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Nonarteritic anterior ischemic optic neuropathy (NAION) and its experimental models

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ABSTRACT

Anterior ischemic optic neuropathy (AION) can be divided into nonarteritic (NAION) and arteritic (AAION) forms. NAION makes up ~85% of all cases of AION. There is no treatment for NAION, and its initiating causes are poorly understood, partly because NAION is not lethal, making it difficult to obtain fresh, newly affected tissue for study. In-vivo electrophysiology and post-mortem studies reveal specific responses that are associated with NAION. New models of NAION have been developed which enable insights into the pathophysiological events surrounding this disease. These models include both rodent and primate species, enabling a 'vertically integrated' multi-species approach to help in understanding the common cellular mechanisms and physiological responses to clinical NAION, and to identify potential approaches to treatment. The models utilize laser light to activate intravascular photoactive dye to induce capillary vascular thrombosis, while sparing the larger vessels. The observable optic nerve changes associated with rodent models of AION (rAION) and primate NAION (pNAION) are indistinguishable from those seen in clinical disease, including sectoral axonal involvement. In-vivo electrophysiological data from these models are consistent with clinical data. Early post-infarct analysis reveals an unexpected inflammatory response, and changes in intraretinal stress response gene expression, sparing of outer retinal function, which occurs in AAION models. Histologically, the NAION models produce an isolated loss of retinal ganglion cells by apoptosis. Changes detectable by immunohistochemistry suggest that other retinal cells mount a brisk response to retinal ganglion cell distress without themselves dying. The optic nerve ultimately shows axonal loss and scarring. Inflammation is a prominent early histological feature. This suggests that clinically, specific modulation of inflammation may be a useful approach to NAION treatment early in the course of the disease.

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1. Introduction

1.1. NAION and AAION: clinical presentation and pathophysiology

1.1.1. NAION: etiology and characteristics

Anterior ischemic optic neuropathy (AION) results from a sudden ischemic insult to the proximal portion of the optic nerve (ON). There are two main forms of AION: nonarteritic (NAION) and arteritic (AAION). The two forms are etiologically distinct. NAION comprises 85% of all cases of AION, with AAION the remainder. NAION is the most common cause of sudden optic nerve-related vision loss and typically affects individuals over 55 years of age (Miller, 1982a), whereas AAION is less common and usually affects persons over the age of 70.

Controversy still clouds the actual etiology of NAION. A well-recognized risk factor is a small optic nerve passage through the sclera, presumably causing crowding of axons within a tight dural sheath (the 'crowded disk', or "disk at risk") (IONDT study group, 1996); however a host of other factors, including age (IONDT study group, 1996), nocturnal or situational (e.g., perioperative) hypotension, diabetes mellitus, hypercholesterolemia, hypertension (Salomon et al., 1999), obstructive sleep apnea (Palombi et al., 2006), use of certain medications or drugs (Pomeranz and Bhavsar, 2005) and possibly a number of genetic sequence polymorphisms involving either mitochondria or genes associated with vascular function may contribute (Salomon et al., 2004; Bosley et al., 2004; Sakai et al., 2007). In addition, although it initially was believed that the optic nerve in pre-insult individuals was functionally normal, some individuals predisposed to NAION can have subtle vascular

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differences from control (non-NAION predisposed) eyes (Leiba et al., 2000; Collignon-Robe et al., 2004), suggesting that there are subclinical changes that may increase susceptibility. These include reduced optic nerve head blood flow as measured by laser Doppler flowmetry, in addition to the small optic nerve outlet (Leiba et al., 2000). The presence of electrophysiologic abnormalities in the clinically normal, fellow eye of patients with NAION supports this notion (Janaky et al., 2006). The combined factors of hypertension and age have led a number of investigators to suggest that NAION may be triggered by temporary loss of vascular homeostasis, with initially subtle tissue edema accumulating in a confined area, resulting in a tissue compartment syndrome (Levin and Danesh-Meyer, 2008). NAION damage is initially confined to the anterior ON, with retrograde pathology manifest both early and later. Levin and Danesh-Meyer suggested that transient venous insufficiency may initiate NAION (Levin and Danesh-Meyer, 2008). A minority of individuals with NAION also have arterial thrombosis or clots transmitted from the heart walls (Kerr et al., 2009) or carotid arteries. Regardless of the initiating event, the subsequent edema and further compression of ON capillaries in the restricted space of the optic nerve, with its closely confining, thick sheath, results in vascular compression and ischemia.

Fluorescein angiography performed in patients with early NAION occasionally reveals restriction of fluorescein flow through the retinal veins, possibly related to edema-associated vascular compression at or near the optic nerve head (Arnold et al., 1996). Choroidal fluorescein flow is normal in eyes with NAION, indicating no restriction in the choroidal blood supply. Fluorescein dye (a low molecular weight fluorescent dye) leakage from the disk reveals breakdown of the blood-retinal barrier (BRB), with fluorescein diffusion into the vitreous, coupled with delayed early venous filling (Arnold et al., 1996). These vascular defects resolve over time. The loss of capillary integrity is similar to that seen in other central nervous system (CNS) infarcts, with breakdown of the blood–brain barrier (Cavaglia et al., 2001). The resolution of fluorescein dye leakage is an important indicator of BRB reconstitution. NAION-induced vision compromise may improve over time. Indeed, about 40% of patients with NAION experience spontaneous improvement in visual acuity of three lines or greater (although their visual field defects are much less likely to improve). Nevertheless, a significant percentage of individuals worsen (Arnold and Hepler, 1994).

1.1.2. AAION: etiology

In contrast to NAION, there is no congenitally abnormal optic disc structure that predisposes a patient to AAION. Rather, patients with AAION almost always have an underlying systemic autoimmune vasculitis. AAION results from inflammatory vascular occlusion of the short posterior ciliary arteries (SPCAs), leading to infarction within the optic nerve head (Arnold, 2003).

Despite etiologic differences, both NAION and AAION result in ON vascular compromise in the region at or near the junction of the eye and ON (anterior optic nerve). NAION and AAION both produce ON axonal ischemia, with localized infarction and loss of vision in the affected eye that may be severe, particularly in AAION. Thus, both AION forms result in ischemic axonopathy, with resultant stasis of axonal flow, disruption of electrical and growth factor-associated signaling, and disconnection of action potential-related communication between retinal and higher CNS structures. In this respect, both NAION and AAION are similar to other sudden axonopathic conditions, such as ON stretch, crush and axotomy (Schlamp et al., 2001; Nadal-Nicolas et al., 2009). Where NAION and AAION differ from each other is in the different physiologic responses to the stimulating event; the presence of an intact immune system in patients with NAION; the underlying factors predisposing to vascular dysfunction, edema and compression/compartmentation (i.e., vasculitis in patients with AAION versus non-inflammatory vasculopathies in patients with NAION); and the time-response of damage to long-axon retinal ganglion cell (RGC) neurons and their supporting glial cells within the CNS white-matter tract that is the optic nerve.

1.1.3. NAION: treatments

NAION is the single leading cause of sudden optic nerve-related vision loss around the world. While typically unilateral, 15–20% of individuals with unilateral NAION will experience NAION in the contralateral eye over the subsequent 5 years, and there is no consistently effective treatment to date, either to improve vision in an eye affected by NAION or to prevent visual loss from NAION in the fellow eye.

The most obvious finding following both NAION and AAION is edema of the optic nerve head (i.e., the optic disk). In both cases, AION-related ON edema may be associated with flame-shaped hemorrhages on or adjacent to the optic disk (Fig. 1). These hemorrhages may be related to vascular compression at the disk or to ischemia-reperfusion injury, with rebleeding from the damaged vessels. In addition, the more severe the infarct, the more pallid the swelling will be (hence, the tendency for AAION-associated disc edema to be pallid) with the pallor presumably related to the severity and extent of the ischemia.

1.2. Electrophysiological findings in NAION and AAION

The visual evoked potential (VEP) is a cortical potential. It is recorded clinically by placing wire electrodes adjacent to the occipital cortex and to a non-visual area of the brain; the stimulus, viewed by the patient, is typically an alternating high contrast checkerboard, although many other types of stimuli have been used. The VEP reflects the patency of the visual system up to primary visual cortex. It is used clinically to examine the function of the optic nerve and its cortical projections.

The predominant feature of the visual evoked potential (VEP) in eyes with NAION is reduction in amplitude, often severe, with little or no change in latency (Wilson, 1978), unlike the increase in latency that occurs in most other optic nerve disorders. When

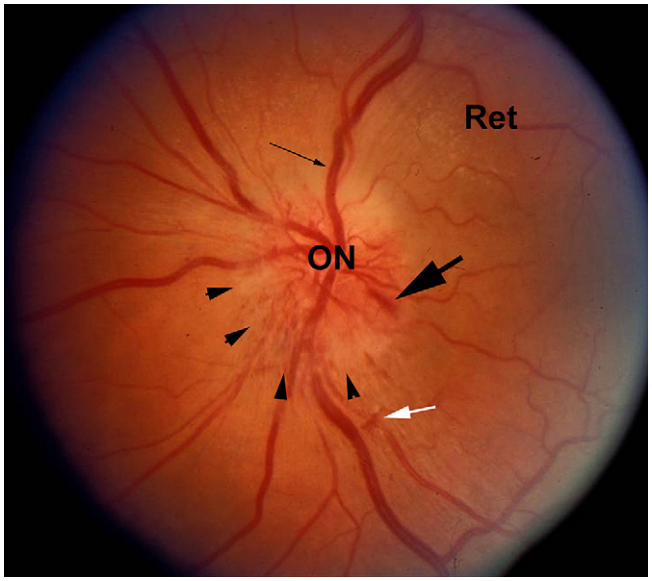

Fig. 1. Fundus photograph of an eye with NAION. The optic nerve (ON) and retina (Ret) are shown. There is obvious disk edema (arrowheads), with slight disk pallor. Venous dilation is apparent (thin arrow), and a disk hemorrhage (large arrow) is visible. A small intraretinal hemorrhage is also present (white arrow).

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