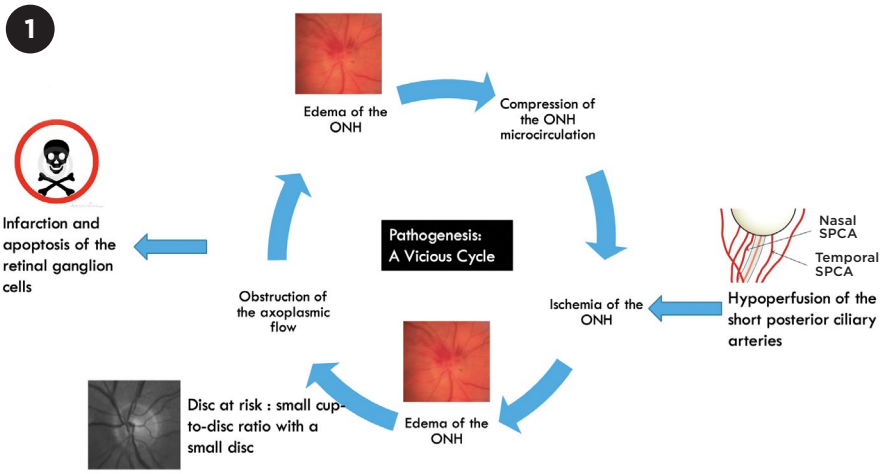
NAION: Diagnosis and Management

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common cause of acute optic nerve injury in individuals over 50 years old. Despite its frequency, several aspects of this disease, including its pathogenesis and effective treatments, remain unknown or unproven.

Although no treatment for NAION exists, a history and clinical examination, as well as additional investigations, are critical in ruling out life- or sight-threatening conditions that can mimic NAION.



Epidemiology

In the United States, the estimated annual incidence of NAION ranges from 2.3 to 10.2/100,000 for the population over 50 years old and 0.54/100,000 for all ages. This disease affects both sexes equally, and the mean age of onset is 66 years. White people are at higher risk of NAION than other ethnic groups.

Pathophysiology

The precise pathogenesis of NAION remains unclear, but it has been hypothesized that transient hypoperfusion of the short posterior ciliary arteries causes acute ischemia to the optic nerve head (ONH), resulting in axonal swelling. This swelling compromises the axoplasmic flow, which subsequently increases the axonal swelling, contributing to the compression of ONH microcirculation, exacerbating the ischemia. This vicious cycle creates a compartment syndrome, eventually leading to infarction and apoptosis of the retinal ganglion cells (Fig. 1).

Risk Factors

Systemic. The best-known risk factors for NAION are vasculopathic, including diabetes, smoking, hypertension, and hypercholesterolemia. Use of medications such as phosphodiesterase-5 (PDE-5) inhibitors (e.g., sildenafil, vardenafil, and tadalafil) has been associated with an increased risk of NAION, perhaps by inducing hypoperfusion of the ONH through local vasodilation.

Patients younger than 50 years without vascular risk factors may have coagulation abnormalities; however, frequently no underlying systemic conditions are found.

Ocular. The term "disc at risk" refers to a small ONH with a small cup-to-disc ratio and crowding of optic nerve fibers, which contributes to the pathogenesis of NAION. Optic disc drusen can also lead to crowding of the disc and are a common risk factor in patients under 50.

Several case reports and case series suggest an association between NAION and ocular surgeries (cataract surgery and LASIK). The authors of these studies hypothesize that the perioperative rise in IOP led to decreased perfusion of the ONH.[1,2]

Clinical Features

Symptoms. NAION typically presents as an acute, monocular, painless loss of vision. Although bilateral presentation is rare, it can occur in the setting of severe blood pressure fluctuation due to surgery, hemodialysis, or excessive blood loss. Ocular discomfort, headache, and periocular pain are not typical

BY **KEVIN YANG WU, MD, DMD,** AND **FRANÇOIS EVOY, MD, FRCPC.** EDITED BY BENNIE H. JENG, MD.

Kevin Yang Wu, MD, DMD

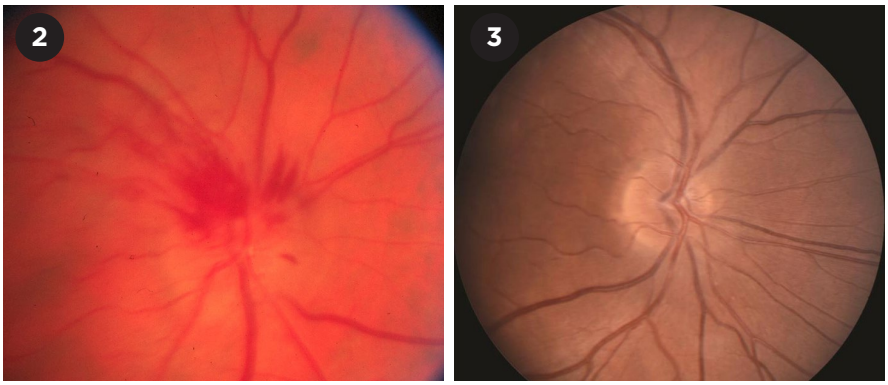
but have been reported in 10% of patients. Presence of pain should prompt investigation for alternative causes of the vision loss.

Signs. Visual loss is usually less severe in NAION than in arteritic anterior ischemic optic neuropathy (AAION). The absence of light perception is rare in NAION and, if present, should lead the clinician to suspect AAION. At presentation, 50% of NAION patients have VA better than 20/64, and 66% have better than 20/200. Some NAION patients may have normal VA.

The typical visual field defect in NAION is inferior altitudinal vision loss. However, other patterns may be detected, including inferior nasal loss or central, cecocentral, and/or arcuate scotomas.

As in other types of optic neuropathy, dyschromatopsia and relative afferent pupillary defect may be present in NAION. The degree of dyschromatopsia in NAION is proportionate to the VA loss, unlike in optic neuritis, in which the dyschromatopsia is much more severe than would be expected for the level of VA.

Fundus findings. Funduscopic exam reveals diffuse or segmental optic disc edema (Fig. 2). Peripapillary splinter or flame hemorrhage, dilated telangiectatic capillaries, and narrowing of the peripapillary retinal arterioles can be observed in NAION. Cotton-wool spots rarely occur and if present should prompt concern for AAION. The fellow eye shows a disc at risk (Fig. 3).



FUNDUS FINDINGS. *(2) Eye with NAION shows optic disc edema, peripapillary splinter hemorrhage, dilated telangiectatic capillaries, and narrowing of the peripapillary retinal arterioles. (3) Eye shows a "disc at risk."*

Diagnosis

NAION is primarily a clinical diagnosis. If a patient with vasculopathic risk factors has a typical history and classic exam findings for NAION, no additional testing is required to confirm the diagnosis. If the history or signs are atypical, further workup and testing can help to rule out other diagnoses.

Differential diagnosis. Several vision- and life-threatening diseases can mimic NAION. These include giant cell arteritis (GCA) manifesting with AAION, optic neuritis, and compressive or infiltrative orbital lesions. See Table 1, with this article at aao.org/eyenet, for distinguishing characteristics of AAION, NAION, and optic neuritis.

Giant cell arteritis. GCA typically occurs in women more than men; patients over 50 years of age are at risk although its incidence increases dramatically after age 70. Its systemic symptoms include headache, scalp tenderness, jaw claudication, fever, malaise, and symptoms of polymyalgia rheumatica such as proximal muscle pain and weakness.

Prodromal ocular symptoms can occur in GCA, and the VA in the associated AAION tends to be worse than in NAION. Funduscopic exam may reveal pallid ONH edema versus hyperemic edema in NAION, and fluorescein angiography shows both ONH and choroidal filling delay. Other red flags for GCA are bilateral simultaneous or rapidly sequential vision loss (i.e., fellow eye involved within one to two weeks), as well as recurrence in the same eye.

On laboratory testing, inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count are elevated in GCA.

Optic neuritis. Although typical optic neuritis is not likely to be confused with NAION (because optic disc edema is absent and onset of vision loss is gradual over days rather than sudden), anterior optic neuritis can mimic NAION and should be suspected when atypical signs and symptoms such as pain with eye movement, dyschromatopsia out of proportion to vision loss, and subacute symptom onset and/or progression are noted.

Recent evidence has shown that optic neuritis associated in anti–myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) can mimic the fundus appearance of NAION, with marked disc swelling and hemorrhages. However, MRI of the orbits with contrast usually shows optic nerve and nerve sheath enhancement, whereas findings in NAION should be normal. Serologic testing for anti-MOG antibodies should be considered in these cases.

Orbital lesions. Compressive and infiltrative orbital lesions can present with proptosis, diplopia with extraocular movement limitation, gradual and progressive visual loss, and ONH edema lasting for more than two months. Neuroimaging is indicated in such cases.

Diagnostic testing. Laboratory tests and imaging can be ordered to rule out alternative diagnoses. Blood tests for ESR, CRP, platelet count, and other inflammatory markers as appropriate should be ordered in patients older than 50 years or in cases that are suspicious for GCA. If these inflammatory markers are positive, Doppler ultrasound and/or temporal artery biopsy should be performed to confirm the diagnosis of GCA, but these procedures should not delay the initiation of therapy with high-dose corticosteroids.

MRI of the brain and orbits with gadolinium contrast and fat suppression should be ordered for atypical features suggestive of optic neuritis or compressive or infiltrative lesions.

Ocular imaging is not routinely

performed but can be useful in case of uncertainty. Some studies suggest that NAION may be differentiated from other causes of optic disc swelling using OCT of the macula or OCT angiography (OCT-A). However, there are numerous technical factors that can cause artifacts and make it difficult to use OCT or OCT-A for diagnosis in clinical practice.[3] Fluorescein angiography reveals delayed filling of the optic disc with normal filling of the choroid in NAION. This feature helps differentiate NAION from AAION, as delayed filling of the choroid suggests GCA.

Additional investigations. Further evaluation in patients with NAION focuses on identifying underlying causes and risk factors. In patients younger than 50 years with no vascular risk factors, a hypercoagulable workup may be considered to rule out a thrombogenic tendency. Also, in these young individuals, spectral-domain OCT with enhanced depth imaging may be helpful to identify optic disc drusen. Polysomnography should be considered if the patient presents with one or more features raising suspicion for obstructive sleep apnea.

In contrast to central retinal artery occlusion, NAION is not associated with embolism from cardiac or larger artery disease (carotid occlusive disease).

Management

Acute treatment. There is currently no medical or surgical treatment shown to improve the prognosis in the setting of acute NAION.

As shown in previous studies, aspirin as an acute treatment does not appear to influence visual outcomes. Low-dose aspirin therapy may be prescribed as secondary prevention based on the patient's underlying vasculopathic risk factors. It is unclear if aspirin is beneficial in preventing occurrence of NAION in the fellow eye.[4]

Systemic glucocorticoid therapy is not recommended by the existing literature. Although corticosteroids can accelerate the resolution of optic disc edema and improve the visual evoked response, they do not provide clinically significant improvement in long-term visual outcomes.[5]

Optic nerve sheath decompression (ONSD) offers no benefit, as shown in the Ischemic Optic Neuropathy Decompression Trial. Patients treated with ONSD had worse visual outcomes than the control group.[6]

Research continues on neuroprotective and neuroregenerative treatments such as stem cell therapy, retinal ganglion cell transplantation, and optic nerve regeneration.[7]

Addressing underlying risk factors. After an acute episode of NAION, the clinician should address the specific underlying etiologies in the follow-up appointments. This should be done in collaboration with the patient's primary care physician. Medical control of underlying vasculopathic risk factors (e.g., diabetes, smoking, hypertension, hypercholesterolemia) is paramount for the primary prevention of cardiovascular and cerebrovascular diseases. However, evidence does not show that such preventive measures have any effect on the occurrence of NAION in the fellow eye.[8] Blood pressure should be managed carefully, as systemic hypotension may be involved in the pathogenesis of NAION.

After communicating with the patient's primary care physician, clinicians may want to consider discontinuing PDE-5 inhibitors because the risk of developing NAION in the fellow eye may be doubled (from 15% to 30%).[9]

Prognosis

There is currently no consensus on the percentage of cases that will deteriorate or improve. However, it has been estimated that approximately 70% of patients will remain static with no change in vision; 20% will have modest improvement in VA; and 10% will experience progressive worsening over the four weeks following initial presentation but will stabilize by two months.[6] Continued progression after the first two months is atypical and should prompt investigation into other causes of vision loss (e.g., compressive orbital lesion). Complete recovery of vision is also unusual and should raise the suspicion of optic neuritis.

Recurrence of NAION in the same eye is uncommon (approximately 5%), as the atrophy caused by ischemic injury relieves nerve fiber crowding in that eye. Ipsilateral recurrence should prompt a reevaluation to rule out GCA or MOGAD.

The rate of occurrence of NAION in the fellow eye is approximately 15% at five years. Evidence suggests that it is not possible to determine who is at risk for the contralateral eye involvement based on the initial presentation.[8]

Conclusion

NAION is the most common nonglaucomatous optic neuropathy in patients older than 50. Despite its frequency, there is no proven treatment to improve visual outcomes and prevent occurrence in the fellow eye. Nevertheless, it remains critical for clinicians to identify modifiable risk factors to reduce cerebrovascular and cardiovascular morbidities and mortalities.

1 McCulley TJ et al. *Ophthalmology*. 2001;108(7):1275-1278.
2 Cameron BD et al. *Ophthalmology*. 2001;108(4):660-665.
3 Ling JW et al. *Int J Ophthalmol*. 2017;10(9):1402-1406.
4 Beck RW et al. *Am J Ophthalmol*. 1997;123(2):212-217.
5 Saxena R et al. *Ophthalmology*. 2018;125(10):1623-1627.
6 Ischemic Optic Neuropathy Decompression Trial. *Arch Ophthalmol*. 2000;118(6):793-798.
7 Gibbons A, Henderson AD. *Front Ophthalmol*. March 15, 2022. www.frontiersin.org/article/10.3389/fopht.2022.848710. Accessed May 4, 2022.
8 Keren S et al. *BMC Ophthalmol*. 2017;17(1):155.
9 Campbell UB et al. *J Sex Med*. 2015;12(1):139-151.

Dr. Wu is an ophthalmology resident and **Dr. Evoy** is assistant professor of neurology and ophthalmology. Both are at the University of Sherbrooke, Sherbrooke, Quebec, Canada. *Financial disclosures: None.*

MORE ONLINE. See Table 1: Characteristics for the Differential Diagnosis of NAION with the online version of this article at aao.org/eyenet. It covers systemic and ocular symptoms, imaging and lab findings, prognosis, and risk of occurrence in the fellow eye.