Ischemic Optic Neuropathies

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Abstract: Anterior ischemic optic neuropathy (AION) is the most common cause of acute optic neuropathy after age 50, but may also occur in younger patients. The diagnosis is clinical and includes painless visual loss associated with a relative afferent pupillary defect and disc edema. In almost all cases, there is an underlying crowded optic nerve with a small cup-to-disc ratio. The visual prognosis is usually poor, although up to 43% of patients may improve over time. The fellow eye is involved in up to 15% of patients within 5 years, but the risk of recurrence in the same eye is less than 5%. There is no treatment for acute nonarteritic AION but it is essential to evaluate these patients for underlying treatable atheromatous vascular risk factors. A coagulation workup should also be considered in younger patients. It is essential to rule out giant cell arteritis in all patients over the age of 50 with ischemic optic neuropathies. Posterior ischemic neuropathy (in which the optic nerve is normal acutely) is rare and should be considered a diagnosis of exclusion.

Key Words: ischemic optic neuropathy, nonarteritic ischemic optic neuropathy, arteritic ischemic optic neuropathy, giant cell arteritis, temporal arteritis

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Ischemic optic neuropathies are the most common acute optic neuropathies in patients over 50 years of age. The term ischemic optic neuropathy (ION) is used as a general term to refer to all presumed ischemic causes of optic neuropathy. Depending on the segment of optic nerve affected, ION is divided into anterior ischemic optic neuropathy (AION) and posterior ischemic optic neuropathy (PION). Optic disc edema from ischemia to the anterior nerve is, by definition, present in AION (Figs. 1, 2) and absent in PION. AION is much more common than PION, accounting for 90% of cases of optic nerve ischemia.[1]

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Ischemic optic neuropathies can be divided into nonarteritic and arteritic etiologies.

Ischemic optic neuropathies can also be divided into nonarteritic and arteritic etiologies. Arteritic ION, classically due to giant cell arteritis (GCA), is an ophthalmologic emergency, requiring prompt recognition and treatment to prevent devastating permanent blindness.[1]

Knowledge of the vascular anatomy of the optic nerve is helpful to understand the mechanisms of ischemic optic neuropathies. The optic nerve blood supply comes from the ophthalmic artery, a branch of the internal carotid artery. The first branch of the ophthalmic artery, the central retinal artery, enters the optic nerve approximately 1 cm behind the eye, and supplies the inner part of the retina. The outer part of the retina is supplied separately by the choroidal arteries, which originate from the posterior ciliary arteries. The posterior ciliary arteries run along the optic nerve from the ophthalmic artery to the choroid, supplying the optic nerve with small penetrating branches. 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. The optic nerve head receives its arterial blood supply from an anastomic 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 from choroidal vessels (Fig. 3).[1] The result of hypoperfusion of these vascular networks is optic nerve ischemia, with varying clinical presentations, depending on the segment of optic nerve involved.

Nonarteritic Anterior Ischemic Optic Neuropathy

Nonarteritic anterior ischemic optic neuropathy (NAION) is presumably secondary to small vessel disease of the short

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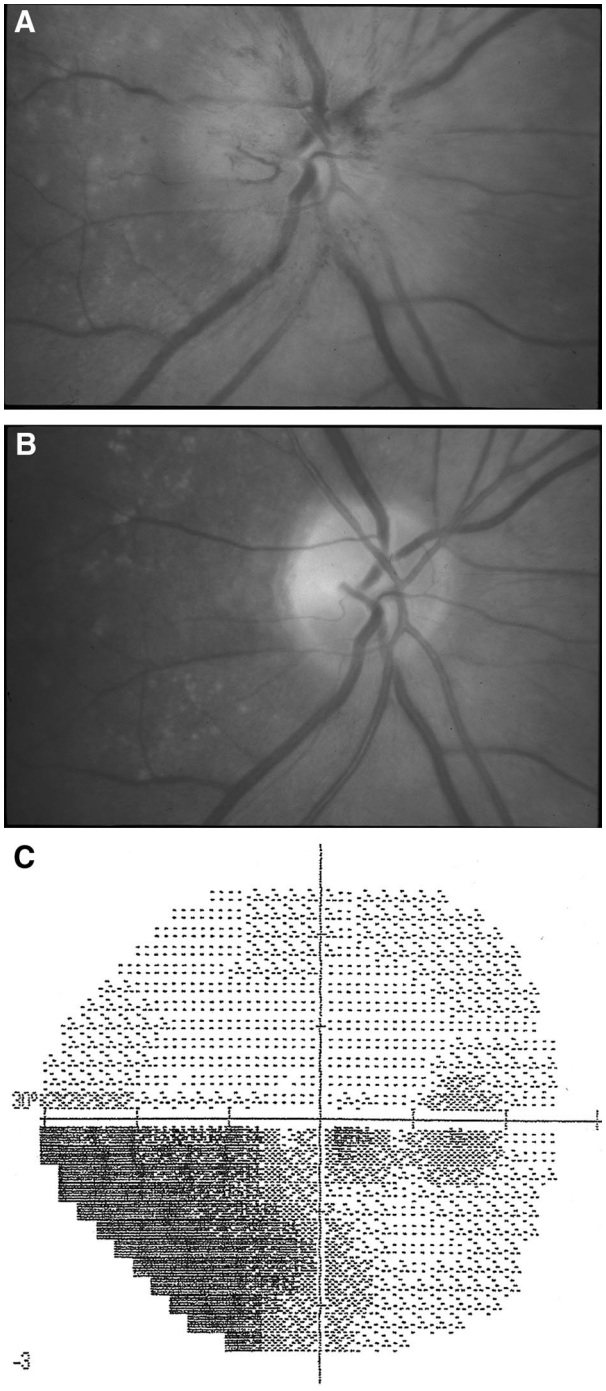

FIGURE 1. Anterior ischemic optic neuropathy. A, Optic nerve appearance during the acute phase showing diffuse disc edema with peripapillary hemorrhages. B, Two months later, the disc edema has completely resolved and there is superior segmental optic nerve pallor corresponding to the inferior visual field defect shown in C. C, Humphrey visual field of the right eye showing an inferior arcuate defect in this patient with nonarteritic anterior ischemic optic neuropathy. Visual acuity is 20/40 in that eye, there is a right relative afferent pupillary defect and color vision is normal.

posterior ciliary arteries, with resultant hypoperfusion and infarction of the anterior optic nerve.[1] Diagnosis is primarily clinical, and, despite its high incidence, NAION remains untreatable. The Ischemic Optic Neuropathy Decompression Trial (IONDT), a large, multicentered prospective treatment trial, has provided valuable information on the natural history of NAION.[2–5]

Diagnosis

NAION typically occurs after the age of 50 years, but cases in younger patients and even children are well documented.[1,6] Incidence is estimated at 2.3 to 10.2 cases per year per 100,000 persons aged 50 and older, and 95% of cases occur in whites.[1] The typical presentation is that of sudden, painless monocular visual loss that progresses over hours to weeks. Premonitory transient visual loss and ocular discomfort are infrequent in NAION.[1,7]

Examination in typical NAION reveals an optic neuropathy, with decreased visual acuity, a relative afferent pupillary defect, visual field loss, and optic disc edema, often with peripapillary hemorrhages. Disc edema may be diffuse or segmental, involving only the superior or inferior portion of the optic disc (Figs. 1, 2). This may correspond with a division of the circle of Zinn-Haller into distinct upper and lower halves.[1] Similarly, the corresponding visual field defect is often an inferior (most common) or superior altitudinal or arcuate defect (Fig. 1). Initial visual acuity varies widely from 20/20 to no light perception. It is better than or equal to 20/64 in 31% to 52% of patients and worse than or equal to 20/200 in 34% to 54% of patients.[1,7] Four to 6 weeks after visual loss, disc edema resolves and optic disc pallor develops, often in a sectoral pattern (Figs. 1, 2).[1]

Although the onset of visual loss is classically sudden (as in all vascular events), progressive worsening of vision over a few days or weeks is not uncommon in NAION. The IONDT also showed that up to 43% of patients who presented with visual acuity worse than 20/64 spontaneously regained 3 lines of visual acuity at 6 month follow-up, with 31% sustaining that benefit at 24 months.[2–5]

An important examination finding, usually considered essential to the diagnosis of nonarteritic anterior ischemic optic neuropathy, is the presence of a small optic nerve with a small or absent physiologic cup in the unaffected eye.

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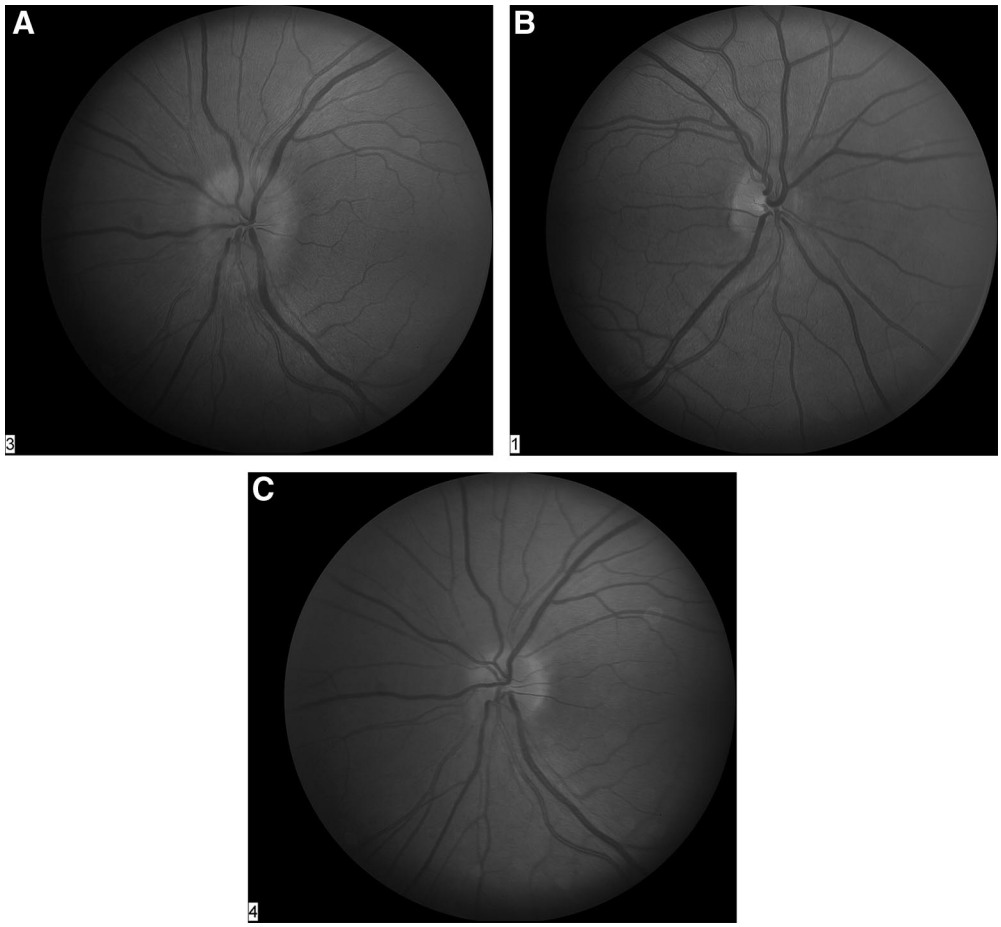

FIGURE 2. Anterior ischemic optic neuropathy. Nonarteritic anterior ischemic optic neuropathy of the left eye in the setting of severe anemia from dysfunctional uterine bleeding. A, Optic nerve appearance at the acute phase showing disc edema of the left eye. B, Opposite eye (right eye) showing the absence of disc edema and the classic disc-at-risk configuration (small cup-to-disc ratio of <0.1). C, Two months later, the disc edema in the left eye is resolving and there is superior segmental optic nerve pallor.

cup (termed "disc-at-risk") in the unaffected eye (Figs. 2, 4).[1,8,9] Therefore, it is imperative to examine both optic nerves and to be able to recognize this absence of cupping. It is thought that an anatomically small, crowded optic nerve predisposes patients to NAION via mechanical factors such as crowding with impaired axonal flow and resultant compromise of the laminar microcirculation.[1,8,9] Whites tend to have small cup-to-disc ratios, which may explain why they predominate among AION patients.[1,10] The absence of a disc-at-risk appearance in a patient with presumed NAION should raise the possibility of arteritic AION or another cause of optic neuropathy.

NAION must be differentiated from other causes of acute optic neuropathies, such as idiopathic optic neuritis, infectious optic neuritis or compressive optic neuropathies (Table 1).[1,11,12] Occasionally, fat suppressed magnetic resonance imaging (MRI) of the optic nerve (with contrast) may be helpful, wherein the finding of enhancement of the optic nerve or optic nerve sheath should suggest an alternative diagnosis other than NAION.[1]

Risk Factors and Recurrence

Although the precise pathophysiology of NAION remains unknown, studies have reported the association of NAION with optic nerve anomalies and systemic disorders (Table 2).[1,8] Many even consider NAION to be a form of ischemic stroke. However, even if NAION and intracranial cerebrovascular disease share similar risk factors, they represent 2 different entities and they do not share the same mechanisms.[1]

As emphasized above, the main risk factor for NAION is the presence of an anomalous optic nerve. A disk-at-risk (small optic nerve with a small or absent physiologic cup) is usually present even in patients who may have another reason to develop NAION (such as perioperative AION or AION

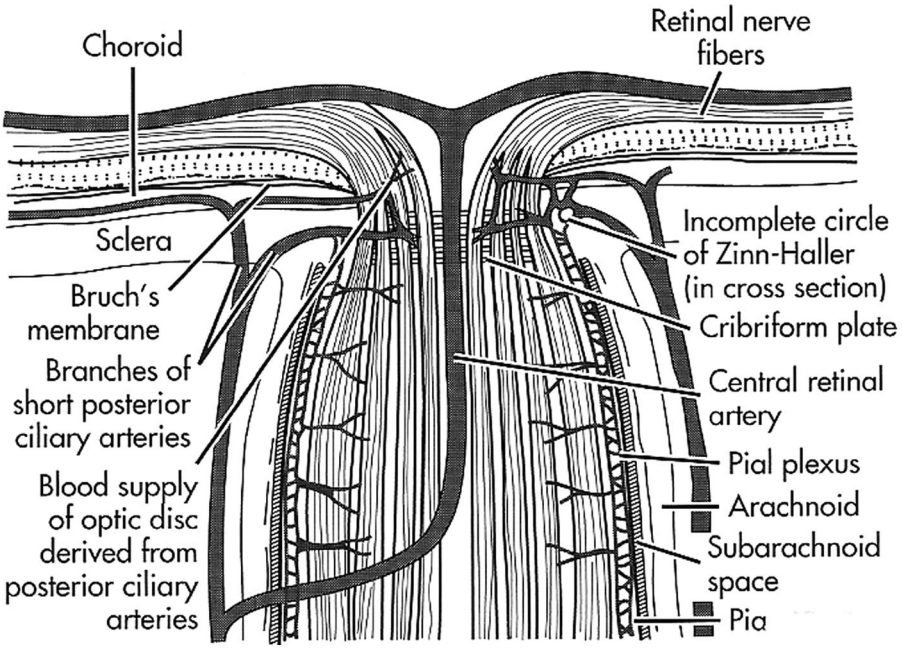

FIGURE 3. Vascular supply to the optic nerve. The eye has a dual vascular supply, with arterial contributions from both the choroidal and central retinal circulations, both of which originate from the ophthalmic artery, a branch of the internal carotid artery. Reprinted with permission from *The Requisites in Ophthalmology—Neuro-Ophthalmology*. Missouri: Mosby, 2000.

occurring in association with medication use). Other optic nerve anomalies such as papilledema, or optic nerve head drusen, can also be complicated by AION, most likely because of impaired axonal flow, and resultant compromise of the laminar microcirculation.[1,8,13]

Systemic diseases associated with an increased risk of nonarteritic anterior ischemic optic neuropathy include systemic hypertension and diabetes.

Systemic diseases associated with an increased risk of NAION include systemic hypertension (in about 50%) and diabetes (in about 25%).[1,4,8,14–16] Ischemic heart disease, hypercholesterolemia, stroke, tobacco use, sleep apnea, and systemic atherosclerosis have also been associated,[1,17,18] but few rigorous population-controlled studies have been performed.

Nonarteritic AION is a disease of the small vessels supplying the optic nerve head and is clinically not associated with ipsilateral internal carotid artery stenosis; embolic AION is extremely rare.[1,16,19] As with small vessel disease affecting the central nervous system, some association between carotid occlusive disease and acute AION has been suggested. However, in most cases of AION, the optic neuropathy is a sign of widespread atherosclerosis affecting both large and small vessels, reflecting shared risk factors such as hypertension or diabetes mellitus. Exceptionally, optic nerve infarction results from reduced perfusion pressure secondary to severe carotid occlusive disease (especially dissections) and poor collateral blood supply.[20] It is therefore not necessary to routinely obtain a carotid ultrasound examination in patients who develop AION. However, if the patient complains of visual symptoms suggestive of hypoperfusion of the eye (ie, blurred vision with changes of posture, with bright light or during exercise), or if the AION was preceded by, or associated with, contralateral neurologic symptoms and signs, transient monocular visual loss, Horner syndrome, or orbital pain, noninvasive carotid imaging should be obtained to identify patients at risk for further embolic or hemodynamic events.[1,20]

Rarely, hypercoagulable states have been associated with NAION; however, case-controlled studies have given various results. It is suggested that thrombotic factors, in particular homocysteine, be measured in patients less than 45 years old with NAION without other vascular risk factors, in bilateral simultaneous NAION, in NAION recurrent in the same eye, in NAION with the absence of a small cup-to-disc ratio, and in familial NAION.[1,21–25]

Acute bleeding with anemia and systemic hypotension can result in unilateral or bilateral AION (Fig. 2) (see below). Similarly, fluctuations in blood pressure, especially in anemic patients, such as those with chronic renal insufficiency receiving dialysis, may precipitate AION.[1,8] Hayreh reported that visual loss in AION was most frequently recognize upon awakening, and proposed nocturnal hypotension as a mechanism.[26] This finding was not confirmed in the IONDT.[4]

Multiple medications have been implicated in the occurrence of NAION, such as amiodarone, interferon-α, nasal decongestants, various vasopressors or vasoconstricting drugs, and phosphodiesterase inhibitors erectile dysfunction drugs.[1,27–32] However, establishing a direct relation-

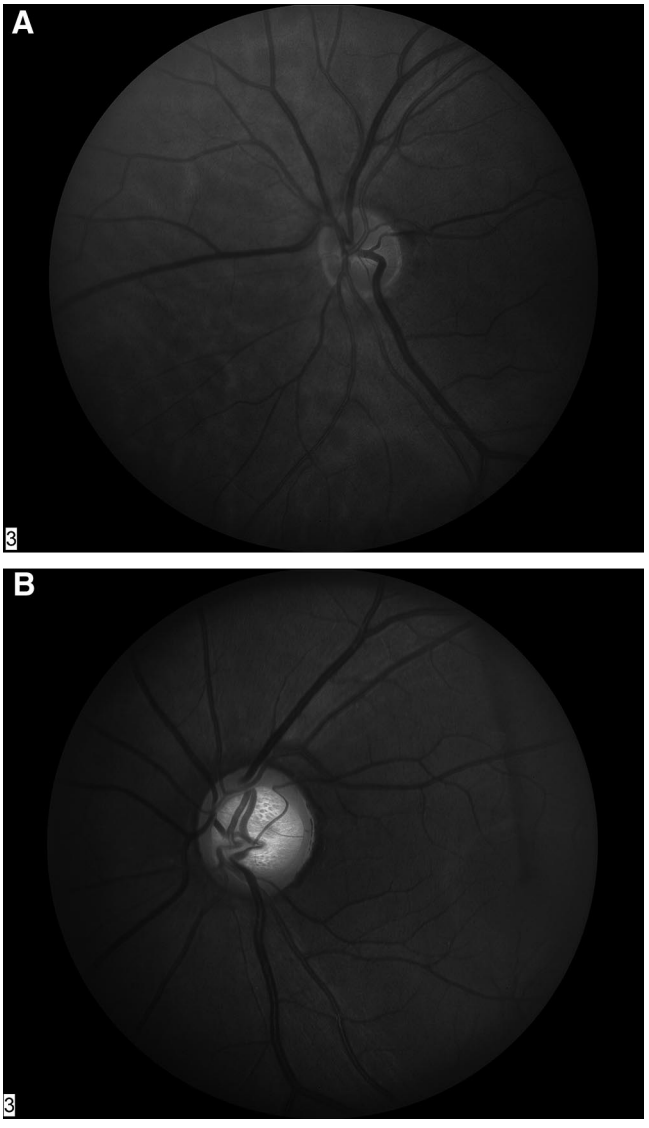

FIGURE 4. Illustration of the cup-to-disc ratio. The ratio of cup size to the diameter of the optic disc determines if the patient has a "disc-at-risk" for NAION. A, Small optic disc with cup-to-disc ratio of <0.1. This is the classic disc-at-risk in NAION. B, Large cup-to-disc ratio (0.85) such as often seen in patients with glaucoma.

ship between use of a specific medication and NAION is problematic because most patients have concurrent vascular risk factors and an underlying disc-at-risk. When possible, it is generally recommended to discontinue such medications in patients with AION. A recent study[31] proposed some criteria to help differentiate amiodarone optic neuropathy from NAION, including bilateral onset or atypical features of NAION, such as an insidious onset of symptoms, milder optic nerve dysfunction and disc edema, or a generous cup-to-disc ratio in the fellow eye of patients. In suspected cases, amiodarone, when possible, should be discontinued under medical attention.

In the past few years, the association of erectile dysfunction drugs and NAION has been of particular interest. The World Health Organization standards suggest a possible association, but there is not enough data to establish a cause-and-effect relationship. Furthermore, there is no evidence that supports the practice of screening erectile dysfunction drug users for a small cup-to-disc ratio, a feature predisposing to spontaneous NAION.[32]

Acute elevation of intraocular pressure, such as during ocular surgeries or during an attack of angle closure glaucoma, may also precipitate NAION.[1,33–35]

NAION recurs in the affected eye in less than 5% of patients.[5] It is possible that atrophy of the nerve after NAION relieves crowding and reduces recurrence risk. Because patients often have a disc-at-risk in both eyes, it is not uncommon to observe bilateral NAION, usually sequentially rather than simultaneously. The risk of second eye involvement is 12% to 15% at 5 years and seems to be related to poor baseline visual acuity in the first eye and to diabetes, but not to age, sex, smoking history, or aspirin use.[1,5,8] There is a modest correlation of final visual acuities between eyes in bilateral, sequential NAION, with approximately 50% of patients having Snellen visual acuities within 3 lines of one another.[5]

Treatment

There is no established treatment for NAION, although a number of medical and surgical treatments have been evaluated. The clinician's primary role in managing patients with this disorder is exclusion of GCA and to detect and control vascular risk factors.[1]

Subtenon injection of vasodilators, intravenous or topical intraocular pressure-lowering agents, vasopressors, stellate ganglion block, levodopa, carbidopa, diphenylhydantoin, anticoagulants, aspirin, oral corticosteroids, hyperbaric oxygen, transvitreal optic neurotomy (opening of the scleral canal), optic nerve sheath decompression, and intravitreal injection of corticosteroids have been used in some cases with NAION and have not proven useful for the treatment of acute NAION (Table 3 summarizes the most recent studies).[2,5,36–48] However, most studies were retrospective, nonrandomized, and small. Although it has been suggested that neuroprotective agents (especially those that can be administered topically or directly in the eye) may be efficacious in acute treatment of NAION, this remains to be demonstrated in a controlled study. Although a few retrospective studies have suggested that aspirin may help prevent fellow eye involvement, this remains unresolved. However, because aspirin is beneficial in primary and secondary prevention of most atherosclerosis-related vascular diseases, it is reasonable to prescribe aspirin in NAION patients.[1]

Diabetic Papillopathy and Pre-AION Optic Disc Edema

Patients may develop disc swelling from AION before they have any visual symptoms.[1,49,50] The asymptomatic disc swelling ("premonitory" or "incipient" AION) is often noted

TABLE 1. Clinical Characteristics of Inflammatory Optic Neuritis, Nonarteritic AION and Arteritic AION

	Optic Neuritis	AION Nonarteritic	AION Arteritic
Age of patients	Younger	Older (>50 yr)	Older (>65 yr)
Race	No difference	No difference	More common in whites
Sex	More common in women	No difference	More common in women
Laterality	Unilateral	Unilateral	Uni- or bilateral
Visual loss	Rapidly progressive	Acute	Acute
	Acuity rarely spared	Acuity variable	Severe visual loss
Pain	Orbital pain frequent with eye movements	Pain infrequent	Headache common
Color vision	Commonly abnormal	Commonly spared if vision good	Correlates with visual acuity
Visual field	Central defects	Altitudinal defect	Any defect (severe)
Optic disc			
Acute	Normal (2/3) or disc edema (1/3)	Disc edema, segmental; small cup-to-disc ratio	Disc edema, pallid; retinal/choroidal infarction
Late	Temporal pallor	Segmental pallor	Diffuse pallor, cupping
Visual prognosis	Good	Variable	Poor
	25% recurrence risk	15% second eye at 5 yr	75% second eye within 2 wk
Systemic diseases	Risk of multiple sclerosis	HTN (51%), DM (24%)	GCA/PMR
		GCA to be ruled out	25% have no GCA symptoms

GCA indicates giant cell arteritis; HTN, hypertension; DM, diabetes mellitus; PMR, polymyalgia rheumatica.

TABLE 2. Disorders and Drugs Suggested to be Associated With AION

- Arteritic anterior ischemic optic neuropathy
  - Giant cell arteritis +++
  - Periarteritis nodosa
  - Churg-Strauss syndrome
  - Wegener's granulomatosis
  - Connective tissue diseases such as systemic lupus erythematosus
  - Rheumatoid arthritis
  - Relapsing polychondritis
- Non-Arteritic anterior ischemic optic neuropathy
  - Anomalous optic nerve
    - "Disc-at-risk": small crowded optic nerve
    - Papilledema
    - Optic nerve head drusen
  - Elevated intraocular pressure (acute glaucoma, ocular surgery)
  - Radiation-induced optic neuropathy
  - Diabetes mellitus/diabetic papillopathy
  - Other vascular risk factors (atherosclerosis)
  - Hypercoagulable states*
  - Acute systemic hypotension/anemia
    - Bleeding
    - Cardiac arrest
    - Perioperative (especially cardiac and spine surgeries)
    - Dialysis
  - Sleep apnea
  - Drugs
    - Amiodarone
    - Interferon-α
    - Vasoconstrictor agents (such as nasal decongestant)
    - Erectile dysfunction drugs (phosphodiesterase inhibitors)

*Hypercoagulable states are rarely responsible for AION and should only be tested for in younger patients under age 50 without other risk factors for AION.

in the fellow eye of a patient with a previous history of AION. The mechanism of disc swelling in these cases is presumed ischemic.[1,49,50]

Similarly, young patients with diabetes mellitus may develop disc swelling in 1 eye with no or very mild visual loss, so-called diabetic papillopathy. The swelling may be unilateral or bilateral and the visual prognosis is usually excellent. In more than 80% of reported cases, diabetic retinopathy is present at the time of onset of diabetic papillopathy. The mechanism remains unknown, although ischemia of the optic nerve head is most likely. Another potential cause of optic nerve swelling in these and other patients is vitreal traction.[1,49]

Arteritic Ischemic Optic Neuropathy

AION is the most common ophthalmic manifestation of GCA (Table 4).[1] Arteritic AION is a neuro-ophthalmic emergency, which is exceedingly important to recognize and differentiate from NAION, to prevent further devastating visual loss. Although GCA is the most common cause of

Arteritic anterior ischemic optic neuropathy is a neuro-ophthalmic emergency, which is exceedingly important to recognize and differentiate from nonarteritic anterior ischemic optic neuropathy, to prevent further devastating visual loss.

TABLE 3. Studies Evaluating the Treatment of NAION Published Since 1996

Author	Year	Treatment	Study Type	No. Patients	Outcome	Conclusions of the Study
Acute treatment of AION						
IONDT[2]	1995	ONSF	P	258 total (127 treated, 131 untreated)	No difference in visual outcome; 24% of surgical patients worsened	There is no role for ONSF in acute NAION treatment
Arnold et al[36]	1996	Hyperbaric oxygen	P	22 treated, 27 untreated	No significant difference in final VA	Hyperbaric oxygen does not improve visual outcome of affected eye
Botelho et al[37]	1996	Aspirin	R	78 total (23 treated, 55 untreated)	No significant difference in final VA	Aspirin does not improve visual outcome of affected eye
Johnson et al[38]	2000	Levodopa	R	37 total (18 treated, 19 untreated)	Improved VA at 6 mo 76.9% of treated 30% of untreated No change in VF	Levodopa may improve visual outcome of affected eye
Soheilian et al[39]	2003	Transvitreal optic neurotomy	R	7 treated	6 of 7 patients had some improvement in VA	Transvitreal optic neurotomy may be helpful in AION with severe visual loss
Fazzone et al[40]	2003	Topical brimonidine	R	31 total (14 treated, 17 untreated)	The group treated with brimonidine had worse visual function at 8–12 wk	Topical brimonidine does not improve visual outcome of affected eye
Simsek et al[45]	2005	Levodopa and carbidopa	P	24 total	—	Levodopa and carbidopa does not improve visual outcome of affected eye
Wilhelm et al[44]	2006	Topical brimonidine	P	36 total (29 analyzed) (18 treated, 11 untreated)	No significant difference in final VA	Topical brimonidine is not harmful, but does not improve visual outcome of affected eye
Jonas et al[46]	2007	Intravitreal triamcinolone	P	3 treated	May not be markedly effective in increasing VA	Need randomized controlled trials
Kaderli et al[47]	2007	Intravitreal triamcinolone	P	10 total (4 treated, 6 untreated)	The treated group showed relatively improved recovery of VA and rapid reduction in optic disc edema—no marked change in VF	A larger trial is merited by the result of this small pilot study
Secondary prevention of AION (prevention of fellow eye involvement)						
Kupersmith et al[41]	1997	Aspirin	R	100 total: 57 treated, 43 untreated	NAION in fellow eye: at 2 yr (17.5% of treated, 53.5% of untreated)	Aspirin may decrease risk of AION in the fellow eye
Beck et al[42]	1997	Aspirin	R	431 total: 153 treated, 278 untreated	NAION in fellow eye: at 2 yr (7% of treated, 15% of untreated) and at 5 yr (17% of treated, 20% of untreated)	Aspirin does not decrease risk of AION in the fellow eye
Salomon et al[43]	1999	Aspirin	R	52 total: 36 treated, 16 untreated	NAION in fellow eye: 22.2% of treated, 50% of untreated	Aspirin may decrease risk of AION in the fellow eye
IONDT[5]	2002	Aspirin	P*	326 total: at baseline† (87 treated, 237 untreated); and after baseline‡ (86 treated, 240 untreated)	NAION in fellow eye: aspirin at baseline (20% of treated, 13% of untreated); aspirin after baseline (15% of treated, 15% of untreated)	Aspirin does not decrease risk of AION in the fellow eye

*Although the IONDT was a prospective trial to evaluate optic nerve sheath decompression, it was not a prospective trial to evaluate aspirin therapy. Aspirin data are observational only.

†Reported starting regular aspirin use ≥1 mo before onset of symptoms at baseline visit.

‡Responded positively to "started regular use" of aspirin on at least 1 study visit after baseline.

R indicates retrospective; P, prospective; VA, visual acuity; VF, visual field; ONSF, optic nerve sheath fenestration.

TABLE 4. Ophthalmologic Manifestations of Giant Cell Arteritis

Ischemic optic neuropathy
Anterior ischemic optic neuropathy
Posterior ischemic optic neuropathy
Choroidal infarction
Central retinal artery occlusion
Branch retinal artery occlusion
Cilioretinal artery occlusion
Ophthalmic artery occlusion
Ischemic ocular syndrome
Corneal edema
Anterior uveitis
Cataract
Iris neovascularization
Ocular hypertension (neovascular glaucoma)
Ocular hypotony
Retinal hemorrhages (venous stasis retinopathy)
Retinal neovascularization
Orbital ischemia
Orbital pain
Diplopia (ischemia of the extraocular muscles)
Proptosis
Cranial nerve ischemia
Diplopia (III, IV, and VI nerve ischemia)
Cerebral ischemia
Brainstem ischemia (diplopia)
Occipital lobe infarction (cerebral blindness)
Visual hallucinations
Tonic pupil
Horner syndrome

arteritic AION, other vasculitides such as periarteritis nodosa should also be considered (Table 2).[1]

Diagnosis

Temporal arteritis occurs predominantly in women and in whites. The prevalence of GCA increases with age and the annual incidence is approximately 20 per 100,000 persons aged 50 years or older.[51,52] Most patients are over age 65, but GCA must be suspected in every patient over 50. Up to 50% of patients with GCA present with ocular symptoms; of those, 70% to 80% have arteritic AION (Table 4).[1,51] The clinical presentation of arteritic AION is similar to that of NAION, but numerous red flags should raise clinical suspicion for arteritic AION rather than NAION (Table 1),[1,7,53–55]: (1) systemic symptoms such as jaw claudication, headache, scalp tenderness, neck pain, proximal weakness, malaise, weight loss, and fever may precede visual loss by months; however, about 25% of patients with positive temporal artery biopsies do not exhibit these systemic symptoms[54]; (2) permanent visual loss from arteritic AION is sometimes preceded by episodes of transient visual loss (30%) or transient diplopia (5%–10%) secondary to ischemia to the optic nerve head, extraocular muscles, or cranial nerves[54,55]; (3) the finding of peripapillary, retinal, or choroidal ischemia in addition to the AION is highly suspicious for GCA (Fig. 4)[1]; (4) the degree of visual loss tends to be more severe in arteritic AION, with initial visual loss being between count fingers and no light perception in 54% of patients, compared with 26% of NAION patients[1,54] if untreated, arteritic AION becomes bilateral within days to weeks in at least 50% of cases[1,54]; (5) the affected swollen optic nerve is often pale acutely in GCA (Fig. 5), whereas pallor is delayed in NAION[1]; and (6) a disc-at-risk is not necessary for arteritic AION, but if present, does not help to differentiate arteritic AION from NAION.[1,7] Indeed, the absence of a crowded optic nerve in the fellow eye of a patient with AION should make the diagnosis of NAION unlikely and should raise the possibility of arteritic AION. A thorough history (looking for systemic symptoms), and a careful ocular examination evaluating the cup-to-disc ratio and looking for other signs of ocular ischemia, are of paramount importance in the diagnosis of arteritic AION. In difficult cases, retinal fluorescein angiography can be very helpful at detecting choroidal hypoperfusion and delayed choroidal filling (Fig. 5).[1]

Diagnostic Tests

Laboratory testing may be useful in the diagnosis of arteritic AION. An elevated erythrocyte sedimentation rate (ESR) is generally well accepted in the diagnosis of GCA. However, different studies have shown a better sensitivity for diagnosis when ESR is combined with C-reactive protein (CRP). Together, they have been reported to be highly predictive of biopsy-proven GCA, with a combined sensitivity of 97%.[56]

Other tests must be obtained in addition to erythrocyte sedimentation rate when giant cell arteritis is suspected; C-reactive protein, fibrinogen, complete blood count, and platelets should always be obtained in addition to the erythrocyte sedimentation rate.

Because normal values of ESR are known to increase with age, and are higher in women, the ESR should be adequately adjusted (Table 5).[56,57] An elevated ESR is useful because it correlates with the disease process, hence facilitating monitoring of the disease. The ESR is greater than 40 mm/h in at least 77% of patients with active, untreated GCA. However, the ESR is a nonspecific marker of a variety of inflammatory, infectious, and neoplastic disorders, and may be normal in 7% to 20% of patients with GCA before treatment. Therefore, a normal ESR does not rule out GCA, and the level of elevation of ESR does not correlate with the severity of the disease.[51,52,58] Therefore, other tests must be obtained in addition to ESR when GCA is suspected; CRP,

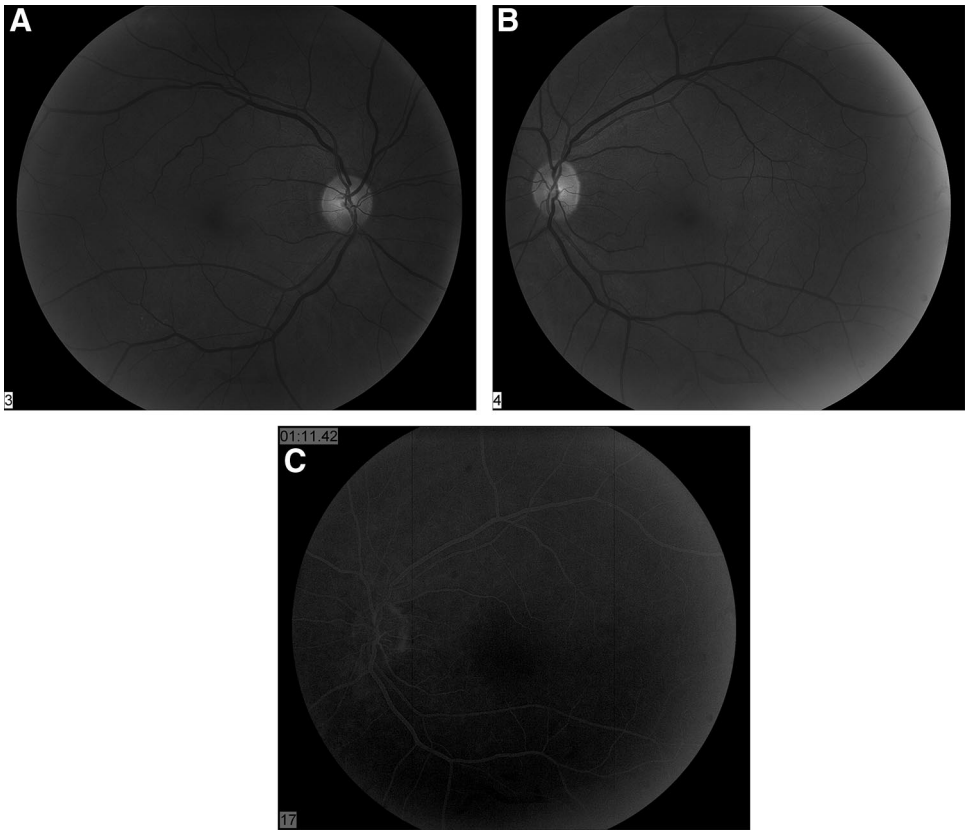

FIGURE 5. Normal appearing optic nerves in a patient with giant cell arteritis. Funduscopic examination of a patient who had 1 episode of transient visual loss in the left eye, associated with new onset headache and jaw claudication. A, Normal appearing fundus right eye. B, Normal appearing fundus left eye. C, Retinal fluorescein angiography of the same patient showing delayed and patchy choroidal filling in the left eye (normal choroids should appear "white" (filled with fluorescein) approximately 30 seconds after injection; in this patient, filling is delayed inferiorly more than 1 minute after injection).

TABLE 5. Formulas Proposed to Determine the Normal ESR Based on the Patient's Age

Hayreh et al[56]	
Men: 17.3 + (0.18 × age)	Women: 22.1 + (0.18 × age)
Miller et al[†57]	
Men: age in years/2	Women: (age in years + 10)/2

*Based on a study of 363 patients with suspected GCA, 106 of whom had biopsy proven disease and 749 controls.
†Based on a study of 27,912 individuals aged 20–65.

fibrinogen, complete blood count and platelets should always be obtained in addition to the ESR.[58]

The CRP is an acute phase plasma protein of hepatic origin that rises before ESR in most disease states, and is often elevated in GCA. Studies have shown several advantages of CRP over ESR, including higher sensitivity and specificity (98.6% and 75.7%, respectively), and relative insensitivity to age, gender, and other hematologic parameters.[59] A recent study,[60] showed that most patients with biopsy-proven GCA have both an elevated ESR and CRP, but that there can be nonconcordance between those 2 tests, either an elevated ESR with normal CRP, or a normal ESR with an elevated CRP. They showed that the use of both tests provides a slightly greater sensitivity for the diagnosis of GCA (sensitivity of 99%) than the use of either test alone.

In active inflammatory disease, fibrinogen and platelet count are frequently elevated, most patients will present with a mild-to-moderate anemia, and approximately one third of patients will have mildly abnormal liver-function tests.[51,52,58]

Fluorescein angiography is often very useful in the diagnosis of GCA (Fig. 5). It is a widely available, safe, and relatively inexpensive diagnostic tool for many retinal, choroidal, and optic nerve disorders. As opposed to NAION (which tends only to affect the posterior ciliary circulation), the multifocal nature of arteritic AION often leads to involvement of both the posterior ciliary and choroidal circulations; therefore, when extensive choroidal hypoperfusion is identified by fluorescein angiography (Fig. 5) in the setting of ION, an arteritic etiology is highly likely.[1,58]

MRI is not a classic diagnostic test for AION. However, MRI of the orbits is often obtained as a component of the diagnostic evaluation for a unilateral optic neuropathy. Although the MRI is normal in NAION, orbital fat enhancement and optic nerve and nerve sheath enhancement have been reported in arteritic AION.[1,58]

The temporal artery biopsy (TAB) is the gold standard for definitive diagnosis of GCA. Although diagnosis of ar-

TABLE 6. Therapeutic Trials in Arteritic AION Since 2000, Comparing IV Steroids With Oral Steroids in Terms of Visual Outcome

Author	Year	Study Type	No. Patients and Treatment	Outcome	Conclusion of the Study
Chevalet et al[63]	2000	P	164 total; 1 pulse of 240 mg IV of methylprednisolone followed by po steroids or po steroids alone	Same cumulative steroids doses in both groups at 1 yr. No difference in time to normalize labs or steroids side effects	No benefit of IV steroids versus po
Chang et al[64]	2001	R	73 total; IV followed by po steroids (43) or po steroids alone (30), different regimens of treatment	Improvement in vision: 40% of IV treated, 13% of po treated	Steroids can improve vision, with superior results for IV steroids compared to po
Hayreh and Zimmerman[65]	2003	LO	145 total; IV followed by PO steroids (48) or po steroids alone (97), different regimens of treatment	No difference in visual outcome or cumulative dose	No benefit of IV steroids versus po

P indicates prospective; R, retrospective; LO, longitudinal observational; IV, intravenous; po, per os.

teritic AION may be suspected on clinical grounds, TAB confirmation of GCA is mandatory, especially given the complication rate associated with the necessary subsequent long-term corticosteroid therapy.[1,51,52,58,61] Treatment must be promptly instituted while the diagnosis is suspected and should not be delayed for TAB. Although treatment with corticosteroids will ultimately diminish the histopathologic findings of active arteritis on a TAB, it will not substantially change the sensitivity of a biopsy performed within 2 weeks of instituted treatment. A negative unilateral biopsy does not necessarily rule out GCA. An adequate specimen must be submitted for pathology (a minimum of 2 cm long is recommended because of skip lesions). In strongly suspected cases, a second biopsy (on the opposite side) should be performed, with an up to 5% chance of positivity.[62]

Treatment and Outcome

Corticosteroid-responsiveness and improved outcome with early treatment make immediate and aggressive initiation of therapy the goal to prevent permanent visual loss. The following treatment suggestions are those generally recommended by neuro-ophthalmologists confronted with patients with a substantial risk of severe visual morbidity.

In a patient with arteritic anterior ischemic optic neuropathy, systemic corticosteroids should be promptly instituted upon suspected diagnosis and should not be delayed for temporal artery biopsy.

In a patient with arteritic AION, systemic corticosteroids should be promptly instituted upon suspected diagnosis and should not be delayed for TAB. In the setting of visual loss, high dose (1–2 g/d for 2–3 days) intravenous corticosteroids followed by high dose oral steroids are recommended, although only a few prospective studies have evaluated this regimen, with different conclusions (Table 6).[63–65] Beginning treatment with IV corticosteroids while the patient is hospitalized has several advantages, particularly in an older population with multiple comorbidities, who present with new onset visual impairment. It permits achievement of a complete work-up, and better control of corticosteroid side effects, such as elevations and fluctuations in blood sugar levels.

If oral prednisone alone is used, doses in the range of 1 to 2 mg/kg/d are suggested. Maintenance therapy in this dose range should be continued for at least 4 to 6 weeks, until normalization of laboratory inflammatory markers occurs, to be followed by a slow taper over the next 12 to 18 months, with careful follow-up of ESR and CRP. The rate of corticosteroid taper is approximately 10 mg per month initially, then decreased to 5 mg per month, and even as low as 1 mg per month, once a dose of 10 or 15 mg per day is reached. A maintenance dose of 5 to 7.5 mg per day is generally adequate after the first 6 to 12 months of therapy. Alternate day corticosteroid regimens are not recommended, because rebound arteritis has been associated with this regimen.[1]

A recent study[66] looked in a prospective manner at the impact of induction therapy with high dose IV corticosteroids compared with oral treatment, as regards the course of therapy. Twenty-seven patients with biopsy-proven GCA were randomized to receive IV methylprednisolone (15 mg/kg of ideal body weight per day) or IV saline for 3 consecutive days, and all patients were started on 40 mg/d of prednisone, followed by a taper schedule. However, because of the relatively low dose of prednisone used, patients with GCA-related vision loss, amaurosis fugax or cerebrovascular accidents were excluded from the study. It was concluded that initial treatment with IV methylpredisolone had long-term benefits, such as a more rapid tapering of oral corticosteroids and a higher rate of sustained remission.

The response of GCA systemic symptoms to corticosteroids is usually rapid and dramatic, with relief of headache and malaise within 24 hours. Unfortunately, only 4% to 15% of patients with arteritic AION experience improvement in

visual loss with therapy.[1,53,67,68] Recent reports have emphasized that, if improvement does occur, it usually consists of improvement in visual acuity, with persistent, often severe, visual field defects.[67,68] Corticosteroid prophylaxis for involvement of the unaffected eye is well recognized; however, progression of visual loss or second eye involvement occasionally occurs despite high dose systemic therapy. If this occurs, it tends to be within a few days of initiation of therapy.[69] Recurrence of symptoms or relapse elevation of the ESR and CRP occurs in over half of patients as corticosteroids are tapered.[53,54,67] Immediate elevation of the corticosteroid dose to the last dose before relapse is recommended.

Long-term corticosteroid therapy is not a benign treatment. Complications occur in most patients, especially in the elderly population. It is recommended to give patients a gastric cytoprotection (until they received a dose of prednisone of 10 mg/d or less), as well as an osteoporosis prophylaxis, for which the American College of Rheumatology has proposed guidelines.[62,70] Consequently, there is substantial interest in the development of corticosteroid-sparing agents for the treatment of GCA; however, none has proven useful in randomized studies to date.[52] Methotrexate, azathioprine, cyclosporine, and tumor necrosis factor blockers such as inflizimab have been used as corticosteroid-sparing agents. Methotrexate is the most studied agent but with conflicting results.[71] A recent prospective trial on infliximab suggested that this drug is of no benefit in GCA, and may even be harmful.[72]

The anti-inflammatory effects of aspirin have been suggested as potentially beneficial for visual outcome, but there are no prospective studies.[1,52] In a study done on mouse chimeras, Weyand et al[73] provided evidence of the complementary action of aspirin and corticosteroids in GCA. Anticoagulation has also been tried, with no proven benefit.[1]

Posterior Ischemic Optic Neuropathy (PION)

PION (also termed retrobulbar ischemic optic neuropathy) is rare compared with the anterior variety of ION. Before making the diagnosis of PION, other causes of retrobulbar optic neuropathy (eg, inflammatory, toxic, compressive) must be excluded.[1,74,75] Although both AION and PION are manifestations of vascular insufficiency to the optic nerve, they represent 2 very different pathophysiologic entities. This distinction is related primarily to the marked difference in vascular supply between the anterior and posterior segments of the optic nerve (see introduction). The posterior segment of the optic nerve is supplied only by the surrounding pial capillary plexus; only a small number of capillaries actually penetrate the nerve and extend to its central portion among the pial septae. As a result, the center of the posterior portion of the optic nerve is relatively poorly vascularized compared with its anterior portion.[1,75] Another important distinction between AION and PION concerns the structural appearance of the optic nerve. There is no known structural variant of the optic nerve that has been identified in patients with PION similar to the disc-at-risk seen with AION.

Acutely, patients with posterior ischemic optic neuropathy present similarly to patients with anterior ischemic optic neuropathy, except that their optic disc is normal acutely, without any disc edema.

Acutely, patients with PION present similarly to patients with AION, except that their optic disc is normal acutely, without any disc edema. The typical presentation of PION is a sudden loss of vision in 1 eye, which is usually painless. Examination reveals decreased visual acuity, visual field loss, a relative afferent pupillary defect, and a normal optic disc head. Occasionally, within a few days of visual loss, a small amount of disc edema may appear as axoplasmic swelling extends forward from the primarily affected retrobulbar optic nerve. Optic disc pallor ensues 4 to 6 weeks later.[1,74,75]

Patients with PION may be separated into 3 distinct groups: perioperative PION (see below), arteritic PION (for which GCA must be excluded in all patients over 50 years old), and nonarteritic PION (a rare diagnosis of exclusion).[74]

Perioperative Ischemic Optic Neuropathy

Perioperative visual loss is an uncommon but devastating injury that has been reported after various types of surgeries. These ischemic optic neuropathies are of great medicolegal importance.

AION may occur rarely after intraocular surgery such as cataract extraction, or after intraocular injections. The presumed mechanism is optic nerve head ischemia secondary to fluctuations in intraocular pressure.[33–35] Ischemic optic neuropathies may also occur after nonocular surgeries and during procedures such as dialysis or even cardiac catheterization.[1,76] Although this complication has been reported after many types of surgery, the 2 most classic are coronary artery bypass procedures and spine surgery.[1,77–79] During coronary artery bypass, AION is probably more common than PION, perhaps more related to fluctuations in blood pressure and blood loss.[1,77]

There has been a growing concern about ischemic optic neuropathy in the setting of spine surgery performed in the prone position.

Over the past decade, there has been a growing concern about ION in the setting of spine surgery performed in the prone position.[79] Ophthalmic complications have been re-

ported to occur in less than 0.2% of spine surgeries.[80] However, most of the reported cases have a poor visual prognosis, typically presenting with profound visual loss as a result of bilateral PION. The visual loss is usually apparent immediately after awaking from anesthesia.[81] The etiology of such ION remains debated and poorly understood. Different studies have noted that PION cannot be explained only by relative hypotension and anemia, as these are common occurrences during spine surgery.[79,81] Chronic hypertension, smoking, vascular disease, diabetes, increased blood viscosity, and anatomic anomalies have been proposed as comorbidity risk factors. Although direct pressure on the globes from the headrest has also been postulated as a factor in a few cases, this could not be a cause of PION (in which elevation of intraocular pressure by external compression could not affect retrobulbar blood flow) but could account for the rare unilateral case of central retinal artery occlusion in this setting. Finally, there may be an anatomic "watershed" region involving the vascular supply of the posterior optic nerves in some individuals, rendering these patients susceptible to fluctuations in blood pressure and oxygen delivery that would not affect other patients undergoing these procedures.[1,74,79]

In 1999, the American Society of Anesthesiologists formed a committee which collected detailed information on cases of postoperative visual loss occurring after nonocular surgery.[82] They analyzed 93 cases associated with spine surgery, including 83 cases of ION and 10 cases of central retinal artery occlusion. Among the cases of ION, blood loss of 1000 mL or greater, or anesthetic duration of 6 hours or longer was present in 96% of patients. However, no control cases of patients undergoing similar surgeries without resultant visual loss were compared.

Radiation Optic Neuropathy

Radiation optic neuropathy is thought to be an ischemic disorder of the optic nerve that usually results in irreversible severe visual loss, months to years after radiation therapy to the brain, skull base, paranasal sinuses, or orbits.[1,83] It is most often a retrobulbar process. Patients typically present with rapidly progressive painless loss of vision in 1 eye, which often becomes bilateral within weeks or months. There is classically marked enhancement of the affected optic nerve on MRI.[1,83] There is currently no known effective treatment, although corticosteroids and hyperbaric oxygen are often prescribed.[1,83,84]

CONCLUSIONS

IONs are a frequent optic nerve disturbance among the over 50-year-old population. Proper recognition by neurologists is important to allow for appropriate investigation and treatment. Under no circumstances is this recognition more important than with the arteritic form of ION, for which rapid initiation of corticosteroid therapy may prevent irreversible blindness. Remember: in all cases of ION, where arteritic AION is suspected; treat it promptly with high-dose corticosteroids; always confirm arteritic AION with a TAB; look for the so-called disc-at-risk in NAION; PION is extremely rare and is a diagnosis of exclusion. Finally, do not hesitate to ask for help from your colleagues in ophthalmology.

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