Review Article

Treatment strategy for non-arteritic anterior ischemic optic neuropathy

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A B S T R A C T

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common cause of sudden optic nerve (ON)-related visual loss in persons over the age of 55. The pathogenesis is still unclear and no effective treatment has been established. The possible pathway is a vicious cycle of ischemia causing consequential compartment syndrome at the optic nerve head, resulting in further ischemia and optic nerve fiber infarction. Many medical and surgical interventions aim to shorten the duration of disk edema. The Ischemic Optic Neuropathy Decompression Trial (INODT) was the only level I evidence of treatment trial but it ended in failure. The use of steroids for acute NAION is still controversial. Several clinical case-serial reports showed some benefits. A recently developed animal model of anterior ischemic optic neuropathy may provide valuable preclinical data for both drug testing and treatment strategies.

1. Introduction

In adults, anterior ischemic optic neuropathy (AION) is the second most common cause of optic nerve-related visual impairment after glaucoma [1]. AION includes nonarteritic, arteritic and perioperative types. Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common type of AION. The pathogenesis of NAION is an interesting and controversial topic. Implicated causative factors include nocturnal hypotension, impaired autoregulation of the microvascular supply, vasculopathic occlusion, and venous insufficiency [2]. Although NAION is a disease of presumable microvascular ischemia at the paraoptic branches of the short posterior ciliary arteries, there is no thrombotic evidence or any systemic disorder tightly associated with NAION except for diabetes mellitus [3,4]. Patients with NAION clinically present with painless blurry vision associated with pallid swelling and hemorrhage of the optic disc, resulting in retinal ganglion cells apoptosis and permanent vision loss [5]. The most common pattern of visual field defect is an altitudinal defect, and about two thirds of the visual field defect is a lower altitudinal visual field defect (Fig. 1).

Acute disk edema in NAION may contribute to further axonal damage via a vicious cycle of ischemia causing edema and compartment syndrome, so medical and surgical interventions aim to shorten the duration of disk edema to prevent further axonal ischemia to decrease neuron death [6,7]. However, there is no generally accepted treatment for NAION. We review and summarize medical and surgical therapies being reported in the literature based on the level of evidence [8].

2. Assessment of level of evidence

We classified recent clinical studies of NAION treatment based on the Oxford Centre for Evidence-Based Medicine - levels of evidence [8] (Table 1). We reviewed all published reports on the treatment of NAION since 1990. Most associated studies are case reports, case series and case controlled studies (Level IV and III). The only class I trial for NAION was the Ischemic Optic Neuropathy Decompression Trial (IONDT) in 1995 [9] (Table 2).

3. Treatment of acute NAION

3.1. Systemic and local treatment with corticosteroids

The rationale for the use of steroids in NAION comes from the postulation that steroids decrease capillary permeability, thereby inducing faster resolution of disk edema. Although there is no proven treatment for NAION, 10% of physicians in the USA choose...
oral steroids and 19% choose high dose intravenous pulse steroid therapy [10]. A retrospective study by Hayreh and Zimmerman showed that systemic steroid treatment was effective in patients with NAION who had an initial visual acuity 20/70 or worse and were seen within 2 weeks of onset [11]. However, their patients were not randomized, and the untreated group had more vascular risk factors, making it hard to interpret whether oral steroids is a treatment of choice in NAION (Level III) [11–13]. Moreover, a recent study in ten patients with NAION showed that high-dose systemic steroid (oral prednisolone 80 mg/day) treatment did not show any beneficial effects in NAION, and three treated patients even had complications caused by steroid application [14]. These controversial results can be explained by a high spontaneous improvement rate in NAION (41%) and a broad spectrum of clinical presentations. These variable clinical manifestations of NAION not only easily bias clinical studies, but also cause difficulty in designing a prospective study [9,15]. The rationale for intravitreal injection of steroids is the same as for systemic steroids. In clinical practice, intravitreal injection of triamcinolone acetonide (TA, 4 mg) is routinely used to treat retinal edema in conditions such as diabetic retinopathy or retinal vascular occlusion [16–18]. However, only case controlled report [19] (Level III) and case series [20,21] (Level IV) applied local intravitreal injection of TA in NAION. The results were inconclusive though some patients had visual improvement.

Fig. 1. (A) Fundus photographs of a right eye with optic disc edema during the active phase of NAION. (B) Normal disc in the left eye of the same patient. (C) Fluorescein fundus angiogram of the eye with NAION showing a relatively dark part of the disc (ischemic area in the upper half of the disc) and reactive hyperemia with dye leak in the disc (edema area in the lower half of the disc). (D) Typical inferior altitudinal visual field defect correlated with an ischemia lesion in the upper part of the optic disc. (E) Optic coherence tomography demonstrating that circumpapillary nerve fiber layer thickness shows obvious fiber thinning in the superior sector and thickening in the inferior sector of the right optic nerve (solid line) compared with a normal symmetric double hump pattern in the left optic nerve fiber layer (dotted line). INF = inferior; NAS = nasal; OD = oculus dexter; OS = oculus sinister; SUP = superior; TEMP = temporal.
3.2. Intravitreal anti-vascular endothelial growth factor agents (anti-VEGF)

VEGF is a signal protein that stimulates angiogenesis and increases microvascular permeability. Anti-VEGF agents such as bevacizumab and ranibizumab inhibit the signaling of VEGF, thereby potentially decreasing optic disk edema [7]. In recent clinical applications, anti-VEGF agents were routinely used in age-related neovascular macular degeneration and in macular edema associated with other retinal vascular disorders. Prescott et al. concluded that anti-VEGF therapy has no beneficial effects in NAION [22]. However, bevacizumab treatment in NAION was limited to one case report and one case series (Level IV), with only one patient got visual improvement [22,23]. A case report of another anti-VEGF agent, ranibizumab, concluded it was effective in reducing optic nerve swelling but there was no improvement in visual acuity (Level IV) [24]. Intravitreal anti-VEGF therapy for NAION requires further research to explore the potential vasoconstrictor effects and the stress on the cardiovascular system [25]. A preclinical trial in animal models or a randomized clinical trial may determine the role of anti-VEGF in NAION.

3.3. Aspirin

Only one study evaluated aspirin use and concluded that aspirin did not improve the visual outcome of NAION [26]. There was no benefit from reducing the risk of development of NAION in the fellow eye after taking aspirin [27]. However, other reports showed that aspirin reduced the incidence of NAION in a second eye [28,29]. Aspirin treatment failed because NAION is a hypotensive disorder, not a thromboembolic disorder [15].

3.4. Other neuroprotective agents

Other interesting treatments for NAION in the past decade involved neuroprotection. Disappointingly, levodopa and carbidopa failed to provide beneficial effects in NAION. In a prospective, double-masked, placebo controlled trial, brimonidine tartrate 0.2% eyedrops showed no therapeutic effects in patients with acute NAION (Level 1, 36 patients) [30]. Intravitreal injection of erythropoietin seemed to be effective (Level IV, 31 cases without control group). Twenty-seven eyes had visual acuity improvement (87%) at 6 months of follow up but there was no improvement in the visual field [31]. However, this study did not have a control group to strengthen its significance.

3.5. The Ischemic Optic Neuropathy Decompression Trial (IONDT)

In 1989, Sergott et al. reported optic nerve decompression improved the progressive form of NAION in a case serial report [32]. This report brought on worldwide debate. To resolve this issue, a multicenter-trial was developed. The Ischemic Optic Neuropathy Decompression Trial (IONDT), a randomized, single-blind, multicenter trial assessed the safety and efficacy of optic nerve decompression in cases of acute onset of NAION (Level 1, 258 patients). A window was made in the optic nerve sheath surrounding the optic nerve and theoretically releasing the pressure surrounding the optic nerve to relieve compartment syndrome. The IONDT found that surgery for NAION was not only ineffectve, but could be harmful, and the trial was stopped early [9]. A database review in 2012 also indicated no evidence of a beneficial effect of surgery for NAION [33].

4. Using an animal model of NAION to investigate pathogenesis and drug efficacy

No effective, standard treatment for NAION has been reported in the literature. A prospective, randomized clinical trial is difficult to
design because of the broad spectrum of disease severity and a spontaneous visual improvement rate of about 40% without treatment. Recent, primate and rodent models of AION (rAION) have been developed and the mechanism of ischemic optic neuropathy has been studied [34–39]. To create a rAION model, a photodynamic application using both a photosensitizing agent and laser was developed [39]. The preferred model involves inducing transient coagulopathy, and the severity of the ischemic area can be adjusted by laser. After injection of a photosensitizing agent (Rose bengal [RB; Sigma-Aldrich (St. Louis, USA)]) through the tail vein, an argon-green laser light was aimed at the optic disc of the animals. This procedure creates photothrombosis on the vascular endothelium with both laser and RB applications. The rAION model is different than a central retinal vein occlusion (CRVO) model. The unit energy of a CRVO is higher and the laser time is longer (>25 s) than in the AION model and the target is the retinal veins near the optic head [40,41]. The method used to create AION in animal models may be quite different from the pathogenesis of human NAION [39]. The rAION model nevertheless provides a platform on which to test several potential treatments and illustrate the pathogenesis of NAION. The results of preclinical trials in the rAION model may bring us evidence to translate into new clinical trials for NAION.

5. Conclusion

NAION remains pathophysiologically unclear, and possible factors are vasculopathic occlusion or venous insufficiency impairing the autoregulation of microvasculature around the optic disc. Controversial treatments remain in the literature. Potential strategies for the future treatment of NAION should aim to avoid compartment syndrome to decrease secondary damage to axons, protect retinal ganglion cells from death (anti-apoptosis) and even use of regenerative medicine such as stem cell therapy.

References