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Nonarteritic Anterior Ischemic Optic Neuropathy – An Update

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Abstract

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common optic neuropathy in the elderly. Despite considerable research efforts, much remains unclear regarding the pathogenesis, risk factors and treatment options, with numerous contradicting reports and no consensuses among physicians. The more established risk factors include hypertension, diabetes mellitus, hypercholesterolemia, characteristic optic disc morphology, and perioperative visual loss. Several case reports suggested a link between certain phosphodiestrase-5 inhibitor erectile dysfunction medications and NAION, but this possible risk factor remains controversial.

There is no established therapy for NAION, and many treatments have been proposed for the acute phase of the disease, of which some failed and others are considered experimental. This review summarizes the proposed pathogenesis theories, risk factors, diagnostic and imaging modalities and proposed treatment options for this blinding disease.

Keywords: Optic neuropathy; Nonarteritic anterior ischemic optic neuropathy

Abbreviations: NAION: Nonarteritic Anterior Ischemic Optic Neuropathy

Introduction

Nonarteritic anterior ischemic optic neuropathy (NAION) is an important cause of visual loss, especially among the older population (mean age, 60 years) with an incidence that varies between 2.3 - 10.2:100,000 [1,2].

The classical clinical characteristics of NAION include sudden painless decrease in visual acuity (VA), occurring over hours to days, often described as blurring, dimness or cloudiness in the affected region of the visual field, most often inferiorly. Patients' VAs may range from 20/20 to no light perception. Many patients report visual loss upon awakening [3,4].VA usually remains stable, with some improvement occurring in 23.8% of the cases [5-7].

Relative afferent papillary defect is frequently present although it may be absent in patients with bilateral optic nerve disease. The optic disc edema in NAION may be diffuse or segmental, hyperemic or pale, but pallor occurs less frequently than in the arteritic form. A focal region of more severe swelling is often seen. Peripapillary retinal hemorrhages are common, but retinal exudates are unusual. Visual field defects are common, mainly altitudinal, although various patterns of visual field defects have been reported [5-7].

Demographics and natural history

Numerous studies explored the natural history of the disease. Boghen DR et al reviewed the natural history of 37 NAION patients as compared to 13 cases of arteritic anterior ischemic optic neuropathy [7] and concluded that (1) the syndrome occurs primarily in 55-70-year-old patients who, for the most part, are otherwise well; (2) mild hypertension is present in about half of the cases; (3) there is no significant association with extracranial carotid occlusive disease; (4) over long follow-up periods there appears to be no increased incidence of stroke; (5) the syndrome should be easily recognized on clinical grounds, consisting of sudden or rapidly progressive monocular visual deficit associated with optic disc swelling, with stable visual defects of variable degree; (6) after an interval of months to many years, the second eye is involved in about 40% of cases; (7) no form of therapy has proved efficacious; (8) pathophysiological mechanisms remain speculative. Hayreh SS et al. [8] investigated systematically the natural history of visual outcome in NAION in a cohort study of 386 eyes. In Patients that were first seen < or =2 weeks after onset of symptoms, about half had visual acuity of > or =20/30 and 38% had minimal to mild visual field defect. 41% of the eyes with visual acuity < or =20/70 at presentation improved at 6 months. Deterioration was documented in 18% of these eyes after two years. 26% of those who had moderate to severe visual field defect at initial visit improved at 6 months and 19% worsened after 2 years.

The Ischemic Optic Neuropathy Decompression Trial Research (IONDT) Group [9] included in their follow up arm 162 patients with visual acuity of better than no light perception, and an age of 50 years or older. 62% of the patients were men and 95% were white. The mean +/- SD age at onset was 66.0 +/- 8.7 years. Hypertension was reported in 47% of the patients in the IONDT, and 24% of the patients had diabetes mellitus. Almost half of the patients had initial visual acuity of 20/64 or better and 34% of the patients had 20/200 or worse. The patients who had visual acuity better than 20/64 were younger, 72% were male, and they had a lower prevalence of hypertension and diabetes mellitus.

The reported rate of fellow eye involvement is up to 23% of patients [10], although the results of the Ischemic Optic Neuropathy Decompression Trial Research (IONDT) Group showed that the incidence of fellow eye NAION was lower than expected, with new NAION diagnosed in only 14.7% of patients over approximately 5 years

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[11]. WuDunn et al. [12] found that visual function in the second eye correlated poorly with that of the first eye, and that older patients with bilateral NAION retained better visual function in the second eye than in the first eye. Recurrence of NAION in the same eye is uncommon (6.4%) [13].

Risk factors

Many risk factors were suggested for this disease: some are more acceptable and well documented, while others are anecdotal case reports. The most disputed risk factor for the development of NAION is the use of PDE-5 inhibitors, such as sildenafil (viagra) and tadalafil (cialis). The risk factors appearing in the current literature are summarized in Table 1.

Established risk factors

Hypertension: Numerous studies suggested that arterial hypertension is an important risk factor for NAION [14-16]. Palombi et al. [16] found that 59% of the patients enrolled in their study suffered from hypertension, which was the most frequent risk factor for developing NAION.

Diabetes mellitus: Jacobson et al. [17] reported that diabetes mellitus is a major risk factor (with an odds ratio of 2.7 and a comprehensive multivariate analysis odds ratio of 5.0), and Hayreh et al in their report from 1994 [14] concurred. Recently Lee MS et al. [18] did a query of Medicare 5% claims files identified patients with a new diagnosis of diabetes mellitus (DM) in 1994. A randomly selected control group was created using 1 to 1 propensity score matching. Patients with a diagnosis of giant cell arteritis, preexisting DM, and age 68 years or older or >95 years were excluded. Patients with DM and controls were followed for the development of NAION over a mean follow-up was 7.6 years. In the diabetes group, 0.7% individuals developed NAION compared with 0.5% individuals ($P < 0.01$) in the control group. In unadjusted Cox regression analysis, having DM was associated with a 43% increased risk (hazard ratio [HR]: 1.431) of developing NAION. After adjusting for other covariates, the risk of developing NAION among individuals with DM was reduced to 40% (HR 1.397). Male gender increased an individual's risk of developing NAION by 32% (HR 1.319; 95% CI, 1.052-1.654). No other covariate was statistically significantly associated with developing NAION. The annual incidence of NAION was 82 per 100 000 persons.

Hayreh et al. [19] recently published a cohort study investigating various aspects of NA-AION in patients with DM and comparing them with those in patients without DM. They found no significant difference in age between the groups, but slightly more women than men (45% vs 38%; $P = 0.078$) were diabetic and had a higher prevalence of hypertension ($P<0.0001$), ischemic heart disease ($P = 0.0001$), transient ischemic attacks ($P = 0.0003$), and second eye involvement by NAION ($P = 0.003$). Initial visual acuity did not differ significantly between diabetic and non diabetic patients; however, of those seen within 2 weeks of onset of NAION, diabetic patients had less severe visual field defect ($P = 0.010$). At 6 months from onset, there was no significant difference in the vision of the two groups. Time to optic disc edema resolution in NAION was ($P = 0.003$) longer in diabetic patients than in non diabetic patients. The optic disc of diabetic patients usually has characteristic diagnostic dilated telangiectatic vessels during the early stages of NAION.

ESTABLISHED	CONTROVERSIAL	ANECDOTAL
Hypertension	Consumption of phosphodiestrase-5 inhibitors	Rickettsia conorii infection
Diabetes mellitus	Consumption of amiodarone	
Hypercholesterolemia	Obstructive sleep apnea	Chlamydia pneumoniae infection
Optic disc morphology	Systemic hypotension	Refractive error
Perioperative visual loss	Thrombophilia and inflammation	genetic factors
	Post ocular surgery	Internal carotid dissection
	Tobacco use	Interferon alpha
	Elevated intraocular pressure	Intravitreal anti VEGF

Table 1: Risk factors for Developing Non-arteritic Anterior Ischemic Optic Neuropathy.

Although DM seems to be an established risk factor for the development on NAION, Odette JD et al. [20] contradicted it in their review of 206 patients. They included only patients who were aged 50 years or older, in contrary to the reports just mentioned. They found that there was no significant difference in log- MAR visual acuity ($P=.77$) for DM and no DM or when accounting for the presence or absence of hypertension ($P=.10$). There was no significant difference in visual field mean deviation ($P=.52$) for DM and no DM or when accounting for the presence or absence of hypertension ($P=.34$). There was no trend for better (or worse) visual field for DM compared with no DM ($P=.79$).

It should be emphasized, however, that only Jacobson at al Lee et al reports were case control studies, which are, by their nature, more appropriate for the analysis than case series studies.

Hypercholesterolemia: Talks SJ el al. [21] conducted a case-control study on 41 patients with NAION, and found that the odds ratio of cholesterol being > 6.5 mmol/l in NAION was 2.7 ($p <0.05$) and of fibrinogen being > 3.6 g/l was 5 ($p < 0.05$). Smoking was also found to be significantly associated with NAION, the odds ratio being 16 ($p < 0.001$).

Deramo et al. [22] compared cholesterol levels between 37 consecutive patients (All patients were 50 years or younger) with NAION and 74 age- and gender-matched patients. The mean total cholesterol level was significantly higher in the patients with NAION compared with the controls (235.4 vs. 204.0 mg/dl, $P < 0.001$), with a 3.3 odds ratio of having high blood cholesterol (≥240 mg/dl) with NAION.

Optic nerve head circulation abnormalities and morphology: As mentioned above, impaired blood flow to the optic nerve head may play an important role in the pathogenesis of NAION. Another example for that was described by Rader et al. [23] who demonstrated proximal constriction (retinal arteries narrower near the disk than further down the stream in the retina) in 19 of 28 eyes (68%). Other studies suggested that an optic disc with smaller cups [24] or without a physiologic cup (small cup to disc ratio) is an important a risk factor as well [25,26].

Perioperative visual loss: The actual incidence of perioperative visual loss (POVL) remains elusive. It is probably a relatively uncommon post surgical complication, but its consequences are devastating. NAION appears to be more common than posterior ischemic optic neuropathy (PION) in association with cardiac procedures, while PION occurs more often in association with spinal surgeries and radical neck dissections, especially among prolonged spine surgeries performed in the prone position. In 1999, the American Society of Anesthesiology (ASA) established the ASA POVL registry. By June 2005, 131 cases of POVL had been reported, of which 95 were spine cases, 12 cardiac cases, 6 major vascular cases, 5 orthopedic cases

and 13 miscellaneous. Eighty-three patients in their spinal surgery group had optic neuropathy: 67% were diagnosed with PION and 23% with NAION [27]. There is no established treatment for perioperative ischemic optic neuropathy.

Newman NJ et al. [28] recently reviewed the current knowledge of persistent visual loss after nonocular surgeries under general anesthesia and found the incidence of perioperative visual loss after nonocular surgeries ranges from 0.002% of all surgeries to as high as 0.2% of cardiac and spine surgeries. The most common site of permanent injury is the optic nerves, and the most often presumed mechanism is ischemia. AION was found to be more prevalent among cardiac surgery patients and PION predominates among those who have had spine and neck procedures. Multiple factors have been proposed as risk factors for perioperative ION, including long duration in the prone position, excessive blood loss, hypotension, anemia, hypoxia, excessive fluid replacement, use of vasoconstricting agents, elevated venous pressure, head positioning, and a patient-specific vascular susceptibility that may be anatomic or physiologic. However, they concluded that the risk factors for any given patient or procedure may vary and are likely multifactorial.

Controversial risk factors

Phosphodiesterase (PDE)-5 inhibitors: Several case series described the appearance of NAION after the consumption of PDE-5 inhibitors, such as sildenafil (viagra) and tadalafil (cialis) in healthy individuals and in single-eye NAION patients who developed a fellow-eye event following the drug consumption [29-33]. Pomerantz et al. [29] reviewed five cases of NAION reported to have occurred in association with use of sildenafil through 2002 and suggested that the drug may be contraindicated in patients with prior NAION and that this group of patients should be consulted about the risk of developing NAION with further use.

According to the Food and Drug Administration (FDA) alert for healthcare professionals, given the small number of events, the large number of users of PDE-5 inhibitors and the fact that this event occurs in a similar population to those who do not take these medicines, the FDA concluded that it is not possible to determine whether these events are related directly to the use of PDE-5 inhibitors, and that they cannot currently draw a conclusion of cause-and-effect (FDA Alert for Healthcare Professionals, 07/2005).

Hayreh [34] was even more strongly against the use of PDE-5 inhibitors in patients at risk. He suggested that patients with cardiovascular risk factors, diabetes mellitus, patients taking anti-hypertensive drugs, and those who have a history of previous NAION should be advised against the use of erectile dysfunction drugs.

Analyses of the databases collected from 67 double blind placebo controlled trials (›14,000 men) in a recent study conducted by the manufacturer [35] that reviewed special safety topics associated with sildenafil, did not reveal any causal link between sildenafil and cardiovascular events and NAION.

The FDA and researchers worldwide, continue to investigate this issue.

Use of amiodarone: Amiodarone is in widespread use as a cardiac anti-arrhythmic agent, which has been associated with the development of NAION. Macaluso et al. [36] described the clinical features of amiodarone induced optic neuropathy and suggested that this is a distinct diagnosis, with clinical features which differ from the classic NAION presentation. They characterized this condition by an insidious onset, slow progression, bilateral visual loss, and protracted disk swelling that tends to stabilize within several months of discontinuing the medication. Johnson LN et al. [37] described the clinical spectrum of amiodarone-associated optic neuropathy in 55 patients. They classified amiodarone-associated optic neuropathy into five clinical categories with respect to temporal characteristics and optic nerve appearance: insidious-onset (43%), acute-onset (28%), retrobulbar (13%) increased intracranial pressure (8%), and delayed-progressive onset (8%). Most cases of optic neuropathy commenced within 12 months of initiating amiodarone, with the median onset being four months. Over 10% of patients will have no visual symptoms at the onset. Ophthalmologic examinations within the first 12 months- and particularly within four months of initiating amiodarone—should improve early detection of amiodarone-associated optic neuropathy. However, in a randomized control trial [38], aiming to determine the incidence, dose, and time until onset of bilateral vision loss from amiodarone, subjects receiving continuous amiodarone for 4 to >60 months at daily doses of>2.0 mg/kg, >3.0 mg/kg or >4.0 mg/kg had maximum possible annual incidences of bilateral toxic vision loss of 0.23%, 0.29%or 0.74%, respectively. The maximum possible annual incidence rate of bilateral vision loss from amiodarone in all 837 subjects (median age 60 years) receiving a mean daily dose of 3.7 mg/kg (300 mg) was 0.13%.They concluded that at the doses commonly used clinically, bilateral vision loss from amiodarone toxic optic neuropathy occurs infrequently, if at all.

Obstructive sleep apnea (OSA): One matched case-control study with 17 NAION cases and 17 controls identified 71% of the NAION cases which had OSA diagnosed by overnight polysomnography [39]. Another study reported that 24 of 27 (89%) newly diagnosed NAION cases exhibited sleep apnea syndrome [16].

Li et al. [40] conducted a matched case-control study on 73 cases of NAION and 73 controls using a questionnaire in order to investigate an association between NAION and OSA. Patients with NAION were significantly more likely to report symptoms and characteristics consistent with sleep apnea syndrome than controls, with an odds ratio of 2.62, when adjusted for medical and health behavior characteristics.

Behbehani et al. [41] prospectively reviewed 108 patients with NAION in order to identify those among them who developed NAION while being treated for OSA with continuous positive airway pressure (CPAP). One patient had bilateral sequential NAION and two patients had unilateral NAION despite treatment with CPAP. All the patients were being treated with CPAP for a period ranging from 4 months to 6 years before the onset of NAION. In this series, CPAP did not prevent the development of NAION in sleep apnea syndrome patients. Although there is growing evidence that OSA is a risk factor for developing NAION, larger prospective studies should be conducted in order to establish this risk factor.

Arterial hypotension: In an optic nerve head, a fall of blood pressure (BP) below a critical level of autoregulation would decrease its blood flow. Fall of BP in the ONH may be due to systemic hypotension.

The most common cause of systemic arterial hypotension is nocturnal arterial hypotension during sleep [3,42]. One study demonstrated that up to 73.3% of NAION patients discovered visual loss upon first awakening, suggesting that nocturnal arterial hypotension may play an important role in the pathogenesis of the disease [3]. Systemic anti-hypertensive drugs, such as beta-blockers, as well as topically administered beta blockers for the treatment of glaucoma may aggravate nocturnal arterial hypotension and reduce the heart rate, and

thus may be a potential risk factor in susceptible individuals [3,5,42-43]. Other less common causes of systemic hypotension include massive haemorrhages, shock, renal haemodialysis, etc. [14].

Thrombophilia and inflammation: Nagy et al. [44] reported that elevated lipoprotein a (LPa) and von Willebrand antigen levels, diabetes mellitus, Factor V (Leiden), hypercholesterolemia, and hyperfibrinogenemia were significant risk factors associated with NAION. Forward stepwise logistic regression analysis revealed that high LPa, diabetes mellitus, and Factor V (Leiden) were the main predictive components, with odds ratios of 16.88 (p=0.012), 5.78 (p=0.022) and 4.44 (p=0.033), respectively.

Pianka et al. [45] found elevated plasma homocystine to be a risk factor for NAION with 18 of 40 patients (45%) with NAION compared with 8 of 81 patients (9.8%) in the control group (P < 0.0001).

Kesler et al. [46] demonstrated that patients with NAION had a microinflammatory response revealed by the presence of increased high-sensitivity C-reactive protein (hs-CRP) concentrations and accelerated erythrocyte sedimentation rate (ESR). This finding, if confirmed in future studies, might shed more light on the eventual pathophysiological processes involved in the disease and pave the way for potential new therapeutic approaches. Kuhli-Hattenbach C et al. [47] investigated the prevalence of various coagulation defects among 35 NAION patients <65 years of age and compared it to 70 controls. They found that overall, thrombophilic defects were found to be present in 51.4% patients and in 17.1% controls (P = 0.0005). The most frequent coagulation disorders were increased levels of factor VIII and lipoprotein (a). Patients without cardiovascular risk factors had a statistically significant higher frequency of coagulation disorders than patients with these risk factors. There was a strong association of coagulation disorders and a personal or family history of thromboembolism. Moreover, the age of <or=55 years at the time of the first thromboembolic event or NAION was a strong predictor of underlying thrombophilia. They concluded that selective screening of young patients, subjects with a personal or family history of thromboembolism, and patients without cardiovascular risk factors may be helpful in identifying NAION patients with thrombophilic defects.

In contrast, Salomon et al. [48] retrospectively analyzed 61 patients with NAION compared with 90 controls and their finding suggested that none of the thrombophilic markers (i.e., protein C, protein S, antithrombin III, lupus anticoagulant, factor V G1691A, factor II G20210A and methylenetetrahydrofolate reductase) constituted a significant risk factor for NAION.

Past ocular surgery: Lam et al. [49] showed that cataract extraction in the fellow eye of single-eye NAION patients increased the risk of NAION occurrence in the fellow eye by 3.6 times (Cox regression, p=0.001).

McCulley et al. [50] reported that three patients out of 5787 cases of cataract extraction were diagnosed as having NAION within 1 year of the procedure, a rate which is statistically higher than the previously reported overall incidence of NAION. The same investigators also evaluated 18 cases of NAION that occurred within 1 year after lens-related surgery in a retrospective review of patients diagnosed with NAION. All 18 cases were diagnosed within 6 months of surgery, which was significantly different from a uniform distribution, which would predict an approximately 50:50 split between the first and second 6-month periods (P <.001). They concluded that intraocular lens surgery is associated with the occurrence of NAION [51].

Nguyen et al. [52] however, refuted this statement and contended that current data do not support a causal relationship.

Tobacco smoking: Previously published data suggested that tobacco smoking may be a risk factor for NAION and that cessation of smoking appears to reduce the risk to that of the nonsmoking population [21,53,50].Chung et al. [53] retrospectively evaluated 137 patients for their smoking status .Talks et al. [21] conducted a case control study and found that smoking was significantly associated with NA-AION, the odds ratio being 16 (p < 0.001).

However, Jacobson DM et al. [54] found no correlation between tobacco smoking and NA-AION in a published case control of 51 patients older than 45 years with first ever acute NA-AION. Similar results were observed in IONDT trial [6], smoking was not associated with increased risk of developing NA-AION in the fellow eye.

A recently published cohort study by Hayreh et al. [55] demonstrated that of 624 patients suffering from NAION, 151 (24.2%) were current smokers, 160 (25.6%) were former smokers, and 313 (50.2%) had never smoked. The prevalence of smoking in NAION patients was not significantly different from the prevalence in the period-matched U.S. population and the period-matched Iowa population.

Elevated intraocular pressure: Some investigators have reported an association of elevated intraocular pressure (IOP) and glaucoma with NAION [56], while others refute this connection [57]. Since the perfusion pressure in the optic nerve is balanced between systemic blood pressure and IOP, a transient rise in IOP could result in ischemia to the optic nerve head from a decrease in the perfusion pressure below a certain critical level.

NAION is probably not associated with carotid artery atherosclerosis: Fry et al. [58] prospectively evaluated 15 consecutive patients with NAION for cervical carotid artery stenosis and compared them with 30 age- and sex-matched asymptomatic patients. There was no difference in the mean stenosis of the internal carotid artery between patients with NAION (mean carotid stenosis, 19%) and asymptomatic patients (mean carotid stenosis, 9%; p > 0.05). The authors concluded that the pathogenesis of NAION does not involve carotid artery stenosis in most patients. Similarly, Tesser RA et al. [59] studied the three-dimensional anatomic configuration of a NAION infarct and found that there was no obvious correlation between the configuration of the infarct and any single vascular territory. The total length of the nerve involved by the infarct was approximately 1.5 mm. They concluded that the morphology of this NAION infarct is not consistent with disease of large or small vessels and, more likely, represents a form of compartment syndrome that causes tissue ischemia.

Anecdotal risk factors

Chlamydia pneumoniae infection: In a study comparing 71 NAION patients to 71 age- and sex- matched controls, patients with NAION had significantly higher IgG antibody titers to Chlamydia pneumonia compared with controls (IgG titer ≥1:128 in 29 patients versus 15 controls, P = 0.017). The odds ratio for patients with an IgG titer ≥ 1:128 was 2.56 [60].

Refractive error: A study that compared 50 NAION patients with 50 age- and sex- matched controls, found hyperopia to be a risk factor for NAION with a mean refractive error (in spherical equivalents) for the NAION group of +0.26 diopter versus a mean refractive error of -0.86 diopter for the controls (P = 0.027) [61].

Hayreh SS et al. [62] investigated refractive error in eyes with

NA- AION and its relationship to cup/disc (C/D) ratio. They found that in patients with NA-AION showed that a higher degree of myopia and higher degree of hyperopia were significantly associated with a larger C/D ratio. Another study prospectively studied 78 patients with NAION and 80 normal volunteers for axial length and refractive error, and found that there was no difference in the refractive error of NAION eyes, as compared to control. No significant difference was found between axial length measurements of NAION eyes and fellow eyes and control eyes [63].

Internal carotid dissection: Biousse et al. [64] studied 110 consecutive patients with internal carotid dissection, of whom 4 (3.6%) had ischemic optic neuropathy (2 anterior, 2 posterior). The authors noted that only five patients with carotid dissections and ischemic optic neuropathy had been previously described in the literature.

Interferon alpha: Some authors reported a possible association between the use of interferon alpha, and the development of NAION: most, but not all cases were reversible upon drug cessation [65,66].

Genetic factors: There have been few reports representing unrelated families in the literature, which identified the disease in more than one family member [12,67]. That has raised two possibilities: first, that in some families there may be a genetic predisposition to NAION. Second, some persons in those families have common systemic risk factors that predispose them to develop NAION [67]. Preliminary study has suggested that the mitochondrial mutation (G4132A) may be associated with familial NAION [68].

Intravitreal anti VEGF: There are currently only few case reports [69,70] in the literature about NAION following intravitreal bevacizumab or ranibizumab for various reasons. It is noteworthy to mention, however, that intravitreal Bevacizumab was also suggested as a treatment for NAION [71], as discussed later.

Pathogenesis

Given the above mentioned risk factors, many theories have been proposed for the underlying cause of NAION, but there is still no consensus and many controversies on the pathophysiology of this illness. One such theory is the "vasculopathic/ atherosclerotic" disease theory.

Arnold [72] reviewed several histopathological studies, electron microscopic corrosion cast studies, optic nerve blood flow studies, and clinical correlations and found that laminar and retrolaminar regions were the most common locations for infarction. There were flow impairments in the prelaminar optic disc during the acute phase, as well as impaired autoregulation of the disc circulation by atherosclerosis, with a possible contribution of vasospasm in the pathogenesis of the disease.

Collignon-Robe et al. [73] found optic nerve head circulatory abnormalities in both NAION and optic neuritis patients. However, Kosmorsky et al. [74] performed transcranial Doppler (TCD) over the right and left middle cerebral arteries simultaneously for 30 minutes in 11 patients with a recent (<121 days) history of NAION and 10 age-matched controls (event > 121 days). None of 11 patients with a recent history of NAION demonstrated microemboli by TCD and one control patient had a microembolic event rate of 12 per hour (six over 30 minutes). The authors concluded that their findings did not support embolism as a frequent cause of NAION. This report was further supported by reports stating no correlation between atherosclerotic events and risk factors (smoking, hyperlipidemia) and NAION.

A different mechanism is strongly related to the timing of symptom's presentation (early morning).This theory relies on the neural influence on choroidal blood flow that occurs during sleep or from stimulation of the parasympathetic system [75,76]. During sleep choroidal thickening with increased choroidal perfusion was observed [77]. However, with nocturnal or "sleep associated" arterial hypotension [78], cerebral autoregulatory mechanisms may result in the shunting/steal of blood from the short posterior ciliary arteries - which had blood originally destined for the optic nerve - now going to the choroid [79,80]. Cerebral autoregulation is exerted by nitric oxide [81] release that could be stimulated by herpes simplex virus located in the Edinger-Westphal nucleus or suprachiasmatic nucleus and by other biologically active compounds [80,82,83] Smaller cups (small cup to disc ratios) were previously mentioned as an important established risk factor for the development of NAION. This results in hypoxemic-ischemic optic neuropathy in a nerve that has crowded optic nerve with small cup-disk ratio [84-86].

Another potential mechanism is venous disorder and compartment syndrome mechanism. Levin and Danesh-Meyer [87] suggested that venous occlusive disease may result in venous congestion and cause initial disc edema as the precipitating factor for the disease. They further suggested that the creation of compartment syndrome and subsequent cytotoxic and vasogenic edema cause infarction and tissue loss.

It is possible to combine the above mentioned theories to a unifying theory named "hypotension-compartment theory" for the development of NAION. This combined theory is strengthened by the finding of association between PDE5 inhibitors to NAION. Systemic arterial hypotension, particularly nocturnal hypotension, may precipitate NAION, given the mild hypotensive effects of PDE5 inhibitors on arterial blood pressure. It is possible that PDE5 inhibitors may accentuate the physiological nocturnal hypotension enough to decrease the perfusion pressure in the posterior ciliary arteries, resulting in ischemia to an optic nerve head and setting off the cascade of a compartment syndrome that occurs in a small, crowded optic nerve. This suggested pathopysiology mechanisms result in optic nerve damage with retinal ganglion cell (RGC) death [72,73]. Few reports exist describing a model for the development of NAION in rodents. Slater BJ et al. [88] found that in rodents induced NAION (rAION) there is later RGC death than in traumatic optic nerve damage models. Apoptosis occurs maximally in the second to third week after infarct, suggesting that the window for successful treatment after ON infarct maybe longer than previously recognized. After NAION, RGCs undergo apoptosis by the caspase activation pathway. NAION-induced RGC death occurs regionally, with sparing of large contiguous regions of RGCs. This regional pattern of death implies that a measure of retinotopic organization occurs in the rodent optic nerve. In support of this theory, Bernstein SL et al. [89] tried to determine whether NAION produces changes in amacrine cell and found that when inducing moderate NAION levels (described as <70% RGC loss) produces isolated RGC loss, with displaced amacrine cell changeslikely due to changes in RGC-amacrine communication. Severe NAION induction (>70% RGC loss) results in both RGC and amacrine cell loss, possibly due to intra-retinal ischemic changes.

Incipient NAION

Hayreh and Zimmerman [90] described the clinical entity of "incipient NAION" as being asymptomatic optic disc edema and no visual loss attributable to NAION. They had seen 670 consecutive patients with NAION between 1973-2000, of whom 54 had incipient NAION at presentation. Over one half (55%) of those 54 patients had

classic NAION in their fellow eye, the incipient form progressed to classic NAION (after a median time of 5.8 weeks) in 25%, and classic NAION developed after resolution of the first episode of incipient NAION in 20%.

Diagnostic and imaging modalities in the research on NAION

The diagnosis of NAION is mostly based on clinical evaluation as described above, and one of the helpful ancillary tools for evaluating the extent of visual field damage is the automated perimetry test, which typically present an altitudinal defect. Other than the widely used automated perimetry, various diagnostic and imaging modalities were used in order to characterize the disease.

Fluorescein angiography and indocyanine green: Delay in optic disc filling is typical to NAION and may aid in the differentiation of NAION from non ischemic disc edema [91].

Fluorescein angiography: It may demonstrate choroidal ischemia, that can may produce peripapillary pallor and edema deep to the retina in AAION, as compared to NAION.

Optical Coherence Tomography (OCT): Contreras et al. [92] compared the optic nerve head characteristics of 23 patients with NAION to 23 age- and sex- matched controls. They reported that although patients with NAION had lower cup-to-disc ratios with a higher level of nerve fiber crowding than the normal population, no difference in optic disc size between patients with NAION and control subjects was revealed by OCT.

Deleon-Ortega et al. [93] demonstrated that RNFL measured by OCT provided better correlation to Humphrey visual field changes than scanning laser polarimetry in NAION patients. Both instruments showed decreased RNFL in NAION eyes with altitudinal visual field defects compared with control eyes.

Bellusci et al. [94] concluded that OCT can identify different patterns of RNFL involvement specific to different classic visual field defects in eyes with NAION.

Chan et al. [24] conducted a quantitative assessment of optic nerve head morphology and retinal nerve fiber layer in NAION with optical coherence tomography and confocal scanning laser ophthalmolscopy. They found that NAION patients have smaller cups and cup to disc ratios in both eyes compared to controls.

Magnetic Resonance Imaging (MRI): Rizzo et al. [95] showed that MRI scan of the optic nerve can demonstrate significantly different findings between patients clinically diagnosed with optic neuritis and those with NAION. The five NAION patients with abnormal scans in the clinically affected eye had an increased short T(1) inversion recovery signal, and there was also enhancement of the optic nerve in two of them. Arnold et al. [96] reported an increased number of CNS white matter lesions in patients with NAION.

It should be mentioned, however, that elecro-oculogram was not performed as a diagnostic tool in NA-AION and consequently an important piece of the puzzle regarding the health of the retinal pigment epithelium and nearby choroid has not been assessed.

Treatment options

Nowdays there is no established effective treatment for NAION although many treatment strategies have been proposed. Hereby we summarized all treatment options published in the literature for NAION. We differentiated acute treatment options and secondary prevention. The results are summarized in Table 2.

Acute treatment options

Systemic corticosteroids: Hayreh and Zimmerman [97] prospectively investigated the effect of systemic corticosteroid therapy, given during the acute phase of NAION (i.e. when optic disc edema is present), on visual outcome.

From a cohort of 696 consecutive eyes with NAION, they evaluated the natural history of visual outcome (N= 332 eyes) and compared them with those who opted voluntarily to have corticosteroid therapy (N= 364 eyes). The patients who received corticosteroid therapy were started on 80 mg Prednisone daily (irrespectively of their weight). After 2 weeks, tapering down of therapy was started in steps of 5 days each: to 70 mg, 60 mg, and then cutting down by 5 mg every 5 days to 40 mg until the optic disc edema was no longer present. After that, it was rapidly tapered off. The results of this study showed that in eyes seen within 2 weeks of NAION onset and with marked visual loss (i.e. initial visual acuity of 20/70 or worse and initial moderate to severe visual field defect), both visual acuity (69.8% in the treated group, compared to 37.1% in the untreated group) and visual fields (40.1% of those who had the corticosteroid therapy, compared to 24.5% of those without corticosteroid therapy) improved significantly for 6 months after the onset of NAION. However, in eyes with mild visual loss (i.e. visual acuity of 20/40 to 20/60), although the visual field improved significantly (p=0.027) in the treated group, visual acuity showed no significant difference between the two (p=0.897 groups) [77].This important study implies that systemic corticosteroids may be beneficial in NAION, however there is some criticism regarding the methodology of the study, mainly because the treatment decision was based on a "patient choice" scheme, instead of the conventional randomization, which may result in a bias.

Intravitreal Bevacizumab (Avastin): Bennet et al. [71] administered intravitreal bevacizumab to an 84-year-old female patient who presented with a 3-week history of visual loss due to fellow eye NAION. They observed a significant resolution of NAION-induced optic disc edema nine days after the injection, with VA improvement from finger counting to 20/100. They suggested that vascular endothelial growth factor inhibition may offer a novel therapeutic approach to limit injury in NAION.

Transvitreal optic neurotomy: Soheilian et al. [98] studied trans-vitreal optic neurotomy in seven eyes of seven selected patients with severe vision loss (<20/800) resulting from NAION who underwent transvitreal nasal radial optic neurotomy 15-90 days (mean 29 days) after diagnosis. Surgery had consisted of a standard 3-port pars planavitrectomy, and a single-stab radial neurotomy performed by a

ACUTE	SECONDARY PREVENTION
Systemic steroids	Aspirin
Intravitreal bevacizumab	Control of reversible risk factors
Transvitreal optic neurotomy	
Levodopa	
HELP- Heparin induced extracorpeal LDL/fibrinogen precipitation	
Reversal of hypotension*	
Intravitreal triamcinolone acetonide	
Brimonidine	
Optic nerve decompression surgery	
ACE inhibitors	

*After Hypotension-Induced Ischemic Optic Neuropathy

Table 2: Proposed treatment options for non-arteritic ischemic optic neuropathy.

microvitreal blade, starting at the margin of the optic nerve on the nasal side, taking care to avoid major vessels.

The mean preoperative visual acuity was 20/2400 and the mean postoperative visual acuity was 20/250, with an average of 10 lines of improvement. In two patients with sufficient visual acuity, preoperative visual fields could be obtained; these patients showed significant improvement in postoperative perimetry. Five patients had some loss of vision, which made it impossible to obtain preoperative visual fields. The authors concluded that relaxation of the scleral ring of the prelaminar and laminar regions of the optic nerve head reduces constriction and may prevent necrosis of salvageable but underperfused nerve fibers, but despite improvement of VA in their patients, the authors cautioned that it may provoke major visual field defects, and that this procedure should be considered experimental, and that it requires a randomized clinical trial [98].

Levodopa: Johnson et al. [99] found levodopa to be beneficial in the treatment of recent-onset NAION. They demonstrated that patients treated with levodopa within 45 days of onset of NAION were more likely to experience improvement and less likely to have worsened VA than untreated patients.

In a previously published study, the same group found significant improvement of VA among subjects receiving levodopa and carbidopa despite long-standing visual loss from NAION, although this study included only 20 subjects with NAION who were randomly assigned to treatment and control groups [100].

Heparin-induced extracorporeal LDL/fibrinogen precipitation (HELP)

HELP selectively eliminates fibrinogen, low density lipoprotein (LDL), cholesterol, triglycerides and LP(a) from blood plasma using extracorporeal circulation, thus improving the hemorheological condition. One prospective, controlled study randomly assigned 40 patients with NAION to either HELP or intravenous fluid hemodilution therapy. The authors found the HELP approach to be safe and more effective than hemodilution in improving the hemorheological and functional features in NAION [101].

Reversal of hypotension after hypotension-induced ischemic optic neuropathy: Connolly et al. [102] described three patients suffering from hypotension induced NAION (one patient developed NAION after an excessively rapid correction of malignant hypertension). Partial recovery of vision was achieved in each patient by rapid reversal of hypotension.

Intravitreal triamcinolone acetonide (kenalog)

Intravitreal administration of steroids for reducing optic disc edema is experimental and controversial. Kaderli et al. [103] demonstrated improvement in both VA and optic disc edema in three NAION patients, while Jonas et al. [104] suggested that this treatment may not be markedly effective, after treating three NAION patients with intravitrealy injected triamcinolone acetonide.

Brimonidine: Yoles et al. [105] reported a possible neuroprotective effect by the use of the alphadrenergic agonist brimonidine in a rat crush model of optic neuropathy, but their results were not repeated in the studies of Fazzone et al. [106] and Wilhelm et al. [107] who did not find this treatment beneficial in humans.

Saylor et al. [108] conducted a pub med search on the available evidence for the neuroprotective qualities of brimonidine titrate in optic nerve and retinal injury.48 articles were reviewed. The literature confirms that brimonidine has a neuroprotective role in animal model, but it did not meet the final neuroprotective criterion of success in humans.

Optic nerve decompression surgery: Despite a number of allegedly encouraging reports, the results of the Ischemic Optic Neuropathy Decompression Trial (IONDT) and several other case series indicate that optic nerve decompression surgery for NAION is not effective, may be harmful, and should be abandoned [15,109-112].

Angiotensin converting enzyme (ACE) inhibitors: ACE inhibitors and angiotensin II type 1 receptor (AT1R) polymorphisms were found to have no part in the mechanism of NAION and so drugs such as ACE inhibitors or AT1R antagonists are not specifically indicated for treatment affected individuals [113].

Hyperbaric oxygen therapy: Arnold et al. [114] treated 20 new-onset NAION patients with hyperbaric oxygen (100% oxygen, 2.0 absolute atmospheres of pressure) in two 90-minute inhalation sessions per day for ten days. This group was compared with 27 untreated patients.

Hyperbaric oxygen therapy did not produce a significant improvement in VA or visual field for patients with acute NAION.

Secondary prevention of fellow eye involvement

Aspirin: Beck et al. [115] retrospectively analyzed a cohort of 431 patients following the development of unilateral NAION, 153 of whom were and 278 of whom were not prescribed aspirin. The 2-year cumulative probability of NAION in the fellow eye was 7% in the aspirin group and 15% in the no-aspirin group, and the 5-year cumulative probabilities were 17% and 20%, respectively. These results suggested a possible short-term but little or no long-term benefit of aspirin in reducing the risk of fellow eye involvement.

Kupersmith et al. [116] reported that aspirin (65-1,300 mg) taken two or more times per week decreased the incidence (17.5% vs. 53.5%) and relative risk (RR = 0.44, p = 0.0002) of second- eye AION regardless of the usual risk factors. Aspirin does not however; seem to improve visual outcomes in NAION [117].

Control of reversible risk factors: Both diabetes [14] and sleep apnea [39] are associated with NAION. Optimal control of diabetes and sleep apnea is recommended. However in one series [41] three patients with sleep apnea developed NAION while treated with continuous positive airway pressure (CPAP), larger studies are needed to determine the benefits of CPAP in preventing NAION in patients with obstructive sleep apnea.

Other modifiable risk factors have been less consistently associated with NAION, including hypertension, anemia [14] and hypercholesterolemia [22]. It seems reasonable to treat these identifiable risk factors to decrease risk of systemic vascular disease. Smoking, as a contributor to poor overall cardiovascular health, should be discontinued [53,55].

Whether drugs as erectile dysfunction drugs and Amiodarone should be discontinued or not remains controversial and needs to be discussed on a case to case basis.

Results of a survey regarding NAION treatment: Atkins et al. [99,118] performed an anonymous e-mail/internet- based survey of 1595 United States neuro-ophthalmologists, ophthalmologists, neurologists and optometrists.

No treatment for acute NAION was offered by 27% of neuroophthalmologists. Most physicians chose aspirin to treat acute NAION. Only approximately 10% of physicians chose oral steroids. Topical brimonidine was chosen by 22% of neuroophthalmologists, despite lack of evidence. For acute treatment 7% of neuroophthalmologists chose intravitreal bevacizumab. Aspirin for secondary prevention of NAION in the fellow eye is prescribed by 96% of neuroophthalmologists.

Summary and Conclusions

In this review the concepts and controversies regarding NAION were discussed the various treatment options for NAION that are published in the literature are presented but the key for treating this blinding disease remains elusive. The relative rarity of this painless optic neuropathy and the difficulty to get the patients immediately to the clinic to start treatment makes it necessary to combine multi-center research efforts, and to study more animal models, in order to develop new treatment strategies and further investigate current treatment options such as treatment with systemic steroids or prophylaxis by aspirin. Meanwhile, it is important to at least identify modifiable risk factors, such as consumption of amiodarone or anti PDE-5 inhibitors in affected patients and consider their cessation, if possible, as well as control of cardiovascular risk factors in order to prevent fellow-eye involvement.

Method of Literature Search

The literature was searched using Medline (1993 to September 2011) with preference given to manuscripts relevant to our topic and published in English-language peer-reviewed journals. Clinical studies were selected if they were randomized controlled trials. Also included were especially relevant case series with three or more subjects, editorials and single case reports which strongly contributed to the understanding of the disease and its management. 400 abstracts were reviewed, and the articles pertinent to our discussion were selected. The search words were “nonarteritic or non-arteritic” and “anterior ischemic optic neuropathy” or “NAION”.

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