Nonarteritic Anterior Ischemic Optic Neuropathy: An Update on Demographics, Clinical Presentation, Pathophysiology, Animal Models, Prognosis, and Treatment

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Abstract

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common acute ischemic optic neuropathy. The condition typically affects middle-aged and elderly individuals, though it may occur in younger age groups. Recent evidence suggests that its prevalence is higher than previously estimated. The clinical presentation of NAION is very classic and includes acute loss of visual afferent function (acuity, field and/or color) with the funduscopic appearance of an edematous optic nerve. The unaffected fellow eye usually has a small, crowded appearance described as a ‘disc at risk’. The pathophysiology of NAION is believed to be multi-factorial with the common pathway being circulatory insufficiency of the small caliber vessels supplying the optic nerve head. However, the exact location and mechanism of ischemia are still under debate. Prognosis of NAION is guarded; up to 50% of patients may have acuity of 20/200 or less with significant visual field loss, though approximately 40% will have improvement in their acuity. There are currently two animal models employed in investigating the histopathologic, molecular, and electrophysiologic changes seen in NAION. Treatment of the condition is quite controversial. Numerous medical and surgical interventions have been tried without clear evidence of benefit. The Ischemic Optic Neuropathy Decompression Trial demonstrated no benefit of optic nerve sheath fenestration in acute NAION. The role of oral corticosteroids is unclear, as is the use of aspirin in the prevention of the condition in the fellow eye. Several other promising agents are currently under investigation for the treatment of acute NAION.

Keywords: NAION; Pathophysiology; Anterior ischemic optic neuropathy (AION)

Introduction

Anterior ischemic optic neuropathy (AION) is an ischemic condition which affects the proximal portion of the optic nerve supplied by the posterior ciliary arteries with resultant acute visual loss. AION is the second most common optic neuropathy in the middle-aged and elderly population following glaucomatous optic neuropathy.

AION can be subdivided into two clinically distinct entities: arteritic anterior ischemic optic neuropathy (AAION), in which the ischemia is attributed to vasculitis usually secondary to giant cell arteritis; and nonarteritic anterior ischemic optic neuropathy (NAION) in which the ischemia is attributed to non-inflammatory small-vessel disease [1]. NAION is by far the more common condition, comprising over 85% of cases of AION. The following discussion will focus on NAION and review the current literature with respect to its demographics, clinical presentation, pathophysiology, animal models, prognosis, and treatment.

Demographics

Although NAION typically affects individuals between the ages of 55-70 [2] with an average age of onset between 57-67 years [3], the condition may develop at any age. It has been noted that 11-23% of NAION patients referred to tertiary care neuro-ophthalmic services were less than 50 years of age [3,4]. There is no sex predilection for NAION. With respect to race, whites appear to be more likely to develop the condition than minority populations [5,6], possibly due to risk factors associated with optic disc morphology [7,8].

Previous studies estimated the annual incidence of NAION in the United States to be 2.3-10.3 per 100,000 with approximately 5,700 new cases per year in the white population over 50 years of age [5,9]. However, a large Medicare database study suggested that the annual incidence is much higher at 82 cases per 100,000 [10].

Very little data exists on the incidence of NAION in other countries aside from the United States. Investigators from the Beijing Eye Study estimated the annual incidence of NAION in Chinese population aged 40 years or greater to be approximately 1 per 16,000, or 6.25 per 100,000 [11]. A retrospective study performed in Croatia found the annual incidence of NAION to be 2.9 per 100,000 in males and 2.5 per 100,000 in females [12].

Clinical Presentation

NAION typically presents with acute, unilateral loss of visual acuity and/or field. The visual loss in NAION is commonly first noted upon awakening, and may progress over several hours to days, and rarely even weeks. Visual acuity may range from 20/15 to no light perception, though severe visual loss may prompt investigation for alternative types of optic neuropathy such as AAION or optic neuritis. Patients also tend to have mild to moderate dyschromatopsia consistent with the degree of acuity loss.
With respect to the visual field defect in NAION, though any pattern of loss may develop, the most common are an inferior altitudinal or arcuate defect. Visual field patterns in NAION resemble the nerve fiber bundle defects of glaucoma and typically obey the horizontal midline.

A relative afferent pupillary defect should present in the affected eye, given that the other eye has not had a previous episode of NAION and that there is no other co-existing optic nerve or retinal disease.

Pain is usually absent in NAION, though may develop in a small subset of patients. Unlike acute optic neuritis, it is rare for patients to have pain with eye movement, and this may be a useful discriminating feature between the two entities.

Examination of fundus in acute NAION reveals optic disc edema, frequently associated with peripapillary flame-shaped hemorrhages (Figure 1). Cotton-wool spots may also be present in NAION, though retinal exudates are rare. The disc edema in NAION typically resolves within 4 to 6 weeks, and is replaced by sectoral or diffuse pallor (Figure 2). A common feature in patients with NAION is a physiologically small cup to disc ratio in the contralateral eye, on the order of 0.3 or less, known as a “disc at risk” (Figure 3) [2,7,13].

There also appears to be a distinct entity known as “incipient NAION” in which the optic disc is crowded and edematous as in NAION, though with no associated visual afferent dysfunction [14-17]. In these cases of asymptomatic optic disc edema, the disc swelling resolves spontaneously and never recurs in 50%, resolves and then recurs symptomatically in 25%, and progresses to symptomatic NAION in the remaining 25%. “Incipient NAION” has been observed with higher frequency in diabetic patients, and the patients who actually progress to NAION may be younger in age than those in whom the disc edema resolves without sequelae [17].

Patients presenting with presumed NAION above the age of 50 should undergo diagnostic testing to rule out AAION with complete blood count, erythrocyte sedimentation rate, and C-reactive protein.

Pathophysiology

Though it is generally accepted that the pathophysiology of NAION results from ischemic injury to the optic nerve head, the precise vasculature affected and mechanism of ischemia remain controversial. Most cases are believed to develop from either hypoperfusion or nonperfusion of the vessels supplying the optic nerve head [18]. It has been suggested that the optic disc is in a watershed zone between the branches of the short posterior ciliary arteries (SPCAs), and thus is vulnerable to ischemia during states of hypoperfusion [19,20].

However, one study using fluorescein angiography in NAION patients demonstrated delayed optic disc filling with preservation of the parapapillary choroidal circulation. This finding suggests that blood flow in NAION is compromised selectively in the paraoptic branches of the SPCAs, not in a generalized watershed distribution as the choroid is spared [21]. Supporting this theory of selective vascular insufficiency is that these branches of the SPCAs have upper and lower territories [22], which correlate with the altitudinal visual field defects commonly seen in NAION [21].

Unfortunately, ocular blood flow imaging techniques such as color and laser Doppler flow studies have not been able to conclusively identify the site of impaired circulation in NAION [23]. In a pilot study, investigators used Fourier-domain optical coherence tomography (OCT) to investigate changes in blood flow in various optic nerve and retinal disorders compared to controls. The authors found that in NAION eyes, there was generalized reduced ocular blood flow while normal venous outflow was preserved [24]. The limitation of this study as with the previous Doppler flow studies was that SPCA flow parameters such as velocity, volume and resistance were not able to be selectively measured.

There are several other factors which may play a role in the ischemia leading to NAION, though these have not yet been proven. They include atherosclerosis and/or lipohyalinosis of small vessels supplying the optic nerve, vasospasm, impaired autoregulation of optic nerve head blood flow, and venous insufficiency [18,23,25]. There has been one large histopathologic study of 193 eyes diagnosed with ischemic optic neuropathy which showed absence of lipohyalinosis, occlusion, and inflammation of small vessels; because these data were not correlated with clinical findings, cases of classic NAION could not be identified [26]. One case report, however, did provide evidence of embolic phenomenon to small-caliber vessels in a rare case of NAION [27].

There are numerous predisposing systemic and ocular conditions which have been implicated in reduced blood flow to the optic nerve head. Proposed systemic risk factors include vasculopathic conditions (i.e., diabetes, systemic hypertension, hypercholesterolemia, ischemic heart disease), nocturnal hypotension, obstructive sleep apnea syndrome, and hyperhomocysteinemia [13,23]. A number
of prothrombotic polymorphisms (including protein C, protein S, antithrombin III, lupus anticoagulant, factor II G20210A prothrombin variant, methylenetetrahydrofolate reductase C677T and A1298C variants, factor V Leiden G1691A variant, platelet glycoprotein receptor IIIa (PIA2) allele, and apolipoprotein E (E4) allele) have been investigated in NAION patients from different ethnic populations and have been found not to be associated with increased risk [28-30]. Smoking also does not appear to be an independent systemic risk factor [31], nor does carotid artery occlusion [32].

Clinical evidence suggests that certain systemic medications are associated with NAION, such as phosphodiesterase-5 inhibitors, amiodarone, and pegylated interferon-alpha [13]. It is important to remember that direct causal relationships between these medications and the development of NAION have not been proven.

The role of genetic risk factors in NAION is also an area of investigation. There are several case series of familial NAION reported in the literature [33-35]. Though the mitochondrial mutation G4132A was found in one familial pedigree [34], this genotype was not identified in two other series of familial NAION [35].

One study from Saudi Arabia found an increase in potentially pathological mitochondrial mutations as well as increased relative mitochondrial DNA content in 19 NAION patients compared with controls [36,37]. However, it has been suggested that metabolic stress associated with atherosclerosis, diabetes, and hypertension, common systemic co-morbidities in NAION patients, may cause such abnormalities in mitochondrial DNA content [38].

Genetic polymorphisms influencing vascular tone have also been studied in relation to the development of NAION. With regards to the renin-angiotensin-aldosterone system, polymorphisms of M235T AGT and A1166C AT1-receptor were not found to be associated with NAION. However, the I allele and II genotype of the angiotensin converting enzyme insertion/deletion polymorphism, which may predispose patients to hypoperfusion and low blood pressure, were found to be more prevalent in patients with NAION below the age of 55 years, predominantly males [39]. A recent study found that the G/T polymorphism in the endothelin 1 gene was significantly associated with the occurrence of NAION in Japanese subjects, though the exact pathogenic influence of this mutation is yet unknown [30]. Though these studies have demonstrated potential genetic risks for NAION, they focus on specific mutations in distinct populations, and therefore may be limited in their generalizability. Thus, the role of hereditary factors in NAION remains unknown to date.

Ocular risk factors may also play a role in the pathogenesis of NAION. These include a small cup-to-disc ratio with crowding of the optic disc, optic disc drusen, and posterior vitreous detachment [18,40]. Certain surgical procedures have also been associated with the onset on NAION including: cataract extraction, strabismus surgery, laser-assisted in situ keratomileusis (LASIK), and intravitreal injections of anti-vascular endothelial growth factor drugs [41-45]. Non-ocular surgeries have also been implicated as risk factors for NAION [13,46].

The damage caused in NAION is believed to be two-fold; the initial insult is ischemia to the optic nerve head which results in hypoxic axonal injury and manifests as edema. Axonal edema leads to interruption of normal retrograde axonal transport of neurotrophic factors to the retinal ganglion cell (RGC). This in turn compromises the health of the RGC by triggering phenomena such as excitotoxicity, oxidative stress, calcium influx, mitochondrial failure, and even apoptosis [47].

In addition to this primary injury, axonal edema of the ischemic optic nerve head may further mechanically compromise blood flow to neighboring axons, particularly in a physiologically crowded optic disc. This “compartment syndrome” is hypothesized to cause secondary damage to neighboring RGC axons with the ensuing cascade of events as described above, leading to further apoptotic loss of RGCs [23]. Therefore, reduction of axonal swelling and prevention of RGC injury and apoptosis are targets for potential neuroprotective therapeutic interventions [47].

Two animal models of NAION have been developed to investigate the histopathologic, molecular, and electrophysiologic changes within the optic nerve and RGCs after ischemic injury [48,49]. In both models, one rodent and one primate, a photosensitive dye is created as follows: a photosensitive dye, rose bengal, is injected intravenously and activated with a laser applied selectively to the optic nerve head. Once activated, the dye damages the vascular endothelium of the optic disc capillaries with resultant thrombosis of vessels and edema of the optic nerve head [48,49]. Though the mechanism of injury in these animal models differs significantly from NAION as does the location of vasculature rendered ischemic [50], the end result is axonal injury of the optic disc similar to that seen in human NAION. These animal models have been used to investigate the mechanisms of injury to RGC axons as well apoptosis. They may in the future be promising in terms of developing appropriate neuroprotective strategies for acute NAION [51].

Prognosis

Most patients experience stabilization of visual function within 2 weeks after the onset of NAION [52], though rarely visual loss may continue until the optic disc edema resolves and is replaced by atrophy. Approximately 41-43% of patients with NAION will have improvement in their visual acuity by six months, though visual field deficits may persist [52,53]. However, more than 50% of NAION patients carry a poorer prognosis with visual acuity worse than 20/200 [54] and with constricted visual fields [55].

Recurrence of NAION is the same eye is low, estimated to occur in only 3-5% of cases, though the rate of recurrence in the contralateral eye is higher at 15-20% over the ensuing 5 years [52,56]. The risk for recurrence in the fellow eye appears to be higher in patients with poorer baseline acuity in the first eye affected with NAION as well as those who have diabetes [56].

Treatment

The treatment for NAION is a controversial topic in that numerous medical and surgical interventions have been employed without conclusive evidence of benefit; thus the ideal treatment continues to be elusive. With regards to acute NAION, a recent extensive review concluded that treatments aimed at preventing thrombosis, promoting vasodilation, reducing optic disc edema, and limiting axonal or neuronal injury have either proven unsuccessful or are lacking in scientific evidence [7]. Three of the treatments studied previously, however, are important to note.

It had been proposed that optic nerve sheath fenestration (ONSF) may be helpful in cases of progressive NAION, possibly by decreasing intrasheath fluid and improving ocular blood flow [57-59]. The Ischemic Optic Neuropathy Decompression Trial (IONDT), a randomized, single-blind study sponsored by the National Eye Institute, was designed to assess the safety and efficacy of ONSF for acute NAION [60]. Preliminary data from this study revealed that...
patients who underwent ONSF fared worse than untreated controls and therefore, the study was terminated prematurely [52,60]. A recent Cochrane Review reported that the IONDT was the only randomized surgical trial for NAION and its results indicated that there was no evidence that ONSF had a beneficial effect [61]. Though ONSF is no longer considered a treatment option, the IONDT did provide valuable information regarding the natural history of NAION.

The role of systemic corticosteroids in acute NAION has also been investigated. A large non-randomized study revealed that patients with optic disc edema from acute NAION who received oral prednisone initiated at a dose of 80 milligrams daily for 2 weeks with a taper had improved visual outcomes compared with untreated controls [62]. Because of the limitations of the study design and potential biases in the two populations studied, these results must be interpreted with caution [7]. Indeed, the controversies surrounding the use of corticosteroids in NAION stem mainly from a lack of Class I evidence supporting the efficacy of the intervention, as well as the potential risks of the intervention [63]. Nevertheless, the judicious use of oral corticosteroids in select cases of acute NAION with progressive loss of visual function may be considered [13].

Anti-vascular endothelial growth factor agents have been considered in acute NAION, based on the premise that by reducing optic disc edema will help resolve a compartment syndrome and prevent further loss of axons. However, the literature thus far suggests that intravitreal injection of bevacizumab does not have a beneficial effect when compared with the natural history of NAION [64,65].

There are several innovative treatments on the horizon for acute NAION currently being investigated. A recent study demonstrated improved visual outcomes in NAION patients treated with intravitreal erythropoietin, a potential neuroprotective agent for RGCs [66]. Though this was a small prospective study, the results are promising.

There is also a multi-centered clinical trial underway investigating a small interference RNA molecule, a caspase 2 inhibitor named anti-platelet therapy with aspirin be considered [7].


Summary

In conclusion, NAION is an ischemic optic neuropathy not uncommonly seen in the adult population and may be associated with significant loss of visual acuity and/or field. Its exact pathogenesis is multi-factorial though it most likely results from vascular insufficiency of the SPCAs; certain systemic as well as ocular risk factors may be implicated as well. Animal models have been developed to investigate the pathophysiology of NAION as well as provide a platform for pre-clinical neuroprotective strategies. Unfortunately there is no consensus on therapy for NAION to date, though several medical interventions are under investigation.

References

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