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Review article

Treatment of anterior ischemic optic neuropathy: Clues from the bench

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ABSTRACT

Anterior ischemic optic neuropathy (AION) is due to optic nerve head ischemia, and there is currently no effective treatment. Age is a significant risk factor for both arteritic and nonarteritic AION (NAION), although we do not fully understand the changes that occur in aging that lead to selective vulnerability of the optic nerve head. Arteritic AION, which is most often seen in the setting of giant cell arteritis, is caused by vasculitis and thromboembolism of the ophthalmic circulation leading to impaired perfusion of the short posterior ciliary artery and infarction of the optic nerve head. More commonly, AION is nonarteritic, and vision loss is typically altitudinal and noted most commonly upon awakening. NAION has been associated with a variety of risk factors, including disc-at-risk, vascular risk factors including diabetes, vasospasm and impaired autoregulation, nocturnal hypotension, and sleep apnea. This review summarizes the clinical presentation of non-arteritic AION and arteritic AION associated with giant cell arteritis and the current and future treatment approaches for human NAION based on lessons from photochemical thrombosis models of NAION.

1. Introduction

Anterior ischemic optic neuropathy (AION) is the most common acute optic neuropathy in adults older than 50 years old, and it typically leads to irreversible vision loss.[1–4] AION is subdivided into arteritic and non-arteritic types. About 10% of patients with AION have the arteritic type, whereas the non-arteritic type (NAOIN) accounts for the majority of cases. AION is due to ischemia of the optic nerve head, which is a watershed zone and therefore vulnerable to changes related to vascular risk factors and compartment syndrome. The incipient event involves acute ischemia of the prelaminar, and, in particular, the laminar and retrolaminar optic nerves due to reduced perfusion in the circle of Zinn–Haller, with the short posterior ciliary arteries thought to contribute most significantly.[4] The pathogenesis of arteritic AION is thought to arise from vasculitis leading to stenosis and thromboembolism involving the ophthalmic, central retinal artery, and especially the short posterior ciliary artery. Although the pathogenesis of NAION is not well understood, vascular, anatomic, and other risk factors are involved.[1,3,4] Some medications such as amiodarone, phosphodiesterase type 5 inhibitors such as sildenafil, and interferon-α have been associated with NAION. Age is a leading risk factor in both arteritic and nonarteritic AION as well as in glaucoma, suggesting that the process of normal aging may play a role in increasing the susceptibility of central axons.[5]

We are particularly interested in an AION animal model because: (1) AION is easily and well modeled in rodents using photochemical thrombosis to induce localized optic nerve head ischemia; (2) acute injury of the central nervous system is potentially better timed and more amenable to therapeutic intervention than a slowly progressive condition such as glaucoma; (3) there is currently no effective treatment for AION; and (4) ischemia plays a role in other optic neuropathies such as glaucoma and papilledema, so findings in AION are also potentially significant to other causes of retinal ganglion cell (RGC) loss.

This review summarizes the state of our understanding in the clinical presentation and treatment of AION with particular emphasis on lesson learned from photochemical thrombosis animal models and their implications on designing future treatment modalities.

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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2. NAION

2.1. Clinical presentation

NAION is the most common type of AION.[4] Historically, NAION was reported in Europe during the 19th century but was not recognized until the 1960s and 1970s.[1,2,6,7] Patients typically present upon awakening with altitudinal visual field defects, relative afferent pupillary defects from unilateral involvement, optic disc edema, and narrowing of the peripapillary retinal arterioles (Fig. 1). Optical coherence tomography (OCT), which uses light interferometry to visualize *in vivo* retinal layers and anatomic changes, has revealed acute retinal nerve fiber layer swelling and thinning over a period of months.[8–11] The macular ganglion cell complex (GCC), which measures the total thickness of the ganglion cell layer and the inner plexiform layer, estimates irreversible RGC loss over time.

2.2. Incidence and risk factors

The incidence of NAION in the USA is 2.3–10.2/100,000 or 1500–6000 new cases/year. The most significant risk factors for NAION include: crowded disc (so-called disc-at-risk), diabetes, atherosclerosis, age, and sleep apnea. Arguably, the most modifiable risk factor after the diagnosis of NAION is sleep apnea. In one study of 635 patients (871 eyes or 925 episodes), 73% note vision loss soon after awakening.[12] This may be related to a combination of nocturnal hypoxemia and hypotension. Systemic hypotension from shock or certain type of prolonged surgery is significantly associated with AION.[13] Other reported risk factors include cataract or other ophthalmic surgeries,[14,15] and the use of phosphodiesterase type 5 inhibitors.[16–19]

2.3. Pathogenesis and treatment of human NAION

The pathogenesis of human NAION is unclear. Important players include vascular factors (diabetes, nocturnal hypotension, atherosclerosis, failure of autoregulation, increased resistance from relatively elevated IOP), hypoxemia (sleep apnea), and compartment syndrome (disc-at-risk, congenital optic nerve hypoplasia). There are relatively few research studies designed to perturb these factors to determine how they contribute to AION or how their alteration may impact outcome.

There are some data suggesting that inflammation may play a role in human NAION. In one valuable case of human autopsy obtained 20 days after the onset of vision loss from NAION, there was an accumulation of Iba1$^+$/ED1$^+$ cells or extrinsic macrophages in ischemic areas of the optic nerve and a presence of Iba1$^+$/ED1$^-$ cells or intrinsic microglia in the area of ischemia and the penumbra.[20] Proinflammatory cytokines are involved in thrombotic events such as myocardial infarction and stroke, and they may play a role

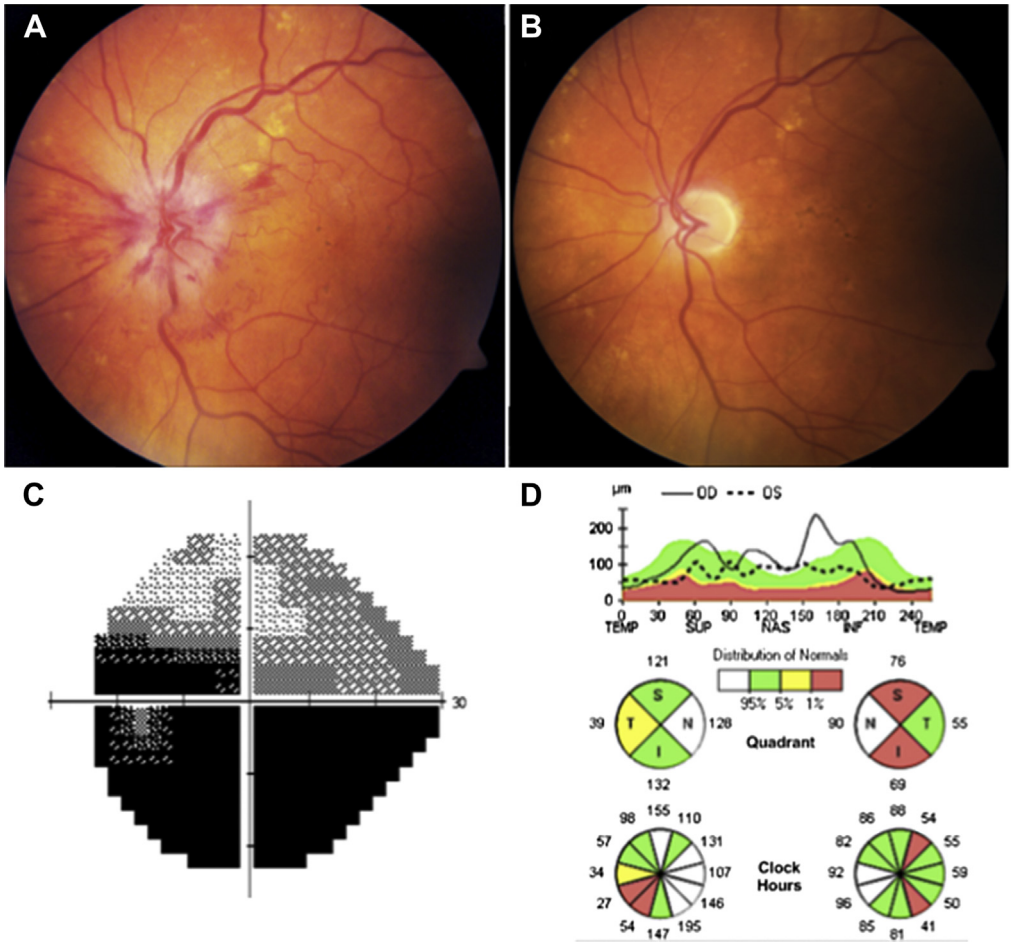

Fig. 1. An 89-year-old Caucasian woman presented upon awakening with left eye visual field loss due to non-arteritic anterior ischemic optic neuropathy. (A) Fundus photo of the left eye shows optic disc swelling, splinter hemorrhage, and narrowing of the peripapillary arterioles. (B) Fundus photo of the left eye 1 year after non-arteritic anterior ischemic optic neuropathy exhibits optic nerve pallor and narrowing and irregularity of the peripapillary arterioles. (C) Humphrey visual field study of the left eye reveals inferior greater than superior visual field loss. (D) Spectral-domain optical coherence tomography shows significant retinal nerve fiber layer thinning of the left eye (shown on the right). OD = right eye; OS = left eye.