Literature Review

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Ischemic optic neuropathy: a review

Chaban M. Iu.

SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine"

Odesa (Ukraine)

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The review aims to summarize the current knowledge on the epidemiology, pathogenesis, risk factors, and clinical and diagnostic features of ischemic optic neuropathy. Special attention is focused on the hemodynamic and electrophysiological changes occurring in this disease and the role of brain-derived neurotrophic factor (BDNF) as a potential diagnostic marker of optic nerve damage. The value of current diagnostic techniques (optical coherence tomography, regional hemodynamic studies and electrophysiological techniques) in providing accurate assessment of optic nerve damage is highlighted.
Methods: *A literature review of 59 publications was conducted.*

Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common optic neuropathy in patients over the age of 50 [1]. 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 [2]. Anterior ischemic optic neuropathy (AION) has an annual incidence of 2.3 cases per 100,000 to 10.2 cases per 100,000 in persons older than 50 years of age in the US [2]. The disease is, however, also common in individuals younger than 50 years. In a retrospective study by Preechawat and colleagues [3], the frequency of anterior ischemic optic neuropathy (ION) patients younger than 50 years was 23%. In the Ischemic Optic Neuropathy Decompression Trial (IONDT), 62% of the patients were men and 95% were Caucasians [4].

ION is classified as anterior ION or posterior ION depending on the segment of optic nerve that is affected. Anterior ION and posterior ION are further categorized into nonarteritic (NAION, not related to vasculitis) or arteritic (AION, caused by small-vessel vasculitis, most often giant-cell arteritis) [5].

Pathogenesis

NAION is precipitated by insufficiency in short posterior artery circulation, which causes an ischemic event of the intraocular optic nerve and subsequent structural and functional changes [6].

The ischemic event in NAION usually takes place in the anterior optic nerve, with the total length of the nerve involved of approximately 5 mm, and causes axonal swelling in the retrolaminar region of the optic nerve head (ONH). This is followed by axoplasmic flow stasis and impaired nutrient transport to neural fibers, leading to further changes in the structure and function of the optic nerve [6-8].

Axonal swelling contributes to the compression of optic disc (OD) microcirculation, exacerbating the ischemia. This "vicious cycle" of increased swelling causing more compression of the capillaries then inducing further ischemia ultimately results in progressive damage to axons and fibers.

Risk factors

"Disc at risk"

Approximately 80-90% of people who develop NAION [4, 8] have a small OD (< 1.2 mm) with a small or absent physiological cup (cup-to-disc ratio ≤ 0.2), a so-called "disc-at-risk" [9, 10]. ONH ischemia or hypoxia causes axopalsmic flow stasis and axonal swelling. With a small or absent physiological cup, the swollen axons compress the capillaries within an increasingly crowded OD, further worsening the blood supply.

The absence of a crowded OD in the fellow eye at the onset should warrant an investigation for an alternative diagnosis [8].

Nocturnal arterial hypertension

24-h ambulatory blood pressure (BP) monitoring studies in about 700 patients [11] demonstrated that, while

BP may be perfectly normal during the day, it drops during sleep—much more in some persons than in others. In a patient who developed NAION, first in one eye and later on in the second, the monitoring graph showed that during her waking hours, the BP was within normal limits but that soon after going to sleep, systolic BP fell from 140 mmHg to 90 mmHg and diastolic from about 80 mmHg to about 50 mmHg. Her BP was low throughout her sleeping hours. This is called nocturnal arterial hypotension. The 24-h ambulatory BP monitoring studies showed that daytime BP is almost invariably normal, but that is not at all a guide to the BP during sleep.

In at least 399 (73.3%) of 544 episodes of NAION, patients discovered visual loss upon first awakening or at first opportunity to use vision critically after sleeping, suggesting that nocturnal arterial hypotension may play an important role [12]. In addition, Hayreh stated that NAION is primarily a hypotensive disorder, arising from a significant nocturnal reduction in BP.

Moreover, antihypertensive medications, especially administered at night, contribute to nocturnal hypotension, thus increasing the risk of ION [13-15].

Obstructive sleep apnea syndrome (OSAS)

OSAS is characterized by episodes of sleep apnea and/or hypopnea during sleep due to upper airway obstruction [16]. Studies have shown that OSAS is present in up to 89% of NAION patients. Moreover, the risk of developing NAION was increased by 1.7–3.8-fold in OSAS patients as compared to controls [8, 16, 17].

The pathogenesis of NAION in the presence of OSAS is still debated. The following concomitant mechanisms have been advocated: a transient hypoxia, an impaired blood flow autoregulation, and an increase in intracranial pressure during the apneic episodes, with subsequent reduction in the ocular perfusion pressure at the ONH level [8, 16].

Metabolic syndrome

Metabolic syndrome is a clinical entity including three or more of the following clinical features: systemic hypertension, diabetes mellitus, hypertriglyceridemia, hypercholesterolemia and central adiposity. The syndrome has been found to increase the risk of NAION by twofold. NAION has been demonstrated to be significantly associated with systemic arterial hypertension, found in 35–50% of patients, and diabetes mellitus, present in 5–25% of cases. Undetected or untreated systemic hypertension and diabetes mellitus are the most important underlying diseases amongst NAION patients, stressing the importance of hypertension and diabetic control [4, 8, 18].

Use of certain medications

1. Phosphodiesterase type-5 inhibitors (PDE-5i)

PDE-5i, like sildenafil and tadalafil, have been widely prescribed for erectile dysfunction [19]. These substances are thought to increase the risk of NAION by causing vasodilation and lowering the perfusion pressure to the ONH. A meta-analysis by Liu and colleagues [20], however, found no association between NAION and PDE5-I use. In a study by Margo and colleagues [21], the relative risk of NAION among men prescribed a PDE-5 inhibitor was 1.02 (95% confidence interval [CI]: 0.92 to 1.12).

Both the FDA and WHO have concluded that there is at present a lack of conclusive evidence of a causal relation between use of PDE5 inhibitors and risk of NAION [22]. Nevertheless, as a precaution, the FDA has advised patients ‘‘to stop taking these medicines, and call a doctor … right away if they experience sudden or decreased vision loss in one or both eyes’’ and that people ‘‘taking or considering taking these products [should] inform their health care professionals if they have ever had severe loss of vision, which might reflect a prior episode of NAION.’’ Similarly, the European Medicine Evaluation Association (EMEA) has advised patients taking or considering taking PDE5 inhibitors to inform their health care professionals if they have ever had severe loss of vision, and to seek referral to an ophthalmologist [22].

2. Semaglutide

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) used for the treatment of type 2 diabetes (T2DM) [23] and chronic weight management in patients with obesity or overweigh [24]. Researchers analyzed data over six years from more than 16,800 neuroopthalmology patients from Massachusetts Eye and Ear hospital (Boston), with no history of NAION, to examine whether semaglutide prescriptions were associated with increased risk of NAION in patients T2DM, obesity, or who were overweight [25]. The authors concluded that the findings suggested an association between semaglutide and NAION [25]. They, however, noted some limitations of their study. First, the retrospective design of the study did not enable query into a causal relationship between semaglutide and NAION. Second, the study was conducted at a specialized neuro-ophthalmology service which limited the representativeness of the study sample, because the sample included only patients with some ocular problems.

Therefore, for now, there is not enough evidence to consider semaglutide a cause for NAION. Patients with a high risk of ocular complications should be under physician’s care, but medication withdrawal is not feasible without additional risk factors

Optic disc drusen (ODD)

Optic disc drusen (ODD) are calcified deposits localized between axons of the prelaminar ONH and occur in approximately 1.8-2.0% of the general population. They are visible ophthalmoscopically in only 0.2-0.3% of the population, whereas the rest are buried in the ONH tissue, necessitating the use of optical coherence tomography (OCT) for accurate diagnosis. ODD may be an independent risk factor for the development of NAION, at least in

younger patients. In a study including 64 NAION patients (127 eyes) 50 years old or younger, 51% of the 74 eyes with NAION and 43% of the fellow eyes without NAION had ODD, with the rate of patients having ODD being significantly higher than that for the general population [26].

Plasma homocysteine level

Studies have pointed to a possible association between increased plasma homocysteine level and the risk of NAION. Pianka and colleagues (2000) [27] found that 45% of with NAION had hyperhomocystinemia compared with 9.8% in the control group. Weger and colleagues [28] confirmed that mean plasma homocyst(e)ine levels were significantly higher in patients with NAION than in controls (11.8 μmol/l vs 9.8 μmol/l). Biousse and colleagues [29], however, noted that the homocysteine level was within normal range in all 14 patients with NAION.

Clinical and diagnostic features

NAION most frequently occurs in patients aged 50 years or older. The mean age at onset in most studies ranges from 57 to 65 years, although many, such as the IONDT, may bias the data by excluding patients under the age of 50 [30, 31]. The disorder has been characterized by the following distinctive features:

1. Acute or subacute onset of visual loss, usually monocular at onset. The bilateral simultaneous form is rare and typically associated with acute severe systemic hypotension, extraocular surgery, or drugs assumption [8]. The recurrence rate of NAION in the ipsilateral eye is estimated to 6.4%, and new NAION in the fellow eye occurred in 14.7% of patients at risk during a median follow up of 5.1 years [32]. NAION is commonly painless or associated to a not defined orbital pain [33]. Marked pain should warrant an investigation for an alternative diagnosis such as giant cell arteritis or optic neuritis of various etiologies.

In the IONDT, initial visual acuities (VA) in the study eye ranged from 20/20 or better to light perception, with 49% of the patients seeing better than 20/64 and 34% of the patients seeing 20/200 or worse [4]. At 6 months, of the patients with an initial VA worse than 20/64, 42.7% showed an improvement in VA of three or more lines, and 12% showed worsening in VA by at least three lines [34].

Hayreh and Zimmerman [35] investigated systematically the natural history of visual outcome in NAION and concluded that almost half of the eyes with NAION presented with an almost normal VA (20/15 to 20/30) at the initial visit.

Therefore, the presence of normal VA does not rule out NAION. In those who were first seen ≤2 weeks after onset with visual acuity ≤20/70, there was improvement in 41% and worsening in 19% at 6 months. In those who were first seen ≤2 weeks of onset with moderate-to-severe visual field (VF) defect, there was improvement in 26% and worsening in 15% at 6 months.

VA and VF showed improvement or further deterioration mainly up to 6 months, with no significant change thereafter. Patients sustaining any additional visual loss (additional decrease in visual acuity (VA) ≥ 0.2 logMAR) within two months after initial onset of symptoms may be classified as having progressive NAION [36].

2. VF defects are another common clinical manifestation of NAION. Although any pattern related to the OD damage can be present, altitudinal loss, usually inferior, and the arcuate defect occur in 55–80% of cases; moreover, 20–25% of cases show central scotomas [8]. Hayreh and Zimmerman [37] evaluated the pattern of various types of VF defects and their prevalence at initial examination of NAION in 312 eyes. They found that a combination of relative inferior altitudinal defect with absolute inferior nasal defect was usually the most common pattern. In addition, the former defect was more common than the latter defect.

In a 2012 Singapore study including 121 patients with NAION [38], after six months, VF defects were found to be unchanged in 77% of cases, improved in 15.5% and worse in 7.5%. Overall visual function (VA plus VF) was unchanged in 81% of cases, and no patient had complete recovery [38].

3. Optic disc edema (ODE) is a typical clinical manifestation of anterior NAION and is always present in early disease [39]. It may be either diffuse (75% of cases) or focal (25%) [4]. Eyes with diffuse ODE during the first episode of NAION seldom progressed [36]. Hayreh and Zimmerman [40] demonstrated that the initial ODE resolves typically within 6-11 weeks from the onset of visual loss and ODE starts to develop pallor in about 2–3 weeks after onset of NAION. If ODE fails to resolve within this period, additional studies should be performed to exclude other diagnoses.

4. Relative afferent pupillary defect (RAPD): is commonly present in unilateral cases, and may be present and asymmetric in bilateral cases, when the affected eye demonstrates no or weaker papillary light response compared with a healthy eye. An eye suffering with NAION will have a RAPD unless there is an optic neuropathy or significant retinopathy in the fellow eye [41].

5. Acquired loss of color vision, dyschromatopsia, is a very sensitive sign of optic nerve dysfunction. In patients with NAION, color vision tends to correlate with visual acuity for acuities better than 20/70. The pattern of field loss that most commonly accompanies spared color vision – a steep-walled off-axis cecocentral scotoma – supports the contention that relative sparing of color vision is due to selective loss of foveal projections in combination with sparing of extra-foveal macular fibers [42].

Optical coherence tomography (OCT)

OCT is a powerful tool that provides an accurate assessment of changes in optic nerve structure at various disease stages.

In the acute stage of NAION, OCT reveals diffuse retinal nerve fiber layer (RNFL) thickening and ODE; the

edema may initially affect isolated segments of the OD with a later extension into a larger continuous one [43].

Gradual RNFL thinning develops after edema regression. At the 6-month visit, RNFL percentage decreases for the superior, nasal, inferior, and temporal quadrants were 51.5%, 28.5%, 41.2%, and 38.2%, respectively [44]. Deleón-Ortega and colleagues [45] found that, in patients with satisfactory visual function after the ischemic episode, RNFL thickness was smaller than normal in all quadrants but the temporal. This may indicate that a relatively normal thickness at the temporal sector may serve as a clinical indicator for preserved central vision.

In addition, OCT can detect early axonal damage before RNFL thinning [46]. Akbari and colleagues [47] demonstrated that thinning of the ganglion cell–inner plexiform layer (GCIPL) is first detectable at 1 month after NAION and occurs before RFNL thinning in NAION, making it a potential prognostic marker for early diagnosis.

Electrophysiology studies

Electrophysiology studies play a key role in the diagnosis of optic disc because they provide an assessment of visual pathway function and retinal structure. Atilla and colleagues [48] found that visual evoked potential (VEP) amplitude was decreased significantly and the delay in latency was statistically significant in eyes with ION compared with controls, indicating ischemia-induced neural conduction abnormality. They could not demonstrate any significant pattern eletroretinography (PERG) abnormality, except decreased N95 amplitude in eyes with ION, which suggested ganglion cell involvement [48].

Parisi and colleagues [49] confirmed the dysfunction of ganglion cells and neural fibers through the analysis of changes in P50-N95 amplitude, which did not correlate with the reduction in VA, stressing the major role of optic nerve damage but not retinal dysfunction.

Methods to assess regional hemodynamics

Hemodynamic abnormalities play a key role in the pathogenesis of NAION. Numerous studies have examined the effect of changes in ocular hemodynamics on the development of the disease.

Fu and colleagues [50] used color Doppler imaging (CDI) to evaluate the retrobulbar hemodynamics and found that the reduction of blood flow volume was more prominent in ophthalmic artery (OA) and internal carotid artery ICA in NAION eyes compared with the contralateral healthy side or with the controls, with no difference in mean blood flow velocity of ICA between the groups. In addition, there was OCTA evidence of reduced peripapillary and OD vessel density in NAION eyes, which stresses the value of a reduction in blood flow volume as a key factor in the development of ischemia in the optic nerve. In a study by Kaup and colleagues [51], peak-systolic velocity (PSV) and end-diastolic velocity (EDV) of the central retinal artery (CRA) ($p < 0.001$, $p = 0.002$) and PSV of the nasal posterior ciliary artery (PCA) ($p < 0.05$) were significantly decreased in patients with NAION compared with healthy controls, but no marked differences between patients and controls were detectable for temporal PCAs. These findings may indicate local blood flow changes in the optic nerve in NAION.

Blood flow abnormalities were found to be associated with VF loss and VA. Particularly, EDV of the CRA was significantly correlated to VF global index mean deviation (MD), whereas resistive index (RI) of the OA was significantly correlated to VA. This stresses the value of hemodynamics alterations in NAION and their effects on functional changes [52].

Wang and colleagues [53] used 3-dimensional OA model reconstruction captured by computed tomographic angiography to demonstrate optic nerve hypoperfusion as a key mechanism in NAION. They found NAION to be associated with a smaller initial OA diameter. These changes were observed only in affected eyes, indicating specificity of the process for the disease, and confirming the pathogeneticity of this process.

Therefore, studies on hemodynamics in NAION have demonstrated reduced blood flow in OA and CRA, which correlated with abnormalities in visual function. This makes studies assessing ocular circulation feasible for the diagnosis and disease progression monitoring.

Immunological techniques

Recent advances in understanding of ischemic damage to the central nervous system have raised new questions on the pathogenesis of neuronal damage in AION and NAION. Neurotrophine deficiency in retinal ganglion cells (RGCs) after ischemic damage may play a significant role in cell death. Brain derived neurotrophic factor (BDNF) is one of the candidates for important trophic factors among RGCs [54].

BDNF is a neurotrophin produced by neurons in the retina, such as RGCs, amacrine cells, astrocytes, retinal glial cells (Muller cells), and photoreceptors, and can be transported between the brain and the retina via the optic nerve. In the retina, BDNF plays a vital role in vision signaling development by regulating laminar refinement in the dendrites of RGCs, which leads to the proper formation of the retinal structure. In mature individuals, endogenous BDNF exerts neuroprotective effects on RGCs by protecting dendritic fields and reducing vision loss after ocular hypertension-induced injury [55].

Another function of BDNF is protection of the retina cells from injuries caused by hypoxia and glucose deprivation, which is especially important in ischemic optic nerve damage [56].

Studies indicate that increased BDNF expression may limit progressive RGC loss in animal models of optic nerve damage [57, 58].

Findings of studies of BDNF expression in human serum suggest that BDNF is a potential additional diagnostic marker of optic nerve disorders [59], including NAION.

Conclusion

To conclude, it may be stated that studies of recent decades on NAION have considerably improved our understanding of the clinical manifestations and risk factors of the disease. Despite numerous publications on the subject, the disease remains inadequately understood; today, there is lack of a unified theory of the pathogenesis and clear classification of, and well-established diagnostic and therapeutic approaches to, NAION. The lack of systematized knowledge makes the diagnosis and effective treatment challenging. Although current modalities and techniques (OCT, regional hemodynamics assessment and electrophysiological studies) can significantly improve the accuracy of the diagnosis and provide objective assessment of the severity of optic nerve damage, the variability of the clinical picture and the absence of specific features still contribute to difficulties in the diagnosis of NAION. Consequently, further research on hemodynamics changes and biomarkers (particularly, BDNF) is essential for improvements in the diagnosis and prediction of treatment outcomes in the disease. The enhanced understanding of pathogenetic mechanisms and developing NAION early detection techniques will contribute to standardization of treatment approaches, designing new therapeutic methods, and identification of the most effective measures for the prevention of NAION development and progression.

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Corresponding author: *M.Iu. Chaban, Post-Graduate Student. SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", Odesa (Ukraine). E-mail: maksym.y.chaban@gmail.com*

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Abbreviations: *AION, arteritic ischemic optic neuropathy; BDBF, brain-derived neurotrophic factor; CDI, color Doppler imaging; CRA, central retinal artery; EDV, end diastolic velocity; EMA, European Medicines Agency; FDA, Food and Drug Administration; ICA, internal carotid artery; IONDT, Ischemic Optic Neuropathy Decompression Trial; NAION, nonarteritic anterior ischemic optic neuropathy; OA, ophthalmic artery; OD, optic disc; OSAS, obstructive sleep apnea syndrome; PCA, posterior ciliary arteries; PDE5 inhibitors, phosphodiesterase Type 5 Inhibitors; RGC, retinal ganglion cells; OCT, optical coherence tomography; PSV, peak systolic velocity; RI, resistance index; RNFL, retinal nerve fiber layer*