Hypothesis

A Venous Etiology for Nonarteritic Anterior Ischemic Optic Neuropathy

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Visual information travels from the eye to the brain via the optic nerve, a 3.5-mm-thick central nervous system structure approximately the same diameter as the cable connecting a video camera to a computer. As might be expected, damage to the optic nerve deprives the brain of visual input and causes visual loss. Nonarteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy of middle and late life, with an annual incidence of up to 10 cases per 100,000 individuals older than 50 years.1 It is characterized by rapid and painless unilateral visual loss, altitudinal visual field defects, and optic disc swelling.

NAION is a perplexing disorder. No treatment is effective, visual improvement is unimpressive,2 and the pathophysiology is unknown.3 A feature common to patients with NAION is a crowded optic disc, the structure through which 1,200,000 axons from the retina converge before passing through the sclera toward targets in the brain. Swelling within the confines of a tight disc can lead to a compartment syndrome4,5 in which cycles of swelling and ischemia reciprocate until infarction ensues. But what causes the initial swelling? Despite the lack of clinical and pathological evidence, the predominantly held assumption is that edema is precipitated by occlusion of microvascular arteriolar branches of 1 or more short posterior ciliary arteries within the optic nerve from systemic or local hypotension. However, the clinical and pathological evidence (detailed later) does not support arterial occlusion in NAION.

Furthermore, there are several unusual features of NAION that distinguish it from several other ischemic disorders of the visual system. For example, patients often have asymptomatic disc edema for weeks to months before visual loss ensues.6 There is some association with the use of phosphodiesterase-5 inhibitor drugs for erectile dysfunction, although this is controversial. Another example is that NAION only rarely recurs in the same eye.

We believe that the reason the etiology of NAION has been enigmatic is a misplaced focus on arterial insufficiency. Instead, we hypothesize that in many cases NAION is precipitated by venous insufficiency, with venous congestion causing initial disc edema. The creation of a compartment syndrome and subsequent cytotoxic and vasogenic (interstitial) edema cause infarction and tissue loss. We discuss how this reframing of NAION pathophysiology explains many of the clinical and pathological features of the disease. Finally, we describe testable implications for diagnosis and treatment.

NAION OFTEN DOES NOT HAVE CLINICAL CHARACTERISTICS OF AN ARTERIAL DISEASE

In the majority of cases of NAION, the optic nerve head appearance differs from what is seen in arterial disease of the optic nerve. Arteritic anterior ischemic optic neuropathy (AAION), a complication of giant cell arteritis, is an example of a pathologically proven arterial optic nerve...
disease resulting from vasculitic occlusion of posterior ciliary arteries supplying the optic disc. AAION causes a swollen disc that is pale, whereas NAION typically causes swelling with normal color or hyperemia. The optic atrophy of AAION exhibits striking tissue loss and significant excavation at the disc, whereas optic atrophy in NAION demonstrates a relatively preserved disc substance, even when corrected for degree of visual loss. Disc hemorrhages are less commonly seen in AAION (or other arterial diseases such as retinal artery occlusion) but are frequent in NAION and retinal vein occlusion). AAION usually causes severe visual loss, similar to the severe neuronal damage from arterial cerebral infarcts. In contrast, NAION causes less severe visual loss, akin to the moderate neuronal damage associated with cerebral venous disease. Overall, the appearance and outcome of disc ischemia in NAION significantly differ from those seen with arterial disease of the disc.

**NAION DOES NOT HAVE PATHOPHYSIOLOGICAL CHARACTERISTICS OF AN ARTERIAL DISEASE**

NAION is commonly thought to be a disease of small arteries supplying the anterior optic nerve. However, NAION pathology is not entirely consistent with this theory. While pathological evidence for vasculitic occlusion in AAION is good, cases of arterial occlusion in NAION caused by thrombus or embolus are exceedingly rare.

The vascular bed of the occlusion in AAION often includes the choroidal circulation as a result of posterior ciliary artery vasculitis. Occlusion of a posterior ciliary artery in the monkey results in choroidal circulation changes. In contrast, the infarct in NAION does not fit the vascular bed of any known artery, and fluorescein angiography in NAION demonstrates normal choroidal filling and mildly delayed arteriolar filling of the anterior (prelaminar) disc alone. The pathological findings of NAION also do not resemble those of a lacunar stroke in that there is no evidence of lipohyalinosis.

**RISK FACTORS FOR NAION ARE NOT SPECIFIC TO ARTERIAL DISEASE**

The most commonly accepted risk factors for NAION are a small optic nerve cup (the opposite of glaucoma) and diabetes. Other risk factors are less proven, eg, hypertension, hyperlipidemia, and thrombophilia. None are specific to arterial disease. Arterial risk factors, eg, atherosclerotic disease, have not been established to be independent risk factors for NAION.

**HYPOTHESIS: NAION IS A PRIMARY VENOUS OCCLUSIVE DISEASE**

If NAION is not an arterial disease, then what causes the ischemia? The prevailing assumption that the ischemia of NAION is necessarily arterial in origin is unsupported by evidence. Instead, we contend that in many cases the ischemia results from venous congestion. The vascular supply of the optic nerve head has been elaborated on by the seminal work of Hayreh. The venous drainage of the anterior optic nerve is via the central retinal vein (CRV), which shares an adventitial sheath with the central retinal artery (CRA). Anatomical or functional occlusion of CRV tributaries within the anterior optic nerve would cause venous congestion of the optic nerve parenchyma, subsequent cytotoxic and vasogenic edema, and consequent further compression of venules feeding the CRV. Venous congestion can cause secondary constriction of small arterioles via the venoarteriolar response, explaining the slower disc filling seen in fluorescein angiographic studies of NAION.

The degree of visual impairment of NAION shows a similar pattern to venous occlusive disease of the central nervous system. As with cerebral infarction secondary to venous occlusion, the degree of permanent damage in NAION is variable and is often milder than that seen with arterial infarction. Pathologically, experimentally, and radiologically, there is early cytotoxic edema followed by vasogenic edema along with capillary hemorrhages not dissimilar to those seen with NAION.

**VENOUS INSUFFICIENCY EXPLAINS SEVERAL IDIOSYNCRATIC FEATURES OF NAION**

Several puzzling features of NAION distinguish it from other optic neu-
ropathies and may be explained by venous congestion being the primary injury in many cases.

The first feature is premonitory asymptomatic disc edema. Some patients have weeks to months of asymptomatic disc edema, which either worsens and becomes symptomatic or spontaneously resolves. It is likely that this phase involves venous congestion of the anterior optic nerve but without frank infarction (ie, cytotoxic and vasogenic edema).

The second is possible association with the use of the phosphodiesterase-5 inhibitor erectile dysfunction drugs. These produce erections parly by vasodilating arteries that fill cavernous venous spaces to systolic blood pressure, secondarily blocking venous outflow and thereby causing venous engorgement. We suggest that the same mechanism in the anterior optic nerve, where the CRA and CRV share a common adventitial sheath, could cause NAION in those patients with discs at risk. Prolonged arterial dilation within the fibrous sheath would decrease optic nerve drainage to the CRV via its tributaries. Although the association between the erectile dysfunction drugs and NAION is controversial, there is at least 1 case with multiple rechallenge episodes.

Third is the high incidence of NAION in diabetes, particularly in younger patients. Although diabetes predisposes to both arterial and venous disease, it also is associated with capillary endothelial leakage and would be expected to produce more vasogenic edema for a given amount of venous pressure elevation.

TESTABLE IMPLICATIONS

If NAION can be precipitated by venous disease, then we would predict that in many cases the anterior optic nerve acutely would have imaging characteristics of venous infarction, not arterial infarction. In venous occlusion, cytotoxic edema is rapidly followed by vasogenic edema, whereas primarily cytotoxic edema occurs in arterial infarction. Vasogenic edema can be differentiated from cytotoxic edema by a greater apparent diffusion coefficient on magnetic resonance imaging. High-resolution imaging of the apparent diffusion coefficient in the small volume of the optic nerve is currently impractical but should be possible in future years with higher field strength magnets and improved techniques. We also predict that premonitory disc edema would show venous congestion without edema, which would be manifested by increased hemoglobin concentration without changes in the apparent diffusion coefficient.

If venous occlusion preceded optic nerve infarct in NAION, we would also predict that decreasing venous congestion would decrease the subsequent optic nerve tissue loss. Most patients with NAION are seen after the infarction has occurred, but some have long-standing premonitory disc edema and would be candidates for abortive therapy. One approach would be to decrease venous congestion using the same therapy considered for priapism, blocking nitric oxide. This would not be expected to prevent NAION from arterial infarction.

In summary, we suggest that NAION has been challenging to elucidate and recalcitrant to treat because of the focus on arterial ischemia, when the problem is more likely of venous origin in many cases. We propose that if experimental studies confirm this hypothesis, then anterior venous ischemic optic neuropathy could become a more precise designation for many cases of what has hitherto been called NAION.

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