#### **REVIEW ARTICLE**

Edward W. Campion, M.D., Editor

## Ischemic Optic Neuropathies

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ISORDERS OF THE OPTIC NERVE REPRESENT A RELATIVELY COMMON cause of visual loss. The optic nerve is a white-matter tract that relays information from the retina to the brain areas of visual processing. Whenever there is damage to an optic nerve, from whatever cause, it is termed an "optic neuropathy." Unlike inflammatory optic neuritis, which is the most common optic neuropathy in young patients, ischemic optic neuropathy (ION) is the result of vascular insufficiency, not of inflammation. ION refers to all ischemic causes of optic neuropathy. Although IONs are considered to be equivalent to a "stroke of the optic nerve," they cannot be directly compared with cerebral infarctions, and their causes and mechanisms reflect the unique anatomy of the optic nerve and its blood supply (Fig. 1). ION is the most common acute optic neuropathy in older patients, with an annual incidence estimated at 2.3 to 10.2 cases per 100,000 persons 50 years of age or older.<sup>1-5</sup>

ION is classified as anterior ION or posterior ION depending on the segment of optic nerve that is affected (Fig. 1). Anterior ION accounts for 90% of ION cases. Anterior ION and posterior ION are further categorized into nonarteritic (not related to vasculitis) or arteritic. The term arteritic refers to ION caused by small-vessel vasculitis, most often giant-cell arteritis.<sup>1,2</sup>

### NONARTERITIC ANTERIOR ION

#### DIAGNOSIS AND CLINICAL PRESENTATION

Small-vessel disease of the anterior portion of the optic nerve results in hypoperfusion and ischemia of the anterior optic nerve. A cascade of events worsens the ischemia, often resulting in poor visual outcomes (Fig. 2). Nonarteritic anterior ION is manifested as isolated, sudden, painless, monocular vision loss with edema of the optic disc. Progressive worsening of vision over a period of a few days or a few weeks is not uncommon and is presumably related to worsening ischemia in the context of a local compartment syndrome associated with the disc edema (Fig. 2).<sup>1,2,5</sup>

The diagnosis of acute nonarteritic anterior ION is primarily clinical and relies on demonstration of vision loss with a relative afferent pupillary defect and edema of the optic disc, which consists of the optic-nerve head (Fig. 3).<sup>5</sup> A crucial finding on examination is the presence of a small, crowded optic-nerve head with a small physiological cup; this small cup-to-disc ratio defines a "disc at risk" (Fig. 1).<sup>7.9</sup> Although this finding is difficult to see during the acute phase of nonarteritic anterior ION when the optic disc is swollen, examination of the normal eye should show a disc at risk. The disc edema typically resolves over a period of 6 to 11 weeks, and disc pallor develops, often in a sectoral pattern (Fig. 3).<sup>1,2</sup>

The severity of vision loss varies from normal visual acuity with visual-field defects to profound vision loss.<sup>5</sup> Although permanent visual impairment persists in nearly all patients with nonarteritic anterior ION, the Ischemic Optic Neuropa-

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N Engl J Med 2015;372:2428-36. DOI: 10.1056/NEJMra1413352 Copyright © 2015 Massachusetts Medical Society. thy Decompression Trial (IONDT) showed that 43% of the patients with a visual acuity worse than 20/64 at presentation regained at least three lines of visual acuity on the Snellen eye chart within 6 months.<sup>5,11</sup>

Imaging of the optic nerve is typically normal in patients with nonarteritic anterior ION.<sup>12,13</sup> Contrast-enhanced magnetic resonance imaging (MRI) of the orbits, performed with fat suppression, is mostly useful to rule out a compressive optic neuropathy or an inflammatory optic neuritis when there is clinical uncertainty.

Recognition of anterior ION is essential.<sup>13</sup> Inflammatory optic neuritis is often overdiagnosed in patients with acute optic neuropathy, which leads to concerns about multiple sclerosis, often with severe consequences for patients. The presence of pain with eye movements and subsequent improvement of vision over a period of a few weeks suggest inflammatory optic neuritis rather than ION, whereas acute, painless visual loss from an anterior optic neuropathy with disc edema and limited improvement suggests anterior ION, even in a young patient.<sup>4</sup>

### PATHOPHYSIOLOGICAL FEATURES AND EVALUATION

Although nonarteritic anterior ION results from disease of the small vessels supplying the anterior portion of the optic nerve, its exact cause remains unknown. A disc at risk is essential for the development of nonarteritic anterior ION (Fig. 2).<sup>7.9</sup> Other optic-nerve anomalies resulting in crowding of the optic-nerve head, such as optic-nerve drusen and papilledema, may also confer a predisposition to nonarteritic anterior ION.<sup>9</sup> The absence of a disc at risk in a patient with presumed nonarteritic anterior ION should raise the possibility of arteritic anterior ION or another cause of optic neuropathy.<sup>13</sup>

The most common systemic disorders associated with nonarteritic anterior ION are hypertension (present in 50% of patients) and diabetes mellitus (present in 25%).<sup>14,15</sup> Hypercholesterolemia, stroke, ischemic heart disease, tobacco use, systemic atherosclerosis, and obstructive sleep apnea have also been associated with nonarteritic anterior ION, but there are few rigorous population-controlled studies.<sup>1,2,4,5,14-16</sup> Although nonarteritic anterior ION and intracranial cerebrovascular disease have similar risk factors, they represent two very different entities and do not require the same workup. For example, because nonarteritic anterior ION results from small-vessel disease, studies of carotid-artery patency are generally not indicated. However, if the patient has visual symptoms suggestive of ocular hypoperfusion (i.e., blurred vision with changes of posture, with bright light, or during exercise) or if contralateral neurologic symptoms and signs, ipsilateral transient monocular visual loss, Horner's syndrome, or orbital pain are present, carotid imaging should be performed to identify patients at risk for further embolic or hemodynamic events.

Hypercoagulability has also been associated, in rare cases, with nonarteritic anterior ION.<sup>1,2,17</sup> However, testing for prothrombotic factors should be performed only in specific unusual situations, such as anterior ION in a young patient with no vascular risk factors, bilateral simultaneous nonarteritic anterior ION, recurrent nonarteritic anterior ION in the same eye, familial nonarteritic anterior ION, a personal or familial history of thrombophilia or clotting disorder, and the absence of a disc at risk.

Acute bleeding with anemia and systemic hypotension can result in unilateral or bilateral nonarteritic anterior ION. Similarly, large fluctuations in blood pressure, especially in patients with anemia, such as those with chronic renal insufficiency who are undergoing dialysis, may precipitate nonarteritic anterior ION.<sup>1,2,4,14,15</sup>

Acute elevation of intraocular pressure may also precipitate nonarteritic anterior ION. This can be seen during ocular surgery (e.g., cataract surgery) or in association with angle-closure glaucoma or intravitreal injection of drugs.<sup>18</sup>

Several medications have been implicated in the occurrence of nonarteritic anterior ION, including amiodarone,<sup>19</sup> vasopressor agents, vasoconstricting drugs (e.g., nasal decongestants),<sup>20</sup> and phosphodiesterase type 5 inhibitors used for erectile dysfunction.<sup>21</sup> However, establishing a direct relationship between the use of a specific medication and the development of nonarteritic anterior ION is difficult, because most patients have concurrent vascular risk factors and an underlying disc at risk.

## RISK OF RECURRENCE AND INVOLVEMENT OF THE FELLOW EYE

Nonarteritic anterior ION recurs in the affected eye in less than 5% of patients. Optic-nerve atrophy after nonarteritic anterior ION may relieve crowd-



ing and reduce the risk of recurrence. Because patients typically have a disc at risk in both eyes, it is not uncommon to observe bilateral nonarteritic anterior ION, usually sequentially rather than simultaneously. The risk of involvement of the second eye ranges from 12 to 15% at 5 years and seems to be higher among persons with diabetes than among those without diabetes but does not appear to be related to age, sex, smoking history, or aspirin use.<sup>4,22</sup>

#### TREATMENT

There is no established treatment for nonarteritic anterior ION such as there is for the arteritic type of anterior ION. Thus, the most important management concerns are distinguishing nonarteritic anterior ION from arteritic anterior ION and detecting and controlling vascular risk factors in cases of nonarteritic anterior ION.<sup>10</sup>

Most proposed therapeutic interventions in nonarteritic anterior ION are based on the pre-

## Figure 1 (facing page). Blood Supply to the Optic Nerve and Anatomy of the Optic-Nerve Head.

The blood supply to the optic nerve comes mostly from vascular networks originating in the ophthalmic artery, a branch of the internal carotid artery. The central retinal artery (a branch of the ophthalmic artery) enters the optic nerve approximately 1 cm behind the eye and supplies the inner retina. The outer part of the retina is supplied separately by the choroidal arteries, which originate from the posterior ciliary arteries. Penetrating branches of the posterior ciliary arteries run along the optic nerve from the ophthalmic artery to the choroid. The posterior part of the optic nerve is supplied by a surrounding pial plexus derived from these small branches off the ophthalmic and posterior ciliary arteries; only a small number of capillaries actually penetrate the nerve and extend to its central portion. As a result, the center of the posterior optic nerve is relatively poorly vascularized as compared with its anterior portion and is therefore especially susceptible to ischemia with abrupt changes in perfusion.6 The optic-nerve head receives its arterial blood supply from an anastomotic arterial circle (the circle of Zinn-Haller), formed by anastomoses between side branches of the short posterior ciliary arteries, branches from the nearby pial arterial network, and branches from choroidal vessels.2 These very small arteries are commonly affected by a number of local disorders, such as atherosclerosis and vasculitis. Emboli do not usually reach these small arteries. Hypoperfusion in the territory of the ophthalmic artery and its branches may cause ischemic optic neuropathy (ION) with differing clinical presentations depending on the location of ischemia along the optic nerve (disc edema if the ischemia is in the anterior portion or a normal-appearing disc initially if the ischemia is in the posterior portion).<sup>1,2</sup> The blood supply to the optic-nerve head might also be compromised when the intraocular pressure is elevated (hence, the rare cases of nonarteritic anterior ION in acute angle-closure glaucoma). The size of the optic-nerve head (optic disc) and the physiological cup depend on the size of the scleral canal (occupied by a meshlike structure called the lamina cribrosa). Because the total volume of optic-nerve tissue (i.e., the nerve fibers, glial tissue, and blood vessels) does not vary substantially in normal eyes, a small scleral canal will result in no cup or a small cup (with a crowded optic nerve and a small cup-to-disc ratio), whereas a large scleral canal will result in a larger cup (large cup-to-disc ratio). The cup-to-disc ratio is measured during funduscopic examination by estimation of the ratio between the diameter of the central cup and the diameter of the entire disc. Small cups are congenital and physiologic but represent the most important contributing factor to nonarteritic anterior ION.<sup>7-9</sup> Whites tend to have smaller cup-to-disc ratios than blacks, which probably explains why the majority of patients with nonarteritic anterior ION are white.

sumed mechanism and cascade of events (Fig. 2). Although multiple therapies have been attempted, most have not been adequately studied, and animal models of nonarteritic anterior ION have emerged only in the past several years.<sup>23,24</sup> The IONDT, a large, multicenter, prospective treatment trial for nonarteritic anterior ION, showed no benefit from surgical intervention.<sup>25</sup> Intravitreal injections of anti-vascular endothelial growth factor agents or glucocorticoids are effective at reducing disc edema but do not seem to improve visual outcomes.<sup>10</sup> Oral glucocorticoids were shown to have an effect on visual outcomes in a large, noncontrolled, retrospective study,<sup>26</sup> but the moderate potential effect needs to be balanced against the high risk of glucocorticoid complications in these patients with vasculopathy, many of whom have diabetes.<sup>10,27</sup> Other interventions, such as hyperbaric oxygen therapy, have not been shown to be effective.<sup>10</sup>

Given the paucity of data regarding the exact pathophysiology of nonarteritic anterior ION and its treatment, the maxim "first, do no harm" is most important in the management of this devastating optic neuropathy. Oral glucocorticoids should be considered only in patients with nonarteritic anterior ION who have persistent disc edema, unusual progressive worsening of vision over a period of more than 2 or 3 weeks, or bilateral or sequential disease with a poor outcome in the first eye.27 Similarly, therapies aimed at secondary prevention of nonarteritic anterior ION in the fellow eye remain of unproven benefit, although many clinicians recommend daily aspirin in addition to aggressive control of vascular risk factors.<sup>10</sup>

### NONARTERITIC POSTERIOR ION

When the posterior portion of the optic nerve is ischemic, there is no visible disc edema and the term "posterior ION" is used. Nonarteritic posterior ION is exceedingly rare, as compared with nonarteritic anterior ION.<sup>6,28</sup> The typical presentation of nonarteritic posterior ION is isolated, painless, sudden loss of vision in one eye, with a relative afferent pupillary defect and a normal-appearing optic-nerve head. As expected with any optic neuropathy, optic-disc pallor develops 4 to 6 weeks later.



The diagnosis of nonarteritic posterior ION is difficult clinically and remains a diagnosis of exclusion, with other causes of posterior optic neuropathy (e.g., inflammatory and compressive causes) ruled out by high-quality MRI of the brain and orbits with contrast and with fat suppression and by an extensive workup for underlying systemic inflammatory disorders. Giant-cell arteritis must be considered in every patient older than 50 years of age who has posterior ION.<sup>6,28,29</sup>

#### ARTERITIC IONS

#### DIAGNOSIS AND CLINICAL PRESENTATION

Giant-cell arteritis is by far the most common cause of arteritic anterior and posterior ION, although in rare cases, other vasculitides may cause ION.<sup>29-32</sup> Anterior ION is the most common ophthalmic manifestation of giant-cell arteritis. Arteritic anterior ION and arteritic posterior ION are ophthalmic emergencies that must be recognized and treated in a timely fashion to prevent devastating visual loss.

Visual loss is the most dreaded complication of giant-cell arteritis, occurring in about 20% of patients.<sup>31,32</sup> The clinical presentation of arteritic ION is similar to that of nonarteritic ION, but several "red flags" should raise clinical suspicion for arteritic ION.<sup>29</sup> Systemic symptoms of giantcell arteritis may precede visual loss by months; however, about 25% of patients with biopsy-confirmed giant-cell arteritis present with isolated ION without any systemic symptoms (so-called occult giant-cell arteritis).33 Transient visual loss caused by optic-nerve or choroidal ischemia often precedes permanent visual loss by days to weeks. Transient or permanent diplopia caused by extraocular muscles or cranial-nerve ischemia may precede permanent visual loss in up to 10% of patients.

The degree of visual loss is often more severe in arteritic anterior ION than in nonarteritic anterior ION.<sup>29,31</sup> In one study, 54% of the patients with arteritic anterior ION were unable to count fingers, as compared with 26% of the patients with nonarteritic anterior ION.31 Untreated arteritic ION becomes bilateral in days to weeks in at least 50% of cases.<sup>31</sup> The affected swollen optic nerve is often pale immediately in giantcell arteritis, whereas pallor is delayed in nonarteritic anterior ION. The finding of associated retinal or choroidal ischemia in addition to ION is highly suggestive of giant-cell arteritis. Finally, a disc at risk is not necessary for arteritic anterior ION; the absence of a crowded optic disc in the second eye of a patient with anterior ION should make the diagnosis of nonarteritic anterior ION unlikely and should increase the probability of arteritic anterior ION.29

Giant-cell arteritis should be considered in all patients with ION who are older than 50 years of age. Urgent laboratory testing for an inflammatory biologic syndrome, including measurement of the erythrocyte sedimentation rate, C-reactive protein level, complete blood count, and platelet count, is always indicated. Together, these tests are highly predictive of biopsy-proven giant-cell arteritis, with a combined sensitivity of 97% for



Figure 3. Nonarteritic Anterior ION in the Context of a Disc at Risk.

The images in Panels A and B were obtained from a patient with acute left nonarteritic anterior ION with disc edema and peripapillary hemorrhages (by definition, all patients with nonarteritic anterior ION have disc edema initially). The optic-nerve head in the normal right eye (Panel A) is small and crowded, with no visible cup, consistent with a disc at risk for nonarteritic anterior ION; the optic nerve is pink, and there is no swelling. In the affected left eye with acute nonarteritic anterior ION (Panel B), the disc edema is segmental, involving mostly the superior portion of the disc, in accordance with division of the circle of Zinn–Haller into distinct superior and inferior halves. The visual field in the left eye (Panel C) is constricted in Humphrey visual-field testing (24-2 Swedish Interactive Thresholding Algorithm standard test) with an inferior altitudinal defect (the absent visual field appears in black). The visual field in the right eye is full (not shown). Six weeks later (Panel D), the disc edema has resolved in the left eye, and there is superior segmental pallor (arrows).

erythrocyte sedimentation rate and C-reactive protein level.<sup>29,34</sup> Normal values in the context of low clinical suspicion are enough to safely rule out giant-cell arteritis. An elevated erythrocyte sedimentation rate, an elevated C-reactive protein level, or systemic inflammatory symptoms should raise suspicion for giant-cell arteritis and prompt immediate glucocorticoid treatment to prevent further visual loss; further workup (including a temporal-artery biopsy) is also indicated.<sup>29,34</sup>

#### TREATMENT

The treatable nature of giant-cell arteritis and the devastating visual consequences of a delayed diag-

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# Figure 4 (facing page). Possible Factors Contributing to Perioperative ION.

The pathogenesis of perioperative ION is probably multifactorial and varies in different surgical settings.<sup>37</sup> The ultimate result is axonal injury, presumably on a vascular basis (i.e., inadequate oxygen availability), although direct axonal or "crush" injury may also contribute. As shown in Panel A, decreased perfusion pressure, decreased oxygen delivery, increased venous pressure, and direct axonal injury are probably the final common pathways for axonal damage. Compromise of venous outflow may be particularly germane to cases of posterior ION after prolonged spinalfusion surgery. Panel B shows proposed mechanisms contributing to these pathways of damage, including tissue hypoxia, anemia, blood loss, hypotension, relative hypotension, increased interstitial fluid in the orbit or optic nerve, perioperative use of vasoconstricting agents, elevation of intraocular pressure (only potentially relevant to cases of anterior ION), patient vascular or thrombotic risk factors, and an anatomical or physiological individual susceptibility (e.g., a vascular "watershed" region in the posterior optic nerves or a small cup-to-disc ratio at the anterior optic nerve) that makes some patients prone to hemodynamic fluctuations that would not normally affect others undergoing these procedures. Panel C shows the six factors that were observed in a case-control study37 to be independent risk factors for ION after spinal-fusion surgery with the patient in the prone position: male sex, obesity, use of a Wilson surgical frame, longer duration of anesthesia, greater estimated blood loss, and administration of a lower percent colloid solution. These factors are shown in blue, with arrows indicating where they might feed into the final common pathways of injury to the optic nerve.

nosis make identification and treatment of the disorder a true medical emergency. Once a patient has lost vision in one eye, the risk of giantcell arteritis-related visual loss in the second eye is highest in the following hours to days.

Giant-cell arteritis is very responsive to glucocorticoids, with an immediate reduction in systemic symptoms, such as headaches, scalp tenderness, fatigue, fever, and myalgias. Glucocorticoids are administered immediately to prevent visual loss in the unaffected eye, but they often do not reverse existing visual loss. Although few studies have evaluated treatment protocols according to individual subtype of giant-cell arteritis, recommendations have been made for the treatment of patients with ischemic complications of giant-cell arteritis.<sup>35</sup> Most neuro-ophthalmologists prescribe high-dose intravenous methylprednisolone to treat patients with acute visual loss.<sup>36</sup>

#### PERIOPERATIVE ION

Both anterior ION and posterior ION may be precipitated by various nonocular surgeries, often with devastating bilateral vision loss.37,38 The two most common procedures associated with ION are coronary-artery bypass grafting and prolonged spinal-fusion surgery with the patient in the prone position, although the reported incidence of this complication even with these procedures remains no more than 0.3%. Anterior ION represents the majority of cases associated with cardiac surgery, whereas posterior ION is more often confirmed among patients who have undergone spine surgery. The causes of perioperative ION are poorly understood, and the contributing factors are probably multifactorial and different in these two procedures (Fig. 4 and video, available with the full text of this article at NEJM.org).37,39

A video showing possible factors contributing to perioperative ION is available at NEJM.org

#### CONCLUSIONS

The diagnosis of ION is primarily clinical, and ION must be differentiated from other causes of optic neuropathies. Giant-cell arteritis must be considered in patients with ION who are older than 50 years of age, and laboratory testing must be performed and the results interpreted on the basis of the level of suspicion. Although ION remains devastating because of the lack of effective treatment, the recent emergence of animal models is likely to stimulate evaluation of new therapeutic interventions.<sup>23,24,40</sup>

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