Nonarteritic anterior ischemic optic neuropathy: cause, effect, and management

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Abstract: Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common form of ischemic optic neuropathy and the second most common optic neuropathy. Patients are generally over the age of 50 years with vasculopathic risk factors (eg, diabetes mellitus, hypertension, and obstructive sleep apnea). The exact mechanism of NAION is not fully understood. In addition, several treatment options have been proposed. This article summarizes the current literature on the diagnosis, treatment, and management of NAION.

Keywords: anterior ischemic optic neuropathy, nonarteritic anterior ischemic optic neuropathy, ischemic optic neuropathy

Introduction

Nonarteritic anterior ischemic optic neuropathy (NAION) is the second most common optic neuropathy after glaucoma caused by infarction of the short posterior ciliary arteries that supply the anterior portion of the optic nerve head. This leads to axonal edema and a compartment syndrome in an already crowded optic disc causing vision loss.1 Annually, there are ~6,000 new cases in the United States.1 Significant research on pathophysiology, prevention, and treatment has been performed and will be discussed in this review, but remains limited.

Clinical presentation and pathogenesis

NAION typically presents with acute unilateral painless vision loss accompanied by sector or diffuse optic nerve edema. It occurs more frequently in the Caucasian population and there is no gender predilection.1,2 It generally affects people over 50 years of age, with a mean onset between 57 and 65 years of age. However, it has also been reported in patients <40 years old both with and without vasculopathic risk factors (ie, NAION of the young [NAIONY]).3 Visual field (VF) defects following a nerve fiber layer distribution are typical VF findings, with inferior altitudinal and arcuate defects being the most common.1,2,4 Patients may describe the vision loss as a “dim or blur”, especially in the area of the field loss.1 Hayreh et al noted that vision loss was often reported upon awakening, and some authors believe that the etiology for NAION is nocturnal hypotension.3 Vision loss from NAION is variable but is typically less severe than the loss from arteritic anterior ischemic optic neuropathy (A-AION). Hayreh et al observed the initial visual acuity (VA) to be 20/30 or better in 49% of cases of NAION.5 An ipsilateral relative afferent pupillary defect will be present in unilateral or bilateral but asymmetric cases. Sector or diffuse disc edema in the acute phase of the disease is
essential for clinical diagnosis. The disc edema may or may not be accompanied by peripapillary hemorrhages. Macular edema and exudates are less common.

Although the exact pathogenesis of NAION remains unproven, it appears to be a multifactorial disease. It is presumed to be due to a transient disruption in the circulation of the optic nerve head leading to hypoperfusion and ischemia. The exact cause of this transient disturbance remains unclear but several hypotheses have been proposed including generalized hypoperfusion, nocturnal hypotension, local autoregulation failure, vaso spasms, venous occlusion, and thrombosis. In addition, patients with NAION typically have a small cup-to-disc ratio as a predisposing factor, and this “crowded optic disc head” has been referred to as the “structural disc at risk” for NAION. Theoretically, when localized swelling occurs in a fixed space anterior to the rigid lamina cribosa, the capillaries could become more easily compressed and secondary ischemia may result. Recent studies of the optic nerve head utilizing optical coherence tomography (OCT) have demonstrated thicker prelamellar tissue in NAION patients. Systemic diseases that may cause decreased perfusion to the optic nerve head secondary to microvascular compromise might increase the patient’s risk of NAION. These include hypertension, diabetes, and hypercholesterolemia. Other risk factors noted in the literature are nocturnal hypotension, smoking, obstructive sleep apnea, anemia, hypercoagulable states, disc drusen, ocular and nonocular surgery, and migraines. The use of vasoactive medications may be an additional risk factor for NAION. Phosphodiesterase type-5 inhibitors (PDE-5i) have recently been implicated in NAION; however, there is still much debate over this topic. A recent observational study reported an increase of 2.21 in the odds ratio of an NAION in patients using PDE-5i up to 30 days prior to the event. Amiodarone has also been associated with NAION.

Prognosis

Although a progressive form of NAION has been reported, the course of NAION typically stabilizes within 2–3 months. The visual prognosis is generally guarded; however, the acuity may improve by up to three lines in 43% of patients. The VF defects are less likely to improve. There is <5% chance of recurrence in the same eye. The initial disc edema usually resolves, and sector or diffuse atrophy ensues typically within the next 6–11 weeks.

Work-up for other etiologies of optic disc edema, however, should be considered if the edema persists beyond this time frame (eg, compressive lesion, optic nerve sheath meningioma, and infectious, infiltrative, or inflammatory optic neuropathies). There is up to a 15% chance of fellow eye involvement at 5 years. The VA and VF defect in a patient with prior NAION cannot directly predict the prognosis of visual impairment if there is second eye involvement. This presentation of optic disc edema in one eye and optic atrophy in the fellow eye can produce a “pseudo-Foster Kennedy” syndrome. The key in differentiating between “pseudo-Foster Kennedy” and a true Foster Kennedy is the history of abrupt vision loss in the affected eye with optic disc edema (acute NAION) and a history of prior visual loss in the contralateral eye with optic atrophy (old NAION). In the true Foster Kennedy syndrome, there is no abrupt vision loss as the pale disc is from a compressive etiology and the fellow edematous disc is secondary to papilledema from increased intracranial pressure.

Management and treatment

NAION is primarily a clinical diagnosis. The most important initial step in management is to exclude giant cell arteritis (ie, A-AION). The presence of pallid edema on exam and symptoms including pain, jaw claudication, scalp tenderness, fever, and malaise should raise suspicion for A-AION.

Patients presenting with typical features generally do not need neuroimaging or additional laboratory testing other than erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or platelet count. Other causes of optic neuropathies should be considered in the presence of atypical features. Table 1 summarizes some of the atypical features. Some patients may require cranial and orbital magnetic resonance imaging (MRI; eg, progressive NAION) and, rarely, head and neck MR-angiogram (MRA) or computed tomography angiography (CTA) may be considered in patients presenting with unilateral head or neck pain to exclude a carotid dissection.

<table>
<thead>
<tr>
<th>Table 1: Atypical features for NAION</th>
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<tbody>
<tr>
<td>Less than 40 years old</td>
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<tr>
<td>Pain</td>
</tr>
<tr>
<td>Bilateral simultaneous onset</td>
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<tr>
<td>Rapidly sequential vision loss</td>
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<tr>
<td>Lack of optic disc edema</td>
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<td>Optic disc edema persisting &gt;4 weeks</td>
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<tr>
<td>Atypical VF defect (homonymous hemianopia)</td>
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<tr>
<td>Absence of a relative afferent papillary defect</td>
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<tr>
<td>Lack of vasculopathic risk factors</td>
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<tr>
<td>Large cup-to-disc ratio in the fellow eye</td>
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<tr>
<td>Recurrent attacks</td>
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<tr>
<td>Macular star</td>
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</table>

Abbreviations: VF, visual field; NAION, nonarteritic anterior ischemic optic neuropathy.
A thorough history, including medications (eg, PDE-5i, amiodarone), past medical history (eg, vasculopathic risk factors), recent surgical history, and social history (eg, smoking), is key. Patients should be evaluated by their primary care physicians for modifiable risk factors including hypertension, hyperlipidemia, diabetes mellitus, and obstructive sleep apnea.

A carotid workup is generally not indicated in typical NAION but can be considered in the presence of ocular ischemic syndrome, retinal emboli, or transient neurological deficits. OCT can be used to monitor the disease course for long term with the assessment of edema and optic atrophy, but NAION remains a clinical diagnosis and there are no diagnostic OCT features of NAION. Some recent studies have demonstrated the use of OCT in the assessment, diagnosis, and management of NAION. Findings include increased peripapillary choroidal thickness associated with optic disc edema and subretinal fluid on spectral domain OCT (SD-OCT) and macular ganglion cell inner plexiform layer thinning associated with VF defect in frequency domain OCT (FD-OCT). Another study found that NAION affected neither the cup-to-disc ratio nor alpha or beta zone of parapapillary atrophy. Ganglion cell layer plus inner plexiform layer (GCL+IPL) thinning has been shown to be better than retinal nerve fiber layer (RNFL) thinning in indicating early structural loss in NAION. The application of OCT-angiography (OCT-A) in NAION is also being studied. OCT-A is a useful noninvasive technique in depicting ocular perfusion in comparison to fluorescein angiography. It can also be used in pregnant patients and those allergic to fluorescein. A case study by Higashiyama et al demonstrated areas of decreased retinal perfusion on OCT-A consistent with the RNFL and ganglion cell complex loss in NAION. Another study by Sharma et al examined the microvascular perfusion during the acute and follow-up stages of NAION. OCT-A demonstrated segmental and global reduction of the peripapillary flow in the acute phase with subsequent spontaneous partial recovery consistent with visual recovery and the natural course of NAION. Furthermore, the temporal sector of the nerve head not only demonstrated the highest flow density in healthy controls, but also demonstrated the most damage in eyes with NAION. They also found that there was no disruption of the microvasculature in the healthy unaffected eye. The authors proposed that this could be subsequent to the temporal watershed zone discussed by Hayreh which correlates with the predominance of nasal field defects in NAION.

To date, no definitive high-grade evidence for an effective treatment of NAION exists (Table 2). The highest level of evidence comes from the Ischemic Optic Neuropathy Decompression Trial (IONDT). This was a prospective, randomized trial that assessed optic nerve sheath fenestration as a treatment for NAION. It was the only randomized controlled trial for NAION. It was based upon the theory that an optic nerve sheath fenestration could reduce the compartment syndrome effect. However, the study concluded that optic nerve sheath fenestration was not an effective intervention and may actually have a harmful effect.

Other treatment options explored include medical therapies such as aspirin, steroids, and neuroprotective agents. Aspirin has been studied as a primary treatment for NAION as well as a preventive measure of fellow eye involvement. A retrospective case-controlled study showed no improvement in the final visual outcome in those treated with aspirin before, during, and following NAION compared with those who did not receive any aspirin. The majority of the retrospective and case-control studies examined aspirin for its use in preventing NAION in the fellow eye. Data from the retrospective studies are controversial. The most convincing data come from the follow-up to the Ischemic Optic Neuropathy Decompression Trial (IONDT) and a large retrospective review by Beck et al. The IONDT follow-up suggested that aspirin did not influence the rate of recurrence. The large retrospective study of 431 patients with NAION by Beck et al suggests a possible short-term benefit of aspirin (cumulative probability of 7% in aspirin group and 15% in non-aspirin group at 2 years) but lacks a long-term benefit in reducing the risk of NAION in the fellow eye (17% aspirin group vs 20% untreated group at 5 years). Despite sufficient evidence of long-term benefit of aspirin, many still recommend it following the initial NAION because of the vasculopathic risk factors associated with NAION. This becomes more important when considering the data on increased risk of ischemic stroke in patients with NAION. A recent retrospective study found a 3.35 times increased risk of developing an ischemic stroke in patients with NAION compared to patients with similar comorbidities but without NAION. However, like much of the data, there is conflicting opinions in this association.

Steroids, administered systemically, periocularly, or intravitreally, have been proposed as treatment modalities with the earliest report dating back to the late 1960s. The initial study demonstrated improvement in 11 of 13 (85%) patients treated with 60 mg/day oral prednisone compared to 5 of 11 (45%) untreated patients. The authors postulated that steroids
would decrease the capillary permeability, subsequently accelerating the resolution of the disc edema and reducing the compressions of capillaries on the optic nerve head and therefore improving blood flow to ischemic axons.31,33 Hayreh and Zimmerman conducted a large nonrandomized study in which patients could elect to be treated with oral prednisone 80 mg/day for 14 days followed by a 2-month taper. The authors observed improvement of visual function in those treated compared to the untreated controls. However, the nonrandomized and unmasked nature of the study, the older age and higher vasculopathic comorbidities of their untreated patients, and the large steroid dose that carries systemic side effects with it weaken the findings.34 Evidence for intravitreal administration of steroids remains controversial.35

Additional treatment efforts aimed at neuroprotection with agents such as intravitreal erythropoietin, oral levodopa, diphenylhydantoin, topical brimonidine tartrate, hyperbaric oxygen, and transcorneal electrical stimulation have been explored.36–45 However, these studies are limited by their small number of patients and absence of control. Emerging on the forefront of neuroprotective efforts is intravitreal small interfering ribonucleic acid (siRNA) injections. siRNA prevents apoptosis by inhibiting the expression of caspase-2. This randomized, double-masked study is still in the patient recruitment phase with no data available yet.46

**Conclusion**

NAION remains a common disease with devastating consequences for patients, unclear pathophysiology, and contradictory data regarding fellow eye involvement and treatment.

In our experience, if you are considering the diagnosis of NAION in a patient presenting with acute vision loss and optic disc edema, we recommend that you think of the following: 1) look for atypical features that would make you

**Table 2 Summary of some of the studies that explored treatment of NAION**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hypothesized mechanism of action</th>
<th>Type of study (level of evidence)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Surgical</td>
<td></td>
<td></td>
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<tr>
<td>ONSD</td>
<td>To resolve the “compartment syndrome”</td>
<td>Masked, prospective, randomized (I)</td>
<td>32.6% surgery patients improved compared to 42.7% of observation group12,20</td>
</tr>
<tr>
<td>RON</td>
<td>To resolve the “compartment syndrome”</td>
<td>Randomized, control (II)</td>
<td>75% of eight treated eyes improved with RON, one eye developed a choroidal neovascular membrane. 25% of eight untreated eyes improved18</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Systemic corticosteroids</td>
<td>Decreased disc swelling</td>
<td>Nonrandomized controlled study (III)</td>
<td>VA improved in 69.8% of 236 treated patients and in 40.5% of 301 untreated. VF improved in 40.1% of treated patients and in 24.5% of untreated7</td>
</tr>
<tr>
<td>Combined systemic corticosteroids and erythropoietin</td>
<td>Decrease disc swelling and neuroprotection</td>
<td>Prospective interventional case series</td>
<td>No benefit in combined corticosteroids and erythropoietin versus systemic corticosteroids alone versus control in final VA</td>
</tr>
<tr>
<td>Oral levodopa</td>
<td>Neuroprotection</td>
<td>Retrospective, nonrandomized</td>
<td>76.9% of 18 treated improved</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Improves blood flow</td>
<td>Retrospective</td>
<td>30% of 19 untreated improved</td>
</tr>
<tr>
<td>Topical</td>
<td></td>
<td></td>
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<tr>
<td>Topical brimonidine</td>
<td>Neuroprotection</td>
<td>Multicenter, randomized, clinical trial (II)</td>
<td>No VF or VA improvements. Both trials NPION and BRAION discontinued due to recruitment difficulties</td>
</tr>
<tr>
<td>In Intravitreal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravitreal steroids</td>
<td>Decreased disc edema</td>
<td>Case controlled (III)</td>
<td>VA improved in 4 treated and 6 untreated18</td>
</tr>
<tr>
<td>Intravitreal erythropoietin</td>
<td>Neuroprotection</td>
<td>Prospective case series</td>
<td>61.2% VA improved with treatment, but no VF improvement19</td>
</tr>
<tr>
<td>Intravitreal anti-VEGF</td>
<td>Reduced vasogenic disc swelling</td>
<td>Various case reports, case series (IV)</td>
<td>A faster resolution of disc edema and improved visual outcome were documented15</td>
</tr>
<tr>
<td>Intravitreal injection of QPI-1007 (siRNA)</td>
<td>Neuroprotection</td>
<td>Clinical trial is still recruiting patients</td>
<td></td>
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</table>

Note: The IONDT was a prospective trial to evaluate ONSD in the management of NAION. Aspirin data were observational only.

Abbreviations: IONDT, Ischemic Optic Neuropathy Decompression Trial; NAION, nonarteritic anterior ischemic optic neuropathy; ONSD, optic nerve sheath decompression; RON, radial optic neurotomy; siRNA, small interfering ribonucleic acid; VA, visual acuity; VEGF, vascular endothelial growth factor; VF, visual field.
consider diagnoses other than NAION (Table 1); 2) ask about vasculopathic risk factors and always look for other medical problems that can be associated with the disc edema such as inflammatory and neoplastic diseases; 3) if the patient is in the appropriate age group, has vasculopathic risk factors, has a disc at risk in the fellow eye, and has no atypical features, then you can make a diagnoses of NAION, but continue to monitor the patient. Once the diagnoses of NAION is made, we recommend counseling the patient about better control of their vasculopathic risk factors including referral to a primary care physician, smoking cessation, weight loss, and exercise. We also recommend an aspirin a day, if there is no contraindication, to all our patients despite the lack of level I evidence to prove benefit. The future holds promise with neuroprotective and inflammatory modulating agents.

Disclosure

The authors report no conflicts of interest in this work.

References