is quite sensitive, and can detect a small amount of unilateral optic nerve dysfunction (3 dB or more).<sup>8</sup> The magnitude of the RAPD reflects the extent to which one optic nerve is affected. Typically the RAPD is seen in the eye with worse acuity, but this may not be the case in the setting of severe peripheral field loss and spared foveal vision. An RAPD in the presence of a homonymous field defect suggests a lesion affecting the optic tract rather than the optic nerve. Other assessments of the pupillary reflex include pupil cycle time (duration for 30 oscillations of pupil constriction-dilation produced by a small beam of light from a slit-lamp) and infrared video pupillography (quantification of the pupil response amplitude to varying stimulus intensities).<sup>8</sup> However, these tests have several shortcomings (including a wide range of normal responses and difficulty of administration), limiting their use in clinical practice.

The appearance of the optic disc, which may be swollen, pale, or normal, provides critical information regarding the likely diagnosis.<sup>9,10</sup> In the setting of disc elevation, the distinction must be made between acquired disc edema (true disc swelling) and pseudopapilledema (including congenital anomalies, myelinated nerve fibers, and optic head drusen) (Figs. 5, 6). Inspection of the peripapillary nerve fiber layer provides important information. In true disc edema, the nerve fiber layer is hazy, obscuring the underlying retinal vessels, whereas in pseudopapilledema the vessels may remain distinct. In addition, the presence of spontaneous venous pulsations may support the diagnosis of pseudopapilledema (although spontaneous venous pulsations may be absent in up to 10% of normal individuals). Although subretinal hemorrhages may be present in patients with pseudopapilledema (particularly in the



**FIGURE 2.** Color plates used to screen for dyschromatopsia. Top, Ishihara color plates; Bottom, Hardy-Rand-Rittler color plates. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

setting of optic disc drusen), splinter hemorrhages are characteristic of true papilledema. The characteristic disc appearances in different types of optic neuropathy are discussed within the following sections.

### UNILATERAL OPTIC NEUROPATHY: DIFFERENTIAL DIAGNOSIS AND CLINICAL CLUES

The differential diagnosis of unilateral optic neuropathy is broad (Table 1). Identification of important clinical features helps to narrow the differential diagnosis for an individual patient. Although idiopathic demyelinating optic neuritis is a common cause, the differential also includes ischemic optic neuropathy, inflammatory and infectious conditions, compression, infiltrative or neoplastic processes, hereditary optic neuropathies, glaucoma, and retinal disorders.

#### Optic Neuritis

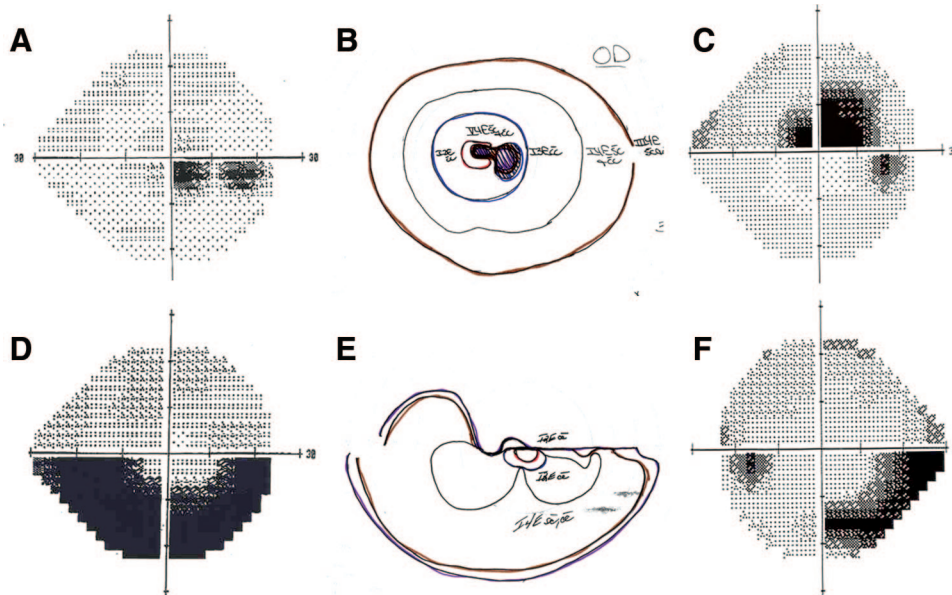
Optic neuritis, an inflammatory optic neuropathy specifically caused by demyelinating disease, most often occurs between the ages of 20 to 50 and is 3 times more frequent in women.<sup>11,12</sup> Visual loss occurs rapidly, reaches its nadir within 7 to 10 days and begins to recover within 1 month. Retro-orbital pain, particularly with eye movements, occurs in almost all cases; it may precede the visual loss and typically persists for 1 to 2 weeks. The prognosis for recovery of vision is generally good, but related to the severity of the initial deficit. Recovery typically begins within 1 month.

Characteristic findings on examination support the diagnosis of typical optic neuritis. Visual field defects, such as diffuse field loss or central scotomas, are common (Fig. 3A). In acute optic neuritis, one-third of patients have mild optic disc swelling; the remainder have retrobulbar inflammation and the optic nerve head will appear normal (Fig. 7). MRI may confirm mild optic nerve swelling, and gadolinium-enhanced T1-weighted fat-saturated sequences may specifically demonstrate retrobulbar optic nerve inflammation (Fig. 8).

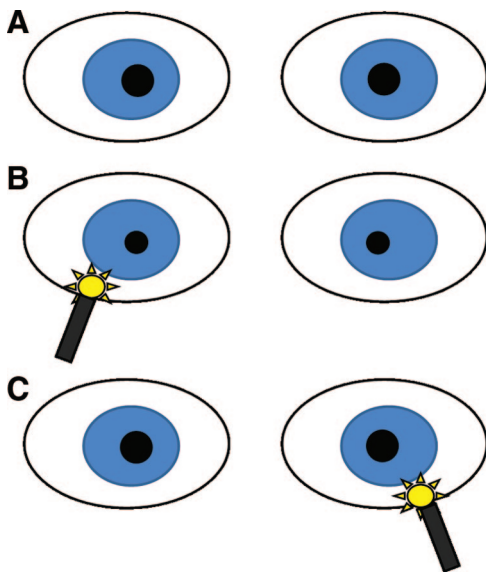
---

*The likelihood of optic neuritis progressing to multiple sclerosis is best predicted by brain magnetic resonance imaging at the time of diagnosis.*

---



**FIGURE 3.** Visual field defects in patients with optic neuropathies (grayscale output of Humphrey automated perimetry [A, C, D, and F] and kinetic Goldmann perimetry [B and E]). A, Central scotoma in a patient with right optic neuritis. B, Centrocecal scotoma (connecting to physiologic blind spot) in a patient with optic neuropathy due to B12 deficiency. C, Superior altitudinal central scotoma in a patient with inferior optic nerve compression due to a meningioma. D, Inferior arcuate altitudinal scotoma in a patient with nonarteritic ischemic optic neuropathy. E, Superior altitudinal scotoma in a patient with arteritic ischemic optic neuropathy. F, Inferonasal step in a patient with glaucomatous optic neuropathy. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)



**FIGURE 4.** Left afferent pupillary defect detected by swinging flashlight test. A, The pupils are equal in darkness. B, Light stimulation causes a consensual pupillary constriction. C, Light stimulation to the affected eye causes a paradoxical dilation of both pupils. This finding indicates relative dysfunction of the left optic nerve. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

The likelihood of optic neuritis progressing to multiple sclerosis (MS) is best predicted by brain MRI at the time of diagnosis.<sup>12–14</sup> In the Optic Neuritis Treatment Trial, the risk of developing MS within 15 years was 72% among patients with one or more

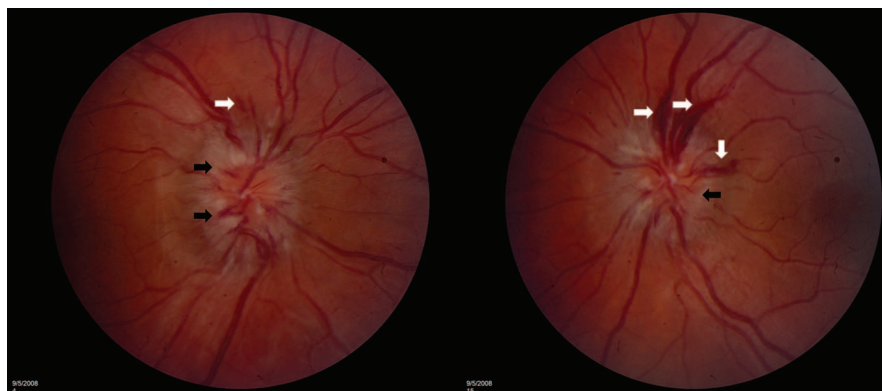
characteristic brain lesions, whereas it was 25% with a normal MRI.<sup>13,14</sup> Optic neuritis should be treated with intravenous corticosteroids to reduce the risk of developing MS over the following 2 years. In the long-term, however, acute treatment with steroids is unlikely to affect the likelihood of progression to MS. Treatment with intravenous corticosteroids may also speed up recovery of visual function, particularly for visual fields and contrast sensitivity, although does not significantly affect long-term visual outcomes. Oral corticosteroids, however, may be associated with an increased risk of recurrence of optic neuritis, and this therapy should be avoided. In addition to intravenous corticosteroids, recent studies support the early use of immunomodulating treatments including interferon  $\beta$ -1a, interferon  $\beta$ -1b, or glatiramer acetate for high-risk patients to reduce the likelihood of progression to MS within 2 to 5 years.<sup>15,16</sup>

After an episode of optic neuritis, the optic nerve will often demonstrate pallor, suggesting that axonal loss has accompanied the episode of demyelination (Fig. 9). Optical coherence tomography, discussed below, provides a relatively easy, noninvasive method of quantifying atrophy of the nerve fiber layer.<sup>17,18</sup> It provides a reliable structural marker that complements clinical assessments of visual function.

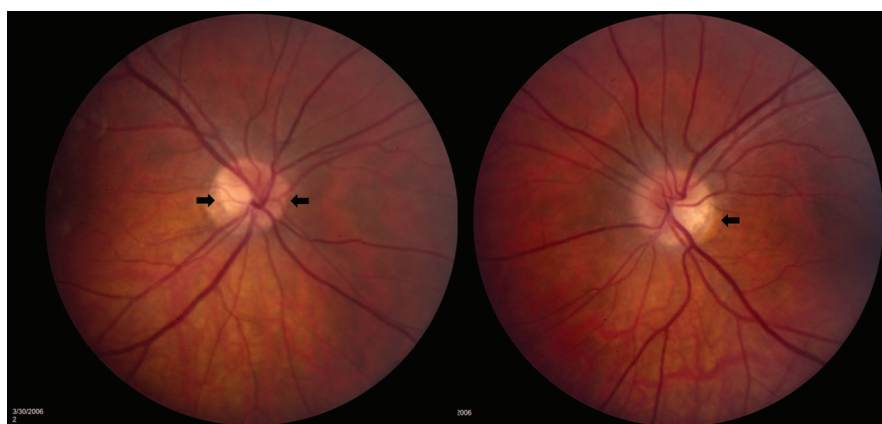
Neuromyelitis optica, or Devic’s disease, is characterized by necrotizing demyelinating lesions of bilateral optic nerves and the spinal cord.<sup>19</sup> It is believed to be a humorally mediated disease distinct from MS. A serum antibody, NMO-IgG, which targets the autoantigen aquaporin-4, may be a useful marker in diagnosing the condition; its specificity for NMO, however, remains unknown. Treatment with rituximab, a chemotherapeutic monoclonal antibody, may be of particular benefit in this group of patients.<sup>20</sup>

Features which are atypical for optic neuritis should prompt a rigorous search for other causes of monocular visual loss.<sup>12</sup> These “red flags” include an unusual temporal profile (progression beyond 2 weeks, or lack of recovery within 1 month), absence of pain, an unusual scotoma (such as an altitudinal defect), or an atypical fundus-

**FIGURE 5.** Fundus photographs in a patient with acute papilledema. Note that swelling of the peripapillary nerve fiber layer causes an obscured view of underlying retinal vessels (for example, black arrows). Splinter hemorrhages, which also suggest true papilledema rather than pseudopapilledema, are seen (white arrows). (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)



**FIGURE 6.** Fundus photographs in a patient with pseudopapilledema. There is a “lumpy-bumpy” disc appearance due to visible disc drusen (for example, black arrows). Note that retinal vessels are not obscured by nerve fiber layer edema. Spontaneous venous pulsations may also indicate pseudopapilledema. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)



**TABLE 1.** Differential Diagnosis for Monocular Visual Loss

Condition	Types	Characteristic Features
Optic neuritis	Idiopathic optic neuritis, multiple sclerosis	Retro-orbital pain; visual recovery starts within 1 month; normal-appearing optic nerve or mild disc swelling
Ischemic optic neuropathy	Arteritis, nonarteritic ischemic optic neuropathy	Typically no pain; disc swelling with nerve fiber layer hemorrhages
Inflammatory optic neuropathy	Sarcoidosis, systemic lupus erythematosus, Sjögren's syndrome	Anterior uveitis or posterior segment vitritis
Infectious optic neuropathy	Paranasal sinusitis, cat scratch disease ( <i>Bartonella henselae</i> ), syphilis ( <i>Treponema pallidum</i> ), Lyme disease ( <i>Borrelia burgdorferi</i> ), toxoplasmosis, cytomegalovirus, cryptococcus	Neuroretinitis (optic disc swelling and retinal exudates)
Compression	Paranasal mucocele, meningioma (optic nerve sheath or skull base), bony compression (fibrous dysplasia), enlarged extraocular muscles, aneurysms	Optic disc swelling in intraorbital compression; atrophy in intracranial or intracanalicular compression; optic nerve head shunt vessels in chronic compression
Neoplasm	Optic nerve glioma, optic nerve glioblastoma multiforme	Progressive visual loss
Hereditary	Leber hereditary optic neuropathy	Circumpapillary telangiectatic microangiopathy, nerve fiber layer pseudoedema
Glaucomatous	Chronic glaucoma, acute angle closure glaucoma	Elevated intraocular pressure and optic disc cupping in chronic glaucoma; excruciating pain and scleral injection in acute angle closure glaucoma
Retinal	Chronic serous chorioretinopathy, retinal artery occlusion, retinal vein occlusion, acute idiopathic blind spot enlargement syndrome	Macular serous detachment (CSR), retinal whitening (RAO), retinal hemorrhage and engorged veins (RVO), peripapillary pigmentary changes (AIBSE)

**TABLE 2.** Diagnostic Testing Considerations

Imaging	MRI brain and orbits, optical coherence tomography, fluorescein angiography
Serologies	NMO-IgG, RPR, titers for Lyme, toxoplasmosis, <i>Bartonella henselae</i> , West Nile Virus, HIV, HSV, ACE, ANA, SS-a, SS-b; lumbar puncture for cell counts, protein, glucose, oligoclonal bands, and PCR for Lyme, HSV, WNV
Genetic testing	Leber hereditary optic neuropathy mitochondrial DNA testing
Electrophysiology	Visual evoked potentials, electroretinogram



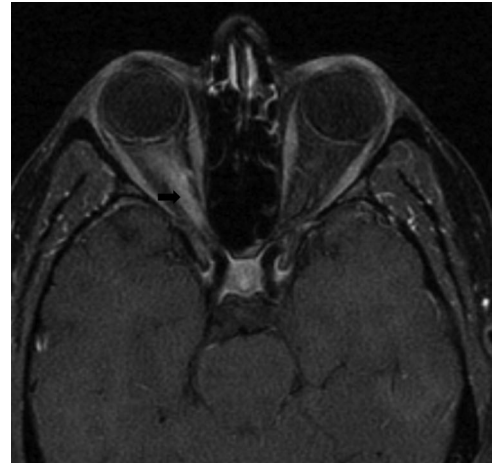
**FIGURE 7.** Fundus photograph of the right eye in a patient with acute right optic neuritis. Note mild nerve fiber layer swelling greatest at the temporal portion of the disc (black arrow), without hemorrhages or cotton wool spots. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

scopic examination (including a nerve that is markedly swollen or atrophic, or retinal abnormalities such as hemorrhages, inflammation, or exudates). These features portend a significantly lower risk of developing MS compared with typical cases of optic neuritis.<sup>13</sup>

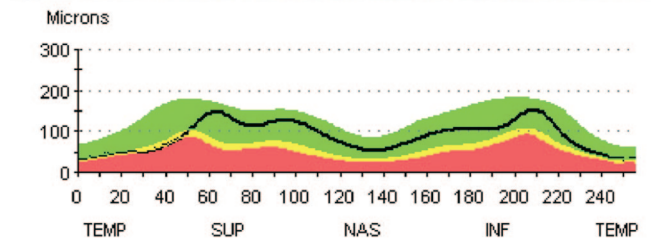
*The coexistence of retinal ischemia with cotton-wool spots and disc swelling is virtually pathognomonic for arteritic anterior ischemic optic neuropathy.*

**Ischemic Optic Neuropathy**

Arteritic anterior ischemic optic neuropathy is usually related to giant cell arteritis (GCA), and is almost always associated with disc swelling. The prevalence of temporal arteritis increases with age, and is quite rare under the age of 60. It is most common in white women. The disc typically has a chalky white edematous appearance, and disc hemorrhages are likely to be present (Fig. 10). The coexistence of retinal ischemia with cotton-wool spots and disc swelling is virtually pathognomonic for arteritic anterior ischemic optic neuropathy. Fluorescein angiography reveals choroidal hypoperfusion (Fig. 11). Rarely, GCA can be limited to the retro-orbital nerve and present without disc



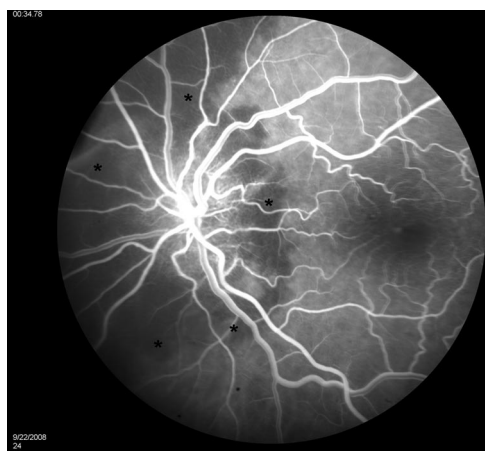
**FIGURE 8.** Axial T1-weighted postgadolinium MRI with fat-saturation in a patient with right optic neuritis. Note swelling and enhancement of the right optic nerve (black arrow) consistent with inflammation.



**FIGURE 9.** Top, Fundus photographs of the left eye in a patient with prior left optic neuritis, demonstrating mild temporal pallor (black arrow). Below, OCT measurement of retinal nerve fiber layer thickness confirms temporal nerve fiber layer thinning (corresponding to the papillomacular bundle). Thickness measurement is shown in black line, with normal range depicted in the green zone; measurements within the yellow zone are borderline and within the red zone are abnormally low. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

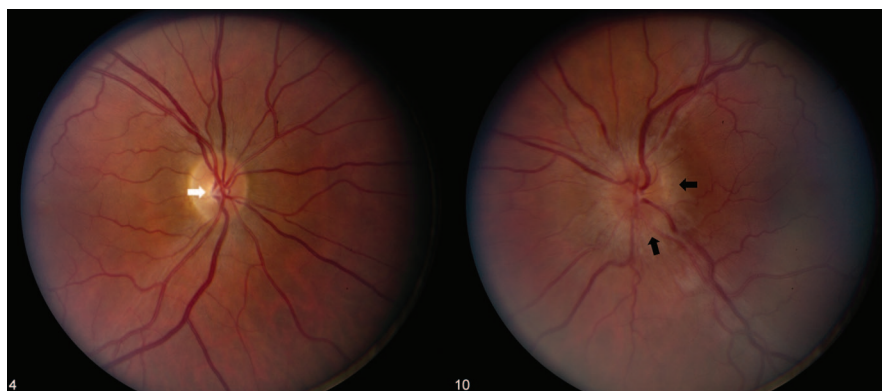


**FIGURE 10.** Fundus photograph of the right eye in a patient with ischemic optic neuropathy from temporal arteritis. Note blurring of the nasal disc margin with pallor and swelling of the nerve head (black arrow). The patient also has inner retinal ischemia, evidenced by large cotton wool spots (black asterisks). (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)



**FIGURE 11.** Late-phase fluorescein angiography of the left eye in a patient with giant cell arteritis, revealing nonperfused choroid (black asterisks) consistent with occlusion of posterior ciliary vessels.

**FIGURE 12.** Fundus photographs in a patient with acute nonarteritic ischemic optic neuropathy in the right eye, demonstrating peripapillary edema (black arrows) with a small cup:disc ratio in the left eye (white arrow), suggesting a “disc at risk.” (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

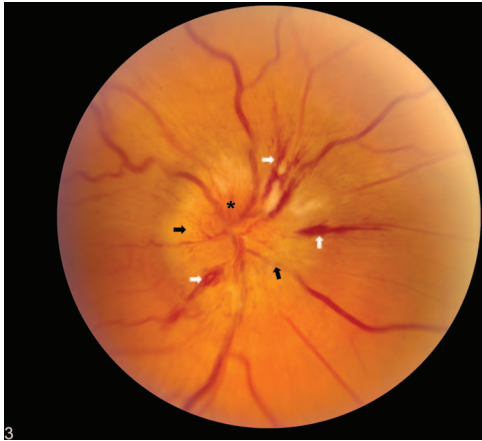


swelling; this situation is termed arteritic posterior ischemic optic neuropathy (PION). GCA typically affects extracranial medium to large arteries, because they possess elastic lamina, which is the initial site of inflammation in this disorder.<sup>21</sup> The condition is associated with polymyalgia rheumatica, consisting of proximal myalgia and arthralgia, as well as with jaw claudication, fever, malaise, and scalp tenderness. The diagnosis is suggested by an elevated erythrocyte sedimentation rate and C-reactive protein, and confirmed by evidence of giant cells and endovascular inflammation on temporal artery biopsy. In suspected cases, treatment with corticosteroids should not be delayed until a biopsy is obtained. Intravenous corticosteroids help mitigate the risk of further visual loss, and decrease the likelihood of fellow eye involvement. The prognosis for recovery in the affected eye, however, is poor despite treatment.

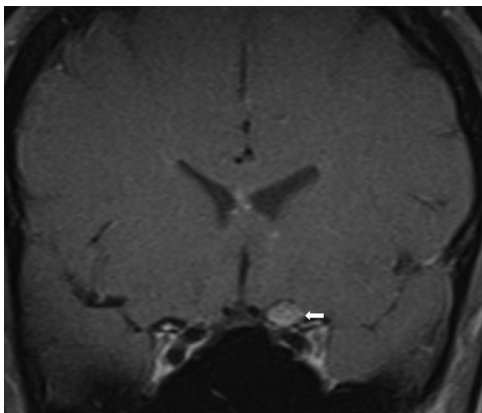
Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common cause of unilateral optic neuropathy in adults over the age of 50, and is commonly associated with vascular risk factors such as diabetes or hypertension.<sup>22</sup> Other risk factors include a crowded optic nerve head (small cup to disc ratio) and nocturnal hypotension, possibly precipitated by antihypertensive therapy<sup>22</sup> (Fig. 12). Swelling of a crowded optic nerve within the scleral canal may provoke a cycle of further vascular compression, ischemia, and swelling. Although the clinical profile of NAION may occasionally overlap with the findings of optic neuritis,<sup>23</sup> typical features of NAION include nerve fiber hemorrhages, altitudinal visual field loss, moderate-to-severe disc edema, and the absence of pain (Fig. 13). Because the optic nerve head is supplied by an end-arterial system (the short posterior ciliary arteries and the circle of Zinn-Haller), sectoral ischemic disc swelling is common. NAION may follow ocular surgery, because an associated increase in intraocular pressure may compromise optic nerve head perfusion.<sup>22</sup>

Many patients with NAION will have a stable deficit, although in some cases visual loss will progress over a month. There can be spontaneous improvement in the first 6 months, although in many patients this reflects improved ability with eccentric fixation.<sup>24</sup> Although prospective, randomized, controlled studies do not exist, there is some suggestion that corticosteroids may improve the visual outcome.<sup>25</sup> These patients have a 30% to 40% lifetime risk of subsequent involvement of the fellow eye. Occasionally, premonitory disc swelling in an asymptomatic eye will be noted, which may progress to frank visual loss or remit spontaneously.<sup>26</sup> Recurrence of NAION in an affected eye is rare, possibly because optic nerve atrophy following the initial event decompresses the nerve. There does not appear to be a significantly higher rate of stroke in patients with NAION, suggesting that its pathophysiology may differ from simple vaso-occlusion.

PION is a rare entity presenting with acute optic nerve dysfunction without nerve swelling.<sup>27</sup> Before diagnosing nonarteritic ischemia,



**FIGURE 13.** Fundus photographs of the right eye in a patient with right nonarteritic anterior ischemic optic neuropathy. Note blurring of the disc margin and swelling of the optic nerve head (black arrows), splinter hemorrhages (white arrows), as well as dilated capillaries and luxury perfusion of the nerve head (asterisk). (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

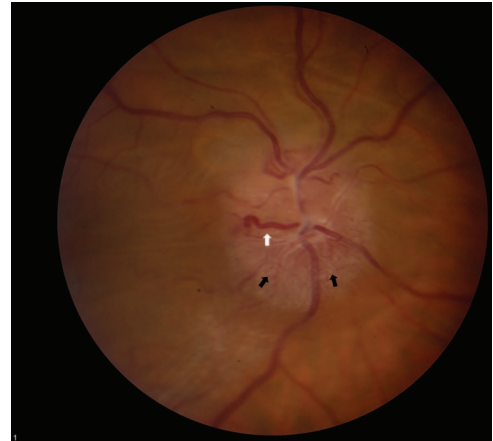


**FIGURE 14.** Coronal T1-weighted postgadolinium MRI in a patient with left optic neuropathy from neurosarcoidosis. Note swelling and enhancement of right optic nerve (white arrow).

it is mandatory to perform a thorough work-up for entities such as GCA and other inflammatory, infiltrative processes. In the correct clinical context, PION may be the result of severe blood loss, anemia, hyperviscosity syndromes, and prolonged surgical procedures (notably spinal surgery). PION often causes a central scotoma, because interruption of the normal blood supply to the posterior optic nerve (via the anastomotic circumferential pial plexus) causes watershed ischemia within the center of the nerve, where the macular fibers lie.<sup>27</sup> In postsurgical PION, tissue perfusion may be compromised as a result of increased orbital venous pressure due to orbital edema and simultaneous arterial hypotension.<sup>22</sup>

### Other Conditions

Inflammatory conditions are an important cause of subacute optic neuropathy. Optic nerve involvement is common in neurosarcoidosis, which can be accompanied by anterior uveitis or posterior segment vitritis<sup>28</sup> (Fig. 14). Visual loss due to this condition is often steroid-responsive. Optic neuropathy may also occur with other inflammatory disorders, such as systemic lupus erythematosus and Sjögren's syndrome.



**FIGURE 15.** Fundus photograph of the right eye in a patient with chronic disc swelling. Note blurred disc margins (black arrows) and an optociliary shunt vessel (white arrow). (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

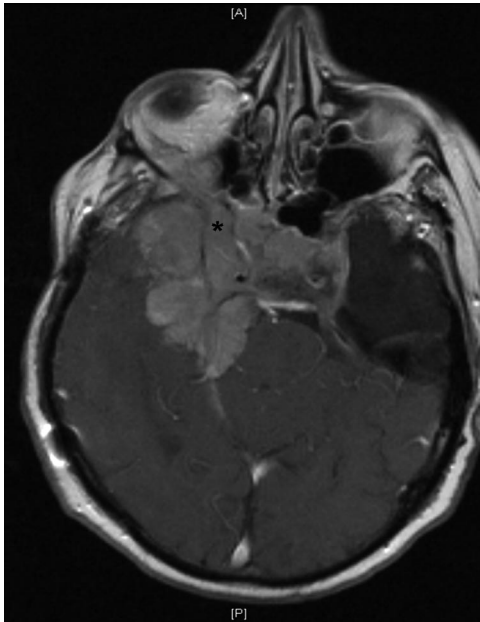
Infectious conditions are other frequent cause of optic neuropathy.<sup>29</sup> Neuroretinitis, in which optic neuropathy coexists with characteristic peripapillary or macular exudates, may be due to cat scratch disease (*Bartonella henselae*), syphilis (*Treponema pallidum*), or Lyme disease (*Borrelia burgdorferi*). In most cases, *Bartonella* infection is self-limited and does not require treatment, but doxycycline may be effective in severe cases. Other infectious causes of optic neuropathy include HIV and opportunistic infections including toxoplasmosis, cytomegalovirus, and cryptococcus. Paranasal sinusitis or mucocele may lead to either compressive or inflammatory optic neuropathy.

A variety of compressive mass lesions can cause a progressive optic neuropathy. The optic disc will be swollen in cases of intraorbital compression, but in cases of retro-orbital compression disc swelling will only occur if intracranial pressure is elevated. Chronic disc edema due to compressive lesions may be accompanied by optociliary shunt vessels and glistening white bodies on the disc surface (pseudodrusen from extruded axoplasm) (Fig. 15). Important causes of compressive optic neuropathy include neoplasm (including optic nerve sheath or skull base meningioma, pituitary adenoma, and craniopharyngioma), sinus lesions, bony processes (such as fibrous dysplasia), enlarged extraocular muscles (as in Graves ophthalmopathy), or aneurysms (Fig. 16).

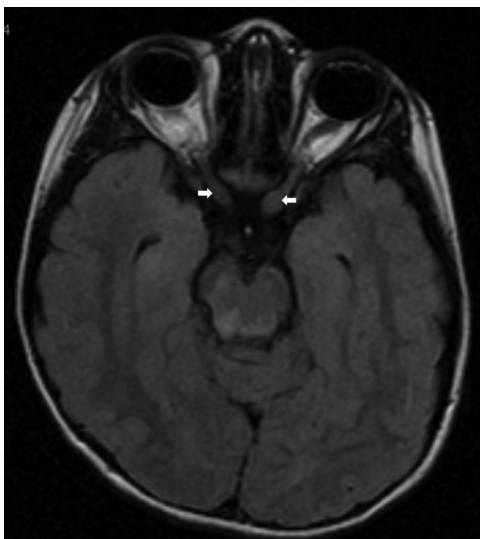
Primary optic nerve neoplasms include benign juvenile pilocytic glioma in children, and rarely malignant glioblastoma in adults<sup>30</sup> (Fig. 17). Juvenile pilocytic astrocytoma is often associated with neurofibromatosis type 1 and may be managed conservatively with frequent ophthalmologic examination through adolescence. When clinical or radiographic progression is detected, chemotherapy should be first-line therapy, followed by radiation and rarely surgery.<sup>30</sup> Malignant optic nerve glioblastoma is much rarer, affects adults, and has a considerably worse prognosis.<sup>31</sup> Other neoplastic conditions include lymphoma, leukemia, carcinomatous meningitis, and optic nerve metastasis. Almost any form of carcinoma can metastasize to the optic nerve; breast and lung carcinomas are the most common.

Optic neuropathy may occur as a delayed effect of radiation therapy, and can sometimes be difficult to distinguish from tumor recurrence.<sup>32</sup> Radiation optic neuropathy is suggested by exposure (typically 50 Gy dosage), characteristic 6 to 24 month time-lag to symptoms, and accompanying radiation changes in proximal tissues. Progression occurs over weeks to months, and spontaneous recovery is rare. Corticosteroids may help by reducing edema in the affected optic nerve.

*In paraneoplastic optic neuropathy there is often evidence of other neurologic dysfunction, and the antibody most commonly identified is directed toward collapsin response mediated protein-5.*



**FIGURE 16.** Axial T1-weighted postcontrast MRI in a patient with an extensive sphenoid wing meningioma (asterisk), causing left optic nerve compression, ocular motor palsies, and proptosis.

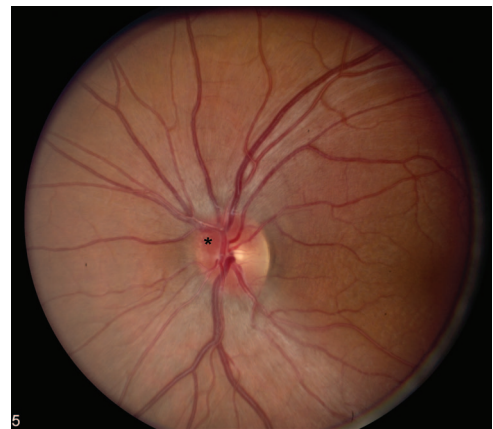


**FIGURE 17.** Axial FLAIR MRI in a patient with bilateral optic nerve gliomas (juvenile pilocytic astrocytomas) (white arrows). The patient had stigmata of neurofibromatosis type 1.

Visual loss in a patient with known or suspected cancer raises the possibility of a paraneoplastic optic neuropathy or retinopathy.<sup>33</sup> In paraneoplastic optic neuropathy there is often evidence of other neurologic dysfunction, and the antibody most commonly identified is directed toward collapsin response mediated protein-5. Paraneoplastic retinopathies, on the other hand, include cancer-associated retinopathy (with antibodies to recoverin protein) and melanoma-associated retinopathy (with antibodies to rod ganglion cells).

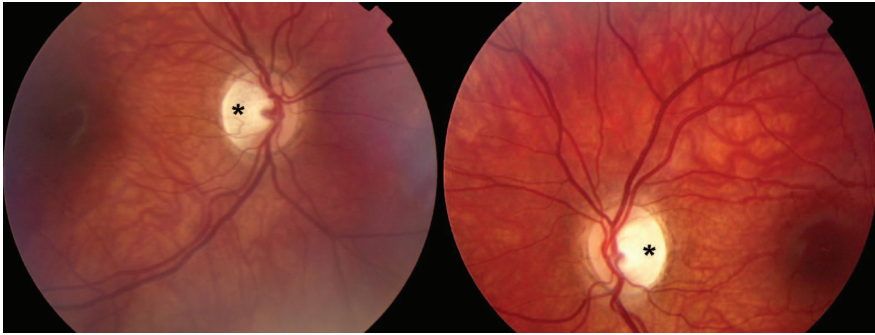
Leber hereditary optic neuropathy (LHON) is an uncommon subacute optic neuropathy which most commonly occurs in the second or third decade.<sup>34,35</sup> The condition arises from mitochondrial DNA mutations that impair cellular energy stores from dysfunction of complex I in the electron transport chain. There is maternal inheritance, with incomplete penetrance within families. Men are affected in 80% to 90% of cases, but the reasons for this gender asymmetry are unclear. Loss of vision is bilateral at onset in up to 55% of cases, and in the remainder the fellow eye will be affected within 9 months. It remains controversial whether there is initial sparing of fibers subserving the pupillary light reflex.<sup>8</sup> Although there is no true disc edema in LHON, the optic disc may appear hyperemic and mildly swollen in the acute phase; fluorescein angiography will confirm the absence of capillary leakage (Fig. 18). Circumpapillary telangiectatic vessels are an important clue to the diagnosis. These early fundusoscopic changes may also be noted in presymptomatic eyes. Thus a patient may present with symptoms of involvement of only one eye, but be clinically suspected of having LHON based on characteristic disc changes in both eyes. The typical fundus changes will resolve as the disease progresses, eventually leaving nerve pallor. Most patients have permanent vision loss, although a minority will experience some recovery of vision. The prognosis depends upon the specific mutation harbored; patients with mtDNA mutation T14484C are more likely to have spontaneous recovery than patients with mutations G11778A or G3460A.<sup>35</sup> There is currently no effective treatment for LHON, but it may be prudent to avoid potential toxins including alcohol or tobacco.

Dominantly inherited optic atrophy typically presents with insidious, asymmetric visual loss in childhood.<sup>35</sup> These patients often have a striking disc appearance, with pallor and excavation of the temporal portion of the disc (Fig. 19). The disorder is due to mutations of the *OPA1* gene, with autosomal inheritance and variable penetrance. The *OPA1* gene product is believed to target the mitochondria and support membrane stability. Because over 90

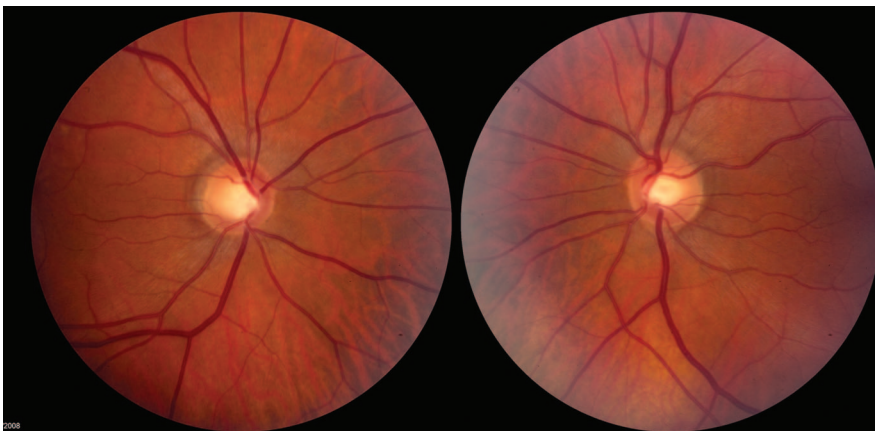


**FIGURE 18.** Fundus photograph of the left eye in a patient Leber hereditary optic neuropathy. Note hyperemia with appearance of slight nasal disc swelling (asterisk). (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)





**FIGURE 19.** Fundus photographs in a patient with dominant optic atrophy. Note extreme temporal pallor, with excavated appearance (asterisks). (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)



**FIGURE 20.** Fundus photographs in a patient with long-standing glaucoma. Note increased cup:disc ratio in the right eye. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

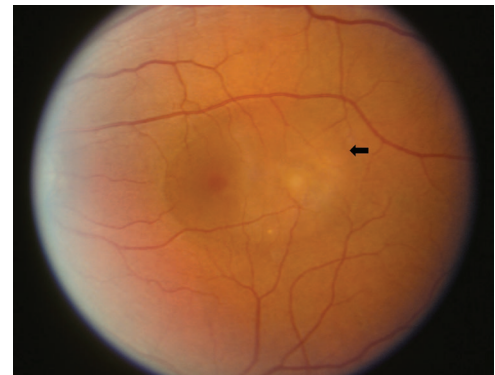


**FIGURE 21.** Axial CT scan (bone windows) from a patient with direct left traumatic optic neuropathy due to avulsion by a BB pellet.

different pathogenic *OPA1* mutations have been described, a simple DNA test does not exist as it does for LHON.

Other rare causes of hereditary optic neuropathy include Wolfram (DIDMOAD) syndrome, characterized by diabetes insipidus, juvenile diabetes mellitus, optic atrophy, and deafness and mitochondrial disorders including mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF), and Leigh subacute necrotizing encephalomyelopathy syndrome.<sup>35</sup> Optic neuropathy will not occur in isolation in these conditions, and diagnosis depends upon recognition of multifocal derangements.

Glaucomatous optic neuropathy is typically easily distinguished from optic neuritis, as it occurs in the setting of elevated intraocular pressure and optic disc cupping<sup>36</sup> (Fig. 20). However, angle closure glaucoma may present with painful acute visual loss, resembling the features of optic neuritis. Distinguishing character-



**FIGURE 22.** Fundus photograph of the left eye in a patient with central serous retinopathy. Note elevation of the inner retina (black arrow) with underlying fluid collection. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

istics include the severity of pain (which can be excruciating) and a red eye with an enlarged, nonreactive pupil. Normal-tension glaucoma is more difficult to recognize, but will present with optic disc cupping and progressive field constriction, despite normal intraocular pressures; many of these patients have a fairly benign natural history.<sup>37</sup>

Direct traumatic optic neuropathy may include nerve avulsion or transection and is easily recognized by the relevant history of injury<sup>38</sup> (Fig. 21). Fundus examination may reveal extensive intraocular hemorrhages. In contrast, posterior indirect traumatic optic neuropathy will present with visual loss in the absence of significant fundus abnormalities. It may result from shearing forces and subse-

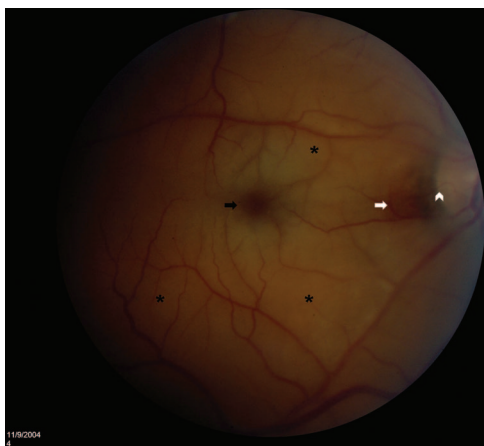
quent edema within the optic canal. Up to one-half of these patients may improve spontaneously.<sup>38</sup> There is weak evidence that corticosteroid therapy may be helpful within the first 8 hours; no other medical or surgical interventions have been proven effective.<sup>39,40</sup>

A number of retinal conditions may present with symptoms similar to optic neuritis, but these can be distinguished from the history and examination. These patients often describe metamorphopsia (distorted or bent images) or photopsia (sparkles of light). In acute idiopathic blind spot enlargement syndrome, examination reveals peripapillary pigmentary changes without disc swelling. Central serous retinopathy presents with acute, painless visual loss due to macular retinal detachment (Fig. 22). The hallmark of retinal artery occlusion is retinal whitening, with a macular cherry red spot from preserved choroidal circulation, and that of retinal vein occlusion is retinal hemorrhage and engorgement of retinal veins (Figs. 23, 24).

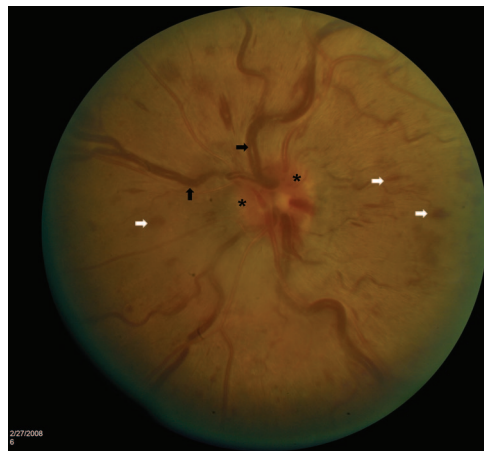
## BILATERAL OPTIC NEUROPATHY: DIFFERENTIAL DIAGNOSIS AND CLINICAL CLUES

### Papilledema

The term papilledema refers specifically to optic disc swelling that occurs secondary to increased intracranial pressure (Fig. 5). Disc swelling in papilledema results from blockage of axoplasmic flow in nerve fibers, with a consequent increase in the volume of axoplasm in the optic disc. Although papilledema is typically bilateral, it can be asymmetric based on anatomic differences in the meningeal covering of the intracranial optic nerves, leading to differences in transmitted pressure. In the acute phase of papilledema, there is a mismatch between a markedly swollen disc and relatively spared optic nerve function, particularly central visual acuity. When acute papilledema is accompanied by decreased acuity (and possible metamorphopsia), the cause is typically extension of fluid within the nerve fiber layer, reaching the macula itself. As increased intracranial pressure and papilledema persist, optic nerve axons are damaged and visual field loss develops. At this stage, optic disc swelling lessens and disc pallor occurs (atrophic papilledema) (Fig. 25).



**FIGURE 23.** Fundus photograph of the right eye in a patient with central retinal artery occlusion. Note severe retinal pallor (asterisks) and macular cherry red spot (black arrow), due to spared choroidal perfusion of the macula. In addition, note small region of spared retinal perfusion (white arrow), due to a visible cilioretinal artery (white arrowhead). (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)



**FIGURE 24.** Fundus photograph of the left eye in a patient with central retinal vein occlusion. Note mild disc swelling and hyperemia (asterisks), engorgement of retinal veins (black arrows), and intraretinal dot-and-blot hemorrhages (for example, white arrows). (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)



**FIGURE 25.** Fundus photograph of the right eye of a patient with chronic papilledema. Note pale, gliotic "champagne-cork" disc appearance, without retinal hemorrhages. (Color figure available online at [www.theneurologist.org](http://www.theneurologist.org).)

Papilledema due to increased intracranial pressure can be the consequence of numerous processes. An expanding mass lesion, such as a brain tumor, cerebral edema due to stroke, or intracranial hemorrhage will increase intracranial pressure, particularly in a younger patient without age-related brain atrophy. Compression of the ventricular system in the posterior fossa is very likely to cause papilledema. Venous sinus thrombosis is another common cause, particularly in pregnancy and other states of hypercoagulability. Cryptococcal meningitis is the infectious etiology most commonly associated with significant papilledema.

Pseudotumor cerebri, or idiopathic intracranial hypertension, can lead to disc swelling and progressive visual loss. The condition is most common in obese women, but moderate weight gain (by 5%–15%) even in nonobese women is a risk factor for disease.<sup>41</sup> Additional risk factors are the use of tetracycline derivatives or vitamin A. Weight loss and discontinuation of offending agents are imperative. In cases of visual loss, treatment with acetazolamide,

followed by optic nerve sheath fenestration in refractory cases, may be indicated.

### Other Causes

Hypertensive emergency may produce bilateral optic disc swelling that is indistinguishable from papilledema. Encephalopathic signs are common, but not always present. Peripapillary cotton-wool spots are also a prominent fundoscopic feature in patients with malignant hypertension.

Diabetic papillopathy is a rare cause of bilateral (or sometimes unilateral) disc swelling in patients with type I diabetes. This entity is distinct from typical NAION in that there is often bilateral, simultaneous optic nerve involvement; often optic nerve dysfunction is minimal, with blind spot enlargement and a mild deficit in acuity. Disc edema is accompanied by capillary telangiectasias overlying the disc surface. The pathogenesis may relate to impaired blood flow causing disc swelling, but not severe enough to significantly impair optic nerve function, as in the case of incipient NAION.<sup>26</sup> In many cases, the optic disc edema resolves without residual visual deficit.

A toxic/nutritional optic neuropathy is suggested by painless, symmetrical visual loss. Occasionally, involvement of one eye may manifest before the fellow eye. The optic nerves may appear normal or atrophic. Classically, toxic/nutritional optic neuropathies are associated with centrocecal scotomas (central scotomas that connect to the normal blind spot). Tobacco-alcohol amblyopia refers to an optic neuropathy putatively related to combined malnourishment and chronic, toxic exposure to alcohol and tobacco. Vitamin B<sub>12</sub> deficiency is a common cause of nutritional optic neuropathy. Finally, ethambutol causes optic neuropathy, with a dose-toxicity relationship. Although most toxic optic neuropathies present with normal-appearing optic discs, disc edema is characteristic of methanol poisoning.

### CONDUCTING AN APPROPRIATE WORK-UP

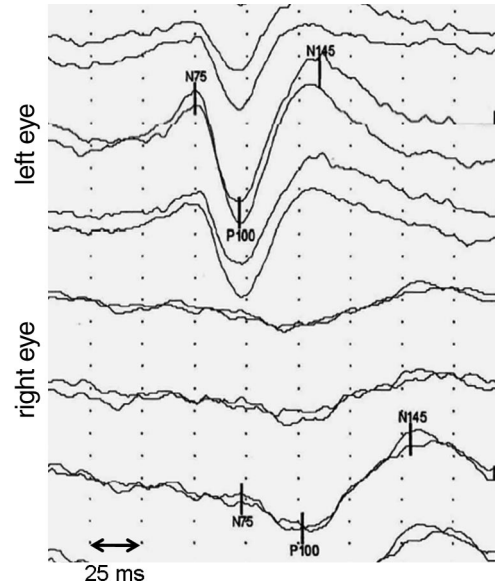
Once the differential diagnosis has been narrowed on the basis of the clinical history and physical examination, an appropriate diagnostic work-up is imperative to confirm the correct diagnosis.

All patients with typical optic neuritis should undergo brain MRI to assess the risk of MS. MRI of the orbits may confirm optic nerve enhancement in the majority of patients with optic neuritis and may be helpful to exclude alternative causes of optic neuropathy. Testing for NMO-IgG (neuromyelitis optica antiaquaporin-4 antibody) is useful in patients with recurrent, bilateral, or severe optic neuritis, especially in patients with longitudinally extensive transverse myelitis.

OCT is usually normal in acute optic neuritis, but may reveal thickening of the nerve fiber layer consistent with mild edema. OCT evaluates tissue thickness to a resolution of less than 10  $\mu\text{m}$ , evaluating the echo time delay of back-scattered near infrared light. It may be helpful in distinguishing some retinal conditions from optic neuropathy. An electroretinogram may be helpful in patients with suspected retinal dystrophy, paraneoplastic retinopathy, retinal artery occlusion or a retinal inflammatory process. Likewise, fluorescein angiography may also confirm retinal inflammatory or ischemic processes, and will demonstrate capillary leakage in papilledema, but not pseudopapilledema.

Visual evoked potentials are not routinely used in the diagnosis of demyelinating optic neuritis, although the finding of a P100 response with prolonged latency provides good evidence for optic nerve demyelination (Fig. 26). Testing may be helpful when there is a question of retinal disease versus optic neuritis or when subclinical optic neuritis is suspected.

In the routine case of optic neuritis, serological tests are of limited diagnostic value. However, in patients with atypical or



**FIGURE 26.** Visual evoked potentials from a patient with right optic neuritis. The P100 response from the left eye is normal (96 milliseconds). From the right eye the P100 response is abnormally prolonged (127 milliseconds), indicating a prechiasmatic conduction delay.

systemic features, serum testing may be considered for syphilis, Lyme disease, toxoplasmosis, cat scratch fever, West Nile Virus, HIV infection, and Herpes virus infection, as well as serum ACE level, antinuclear antibodies, and Sjogren antibodies. In cases of suspected inflammatory or infectious optic neuropathy, lumbar puncture is necessary.

Finally, genetic testing for Leber optic neuropathy is useful in patients with painless visual loss that is severe or bilateral, particularly if they are young men. In the appropriate setting, genetic testing for other hereditary conditions, such as mitochondrial diseases, may be considered.

### CONCLUSIONS

A patient with an optic neuropathy may demonstrate a number of abnormalities on careful examination, including decreased acuity, color vision, a RAPD, visual field loss, and an abnormal disc appearance. Recognizing patterns of these deficits permits the clinician to distinguish an optic neuropathy from other causes of monocular vision loss. Furthermore, knowledge of the characteristics of various causes of optic neuropathy helps to narrow a broad differential diagnosis and execute an efficient, targeted work-up.

### REFERENCES

1. Frisen L. The neurology of visual acuity. *Brain*. 1980;103:639–670.
2. Kniestedt C, Stamper RL. Visual acuity and its measurement. *Ophthalmol Clin North Am*. 2003;16:155–170, v.
3. Baier ML, Cutter GR, Rudick RA, et al. Low-contrast letter acuity testing captures visual dysfunction in patients with multiple sclerosis. *Neurology*. 2005;64:992–995.
4. Balcer LJ, Baier ML, Pelak VS, et al. New low-contrast vision charts: reliability and test characteristics in patients with multiple sclerosis. *Mult Scler*. 2000;6:163–171.
5. Melamad A, Hagstrom S, Traboulsi E. Color vision testing. *Ophthalmic Genet*. 2004;25:159–187.
6. Lanthony P. Color vision defects in optic neuropathies. Clinical forms. *Ophthalmologie*. 1987;1:27–30.

7. Levatin P. Pupillary escape in disease of the retina or optic nerve. *Arch Ophthalmol*. 1959;62:768–779.
8. Bremner FD. Pupil assessment in optic nerve disorders. *Eye*. 2004;18:1175–1181.
9. Jonas JB, Budde WM, Panda-Jonas S. Ophthalmoscopic evaluation of the optic nerve head. *Surv Ophthalmol*. 1999;43:293–320.
10. Prasad S, Balcer LJ. Abnormalities of the optic nerve and retina. In: Bradley WG, Daroff RB, Fenichel GM, et al, eds. *Neurology in Clinical Practice*, 5th ed. Philadelphia, PA: Elsevier; 2008:183–196.
11. Group ONS. The clinical profile of optic neuritis. Experience of the Optic Neuritis Treatment Trial. *Arch Ophthalmol*. 1991;109:1673–1678.
12. Balcer LJ. Clinical practice. Optic neuritis. *N Engl J Med*. 2006;354:1273–1280.
13. Group ONS. Visual function 15 years after optic neuritis: a final follow-up report from the Optic Neuritis Treatment Trial. *Ophthalmology*. 2008;115:1079–1082, e1075.
14. Volpe NJ. The optic neuritis treatment trial: a definitive answer and profound impact with unexpected results. *Arch Ophthalmol*. 2008;126:996–999.
15. Jacobs LD, Beck RW, Simon JH; CHAMPS Study Group. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med*. 2000;343:898–904.
16. Kappos L, Weinschenker B, Pozzilli C, et al. Interferon beta-1b in secondary progressive MS: a combined analysis of the two trials. *Neurology*. 2004;63:1779–1787.
17. Frohman E, Costello F, Zivadinov R, et al. Optical coherence tomography in multiple sclerosis. *Lancet Neurol*. 2006;5:853–863.
18. Frohman EM, Costello F, Stuve O, et al. Modeling axonal degeneration within the anterior visual system: implications for demonstrating neuroprotection in multiple sclerosis. *Arch Neurol*. 2008;65:26–35.
19. Jarius S, Paul F, Franciotta D, et al. Mechanisms of disease: aquaporin-4 antibodies in neuromyelitis optica. *Nat Clin Pract Neurol*. 2008;4:202–214.
20. Jacob A, Weinschenker BG, Violich I, et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Arch Neurol*. 2008;65:1443–1448.
21. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet*. 2008;372:234–245.
22. Fontal MR, Kerrison JB, Garcia R, et al. Ischemic optic neuropathy. *Semin Neurol*. 2007;27:221–232.
23. Rizzo JF III, Lessell S. Optic neuritis and ischemic optic neuropathy. Overlapping clinical profiles. *Arch Ophthalmol*. 1991;109:1668–1672.
24. Hayreh SS, Zimmerman MB. Nonarteritic anterior ischemic optic neuropathy: natural history of visual outcome. *Ophthalmology*. 2008;115:298–305, e292.
25. Hayreh SS, Zimmerman MB. Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. *Graefes Arch Clin Exp Ophthalmol*. 2008;246:1029–1046.
26. Hayreh SS, Zimmerman MB. Incipient nonarteritic anterior ischemic optic neuropathy. *Ophthalmology*. 2007;114:1763–1772.
27. Hayreh SS. Posterior ischaemic optic neuropathy: clinical features, pathogenesis, and management. *Eye*. 2004;18:1188–1206.
28. Prasad S, Moss HE, Lee EB, et al. Clinical reasoning: a 42-year-old man with sequential monocular visual loss. *Neurology*. 2008;71:e43–e49.
29. March GA Jr, Lessell S. Infectious optic neuropathy. *Int Ophthalmol Clin*. 1996;36:197–205.
30. Listernick R, Ferner RE, Liu GT, et al. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann Neurol*. 2007;61:189–198.
31. Spoor TC, Kennerdell JS, Martinez AJ, et al. Malignant gliomas of the optic nerve pathways. *Am J Ophthalmol*. 1980;89:284–292.
32. Danesh-Meyer HV. Radiation-induced optic neuropathy. *J Clin Neurosci*. 2008;15:95–100.
33. Damek DM. Paraneoplastic Retinopathy/Optic Neuropathy. *Curr Treat Options Neurol*. 2005;7:57–67.
34. Man PY, Turnbull DM, Chinnery PF. Leber hereditary optic neuropathy. *J Med Genet*. 2002;39:162–169.
35. Newman NJ. Hereditary optic neuropathies: from the mitochondria to the optic nerve. *Am J Ophthalmol*. 2005;140:517–523.
36. Jonas JB, Budde WM. Diagnosis and pathogenesis of glaucomatous optic neuropathy: morphological aspects. *Prog Retin Eye Res*. 2000;19:1–40.
37. Anderson DR, Drance SM, Schulzer M. Natural history of normal-tension glaucoma. *Ophthalmology*. 2001;108:247–253.
38. Sarkies N. Traumatic optic neuropathy. *Eye*. 2004;18:1122–1125.
39. Yu Wai Man P, Griffiths PG. Surgery for traumatic optic neuropathy. *Cochrane Database Syst Rev*. 2005:CD005024.
40. Yu-Wai-Man P, Griffiths PG. Steroids for traumatic optic neuropathy. *Cochrane Database Syst Rev*. 2007:CD006032.
41. Daniels AB, Liu GT, Volpe NJ, et al. Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). *Am J Ophthalmol*. 2007;143:635–641.