

Ischemic Optic Neuropathies: Current Concepts

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Abstract

Ischemic optic neuropathy (ION) is the term ascribed to optic nerve disease that is the result of a transient or permanent interruption of the blood supply to any portion of the optic nerve. Anterior ischemic optic neuropathy (AION) refers to ischemia of the optic nerve head, whereas posterior ischemic optic neuropathy (PION) indicates ischemia of the posterior optic nerve. IONs are primarily classified as arteritic ION and non-arteritic ION. A subset of ION that occurs around the time of surgery is termed peri-operative ION. These phenomena will be discussed as distinct entities.

Keywords: Arteritic ION, disc-at-risk, ischemic optic neuropathy, non-arteritic ION

NON-ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY (NAAION)

NAAION is the most common cause of acute optic nerve disease in those aged over 50,^[1] by definition affecting the anterior portion of the optic nerve. The annual incidence of NAAION is estimated at 10.3 per 100,000 individuals with a median age of onset of 72. It can occur in younger individuals, however, with one tertiary referral center reporting that 23% of its cohort of all anterior ischemic optic neuropathy (AION) comprised of those under 50 years of age.^[2]

CLINICAL FEATURES

NAAION presents with sudden or rapidly progressive unilateral painless loss of vision in one eye. The presence of ocular pain is atypical and should warrant consideration of optic neuritis or arteritic anterior ischemic optic neuropathy (AAION) [Table 1]. The visual reduction may be described as diffusely blurred or in vertical hemi-field distribution, commonly inferiorly. This blurring can progress over several weeks in up to a third of patients, likely the result of a cycle of disc edema exacerbating a local compartment syndrome and prolonging ischemia.^[3-5]

Visual acuity at presentation is highly variable, with approximately half of patients seeing better than 20/64 and 1 in 3 less than 20/200.^[6] Any color vision detriment is commensurate with the level of visual loss, in contrast to optic neuritis in which it is commonly disproportionately affected. A relative afferent pupillary defect (RAPD) is expected when the optic neuropathy is unilateral.

Examination of the fundus in acute NAAION reveals optic nerve head edema which may be diffuse or segmental [Figure 1a]. This edema typically resolves over 6–11 weeks and is replaced by disc pallor.^[4,5] Disc edema that persists beyond this period should prompt investigation for alternative diagnoses such as compressive optic neuropathy.

Peripapillary hemorrhages are identified in up to three-quarters of NAAION and the cup-to-disc ratio as noted in the fellow eye is typically small, consistent with the so-called disc-at-risk for NAAION [Figure 1b].^[6] Visual field testing usually reveals altitudinal loss, most commonly inferiorly, but central scotomas are seen in up to 25% [Figure 2].^[7]

PATHOPHYSIOLOGY

A definitive mechanism of NAAION has not been proven. It is postulated that hypoperfusion of the pre-laminar portion of the optic nerve head supplied by the short posterior ciliary arteries (PCAs) may be the inciting event of a compartment syndrome, rather than a thromboembolic phenomenon. The resultant axonal edema in a structurally pre-disposed crowded optic nerve head (disc-at-risk with a small cup-to-disc ratio) leads to the death of ganglion cells. Since nearly all individuals will have symmetrically-sized optic nerve heads, the absence of a disc-at-risk in the fellow eye of a patient with presumed NAAION should warrant a search for an alternative diagnosis. In the same regard, optic nerve head anomalies such as disc drusen may have the same crowding effect and may play a role in the pathogenesis of NAAION in younger patients.^[8]

Although vascular insufficiency is thought to play a role in the pathophysiology, there is a lack of adequate population-controlled

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Table 1: Comparison of NAAION, AAION, and optic neuritis

	NAAION	AAION	Optic Neuritis
Age	Any Most common after 50	Above 50	Any Most common in young
Onset of visual loss	Acute Progression over 2 weeks	Acute	Acute Progression over 2 weeks
Premonitory symptoms	Uncommon	Common	Uncommon
Ocular Pain	None	Headaches	Common, worse with eye movement
Disc edema	Always present acutely	Present in anterior form, often pallid	Present in 1/3 only of typical optic neuritis; common in infectious or MOG optic neuritis
Possible associated ocular findings	Crowded optic nerve head in fellow eye required for diagnosis	Cotton wool spots, retinal artery occlusion	Intraocular inflammation, retinal vasculitis, or infiltrates in infectious or systemic diseases
MRI Brain and Orbit findings	None	Optic nerve sheath and orbital fat enhancement or evidence of large vessel vasculitis on MRA	Optic nerve enhancement. Possibly associated with CNS demyelination.
Treatment of acute episode	None	High-dose steroids	Observation or high-dose steroids

MOG=Myelin Oligodendrocyte Glycoprotein; MRA=Magnetic Resonance Angiogram; CNS=Central Nervous System

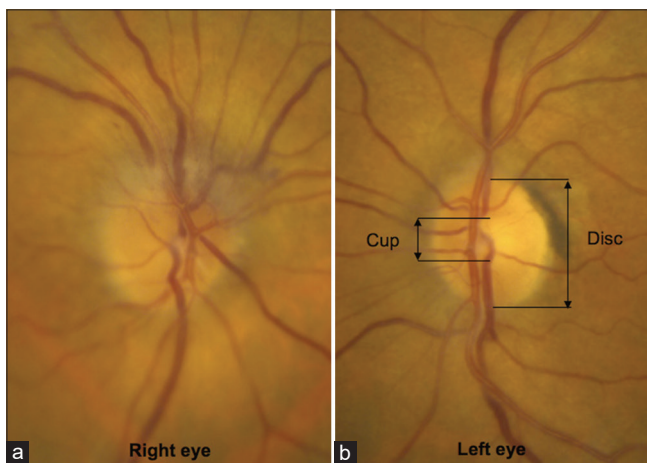


Figure 1: (a): Fundus photograph demonstrating superior segmental optic nerve head swelling in the right eye of a patient with NAAION. (b): Fundus photograph of the left eye demonstrating small cup-to-disc ratio or *disc-at-risk* appearance of the optic nerve

studies to definitively identify risk factors. Up to 50% of patients have associated hypertension and 25% have diabetes mellitus.^[6] It has been suggested that vascular disease may impair autoregulation of the optic nerve head blood flow; therefore, investigating vascular risk factors seems prudent. However, large vessel or cardiac investigations are usually unwarranted, as embolic causes are exceptional. Retrospective studies suggest that obstructive sleep apnea confers a greater risk of NAAION; therefore, the use of a screening questionnaire is advised to determine the need for diagnostic overnight polysomnography.^[9] Other associations may include the use of amiodarone and phosphodiesterase inhibitors.^[2]

INVESTIGATIONS

NAAION is a clinical diagnosis; however, in all patients above the age of 50 in whom the diagnosis is suspected, a full blood count, c-reactive protein, and erythrocyte sedimentation rate are essential tests in helping exclude AAION.

Optical coherence tomography (OCT), a non-invasive, office-based imaging modality that renders a high-resolution cross-sectional image of the retina and optic disc can assist in the identification and monitoring of disc edema. Enhanced depth imaging OCT can additionally identify buried optic nerve head drusen.^[8] OCT Angiography enables detailed visualization of the microvasculature of the retina and optic nerve head and has demonstrated peripapillary capillary dilatation in the acute phase, which may represent a form of luxury perfusion, followed by attenuation of vessels.^[10] Its role in the diagnosis of NAAION has yet to be established. Magnetic resonance imaging (MRI) of the orbits with contrast and fat suppression can rule out alternative causes such as optic neuritis or compression such as from optic nerve sheath meningioma or an orbital mass, as there will be no optic nerve enhancement in cases of NAAION.

Obtaining a history of vascular risk factors is reasonable for a patient's general health, but additional studies are usually not necessary. A thrombophilia screen is not routinely indicated unless there is a personal or family history of a clotting disorder, evidence of recurrent disease, or an absence of vascular risk factors in a young patient, especially if there is no obvious disc-at-risk. Similarly, carotid doppler ultrasound is not part of routine investigations unless there are other symptoms consistent with carotid insufficiencies such as ocular ischemic syndrome with light induced visual loss, transient monocular visual loss, or contralateral neurological symptoms.^[11]

MANAGEMENT AND PROGNOSIS

The natural history of NAAION is highly variable with 50% of patients achieving visual acuity of 20/30 or better and nearly one-quarter achieving 20/200 or worse.^[12] Recovery of at least three Snellen acuity lines at 6 months was demonstrated in 42.7% of patients who had initial visual acuity of 20/64 or worse.^[3] The risk of recurrence in the same eye is estimated at 3–8%, whereas the 5-year risk of the fellow eye being affected is 15–24%.^[13,14]

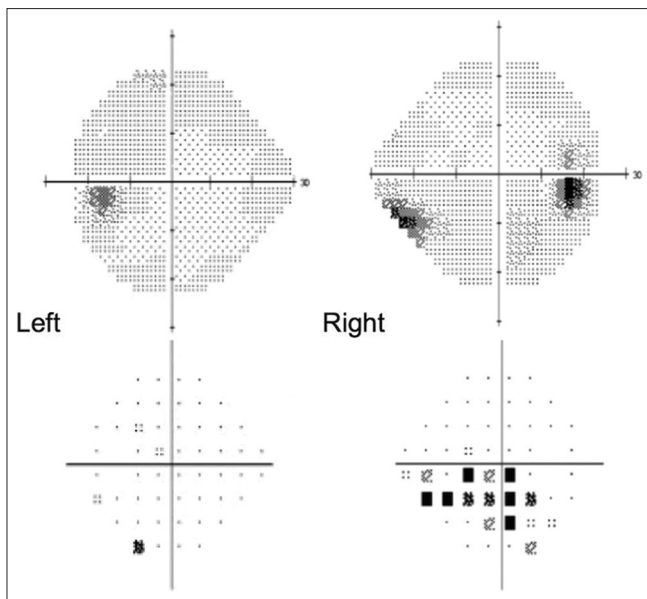


Figure 2: Humphrey visual fields of the same patient in Fig. 1 demonstrating inferior field loss in the right eye

At present no proven treatment exists for NAAION and clinical trials are scarce. Most studies have aimed at reducing the compartment syndrome either with surgical decompression or by reducing the optic nerve edema. None have resulted in improvement of visual function. Similarly, none of the neuroprotective agents tested have improved visual outcomes significantly.

The ischemic optic neuropathy decompression trial, a randomized prospective trial comparing optic nerve decompression surgery to observation, ceased recruitment prematurely when preliminary findings suggested no benefit and potential harm related to surgery.^[3]

Intravitreal therapy with bevacizumab, an anti-vascular endothelial growth factor, has not been proven to be beneficial. The same route of delivery of triamcinolone and anti-apoptotic caspase 2 inhibitor QRK207 has not demonstrated clear evidence of efficacy.^[15] A phase three trial of RPh 201, thought to enhance neuronal recovery by an unknown means, was terminated early.^[16]

The role of steroids in NAAION is much debated but the only prospective randomized controlled trial, which did not include patients with diabetes, suggested that a tapering regime of oral prednisolone, commenced at 80 mg per day, shortened the duration of disc edema and improved electrophysiological parameters of the optic nerve, but did not result in a visual acuity benefit.^[17]

The use of aspirin in the acute treatment of NAAION has not been studied, but its use in preventing recurrence or second eye involvement has been suggested. Retrospective studies have provided conflicting results and the scarcity of the disease and low prevalence of recurrence would prove challenging for a prospective trial of adequate power.^[18,19]

Treatment of vascular risk factors, including smoking cessation and treatment of sleep apnea, is an advisable strategy to reduce the lifetime risk of further episodes, as well as systemic health, though the proven impact of these measures remains unknown.

NON-ARTERITIC POSTERIOR ISCHEMIC OPTIC NEUROPATHY

Absence of disc edema, but presence of optic nerve signs and symptoms, could reflect ischemia of the posterior portion of the optic nerve. This rare entity is termed non-arteritic PION. This must be a diagnosis of exclusion, however, and can only be made in the context of a completely normal MRI of the orbits with contrast and fat suppression ruling out a compressive cause. Giant cell arteritis (GCA) causing an arteritic PION must be excluded in all patients over 50 years of age.^[20]

ARTERITIC ISCHEMIC OPTIC NEUROPATHY (AION)

AION is almost always caused by GCA, a large vessel vasculitis in people over the age of 50. Other large vessel vasculitides are only rarely implicated. Differentiating this condition from non-arteritic ION is crucial, as treatment of GCA necessitates immediate high-dose steroids to reduce the risk of fellow eye involvement and systemic complications.

CLINICAL FEATURES

Arteritic ION is the most common manifestation of end organ ischemia in GCA, occurring in up to 20% of patients.^[21] The clinical presentation may be similar to that of non-arteritic ION; however, in contrast, visual loss is not uncommonly preceded by transient monocular visual loss due to the optic nerve or choroidal ischemia, or transient diplopia, due to extraocular muscle or, less commonly, cranial nerve ischemia. Additional systemic symptoms such as jaw claudication, scalp tenderness, and headache are classic. Extra-cranial large vessel vasculitis may produce fever, malaise, and weight loss. However, an occult form of GCA, so termed because visual loss occurs without systemic symptoms, occurs in 25% of cases. Hence the lack of any systemic symptoms should not rule out GCA as the cause of ION in a patient older than 50 years of age.^[22]

AAION typically presents with severe visual loss, worse than 20/200 in over 60%.^[23] Examination findings may be indistinguishable from that of NAAION, but pallid or “chalky-white” disc edema is more suggestive of AAION and represents severe optic nerve head infarction. Accompanying signs of ocular ischemia such as cotton wool spots or retinal artery occlusion are also very suggestive of GCA. In cases of AION where the fellow eye does not exhibit a crowded optic nerve head, one must be careful to exclude AAION for which a crowded disc is not a pre-requisite. Sudden visual loss with RAPD and normal optic nerve head (no disc edema) suggests PION, which should always raise concern for GCA, as non-arteritic PION is very rare.

PATHOPHYSIOLOGY AND INVESTIGATIONS

Thrombotic occlusion of the short PCAs as a result of large vessel vasculitis accounts for optic nerve head infarction seen in arteritic ION. The short PCAs that originate from the ophthalmic artery additionally supply the highly vascular choroid; therefore, fundus fluorescein angiography and indocyanine green angiography, dye tracing methods that enable visualization of the retinal and choroidal vasculature, may reveal choroidal filling delay in GCA.^[24]

Inflammatory markers and full blood count can reveal abnormalities with an abnormally high-C-reactive protein and erythrocyte sedimentation rate, conferring a sensitivity of 99% in biopsy-positive GCA. It must, however, be noted that “inflammatory marker negative” disease, more likely in occult GCA, does occasionally occur, thus these parameters cannot be wholly relied upon in a suggestive clinical context.^[25,26] A high platelet count is additionally supportive of a diagnosis of GCA.^[27] MRI of the orbits with contrast may identify evidence of optic nerve sheath and orbital fat enhancement, which are highly suggestive of vasculitis such as GCA in the setting of presumed ION.^[28] Temporal artery ultrasound performed within a few days of initiating glucocorticoid treatment is 77% sensitive and 96% for GCA, identifying stenosis, occlusion, vessel non-compressibility, and a hypoechoic vessel wall thickening termed the *halo* sign.^[29] Recent studies have suggested that in the correct clinical context, proceeding with a temporal artery biopsy after a conclusive ultrasound, may not be necessary.^[30] However, the temporal artery ultrasound quality is operator dependent and may not be reliable in all centers. The gold standard temporal artery biopsy can be performed within a few weeks of initiating glucocorticoids with the identification of a predominantly mononuclear cell infiltrate or granulomatous inflammation consistent with GCA. Glucocorticoids in general reduce the sensitivity of investigations, but initiation should not be delayed when there is reasonable suspicion of arteritic ION.

MANAGEMENT AND PROGNOSIS

Acute management consists of high-dose glucocorticoids, either oral prednisolone or intravenous methylprednisolone. Although the evidence favoring intravenous methylprednisolone for ischemic complications of GCA is retrospective, suggesting improved visual outcomes in comparison to oral prednisolone, in view of the severity of the disease most would opt for it, especially in the context of evolving visual symptoms or second eye involvement.^[31] A 12–18 month prednisolone taper is generally required to sustain clinical remission. However, if the condition is refractory, relapsing, or if there is significant steroid toxicity, then steroid sparing agents such as methotrexate or tocilizumab, a humanized monoclonal antibody to the interleukin-6 receptor, can be considered.^[32-34]

Prognosis in the absence of treatment is poor, with 50% of patients suffering fellow eye involvement within a few days or weeks.^[21] Once the visual loss has taken place, reversal with

treatment is extremely unlikely. Therefore, prompt initiation of treatment is required to ensure an unaffected optic nerve is protected.

PERI-OPERATIVE ISCHEMIC OPTIC NEUROPATHY

Peri-operative ION is a distinct subset of non-arteritic ION triggered by ocular or non-ocular surgery. Cataract surgery has been suggested to be a risk factor in triggering non-arteritic ION, independent of vascular risk factors. Additionally, a history of non-arteritic ION in the non-operated eye appears to confer greater risk.^[35] The mechanism is yet to be elucidated, but cases in which NAAION develops in the hours or days after surgery may be explained by fluctuations in intraocular pressure which affect the perfusion pressure of the optic nerve head. This is supported by its rare association also with laser *in situ* keratomileusis and intravitreal injections.^[36,37] The delayed form of peri-operative ION which can occur months later has been postulated to be related to inflammation incited by surgery. This theory stems from a lower incidence of ION with modern advanced cataract surgery which utilizes phacoemulsification, an ultrasound technique that is significantly less inflammatory than older extracapsular and intracapsular extraction techniques. Additionally, among cases of peri-operative ocular surgery ION, surgical complications leading to prolonged surgery and therefore potentially greater inflammation have been identified.^[35]

With regard to non-ocular surgery, cardiac and spinal surgery is the most commonly implicated procedures for peri-operative ION, usually in the proceeding 24–48 h. Devastating visual loss may occur and is commonly bilateral. Cardiac bypass surgery is associated with a risk of non-arteritic ION in up to 1% of cases, with AION more common than posterior.

Spinal fusion surgery, with the patient lying prone, is associated most often with non-arteritic PION. Male sex, blood loss, prolonged duration of anesthesia in the prone position, obesity, administration of lower percentage colloid solution, and use of a Wilson surgical frame have been identified as independent risk factors,^[38,39] suggesting that the pathophysiology may involve issues with venous outflow and orbital/optic nerve congestion.

CONCLUSION

The diagnosis of ION is clinical but care must be taken to exclude alternative causes of optic neuropathy when the presentation and course are not typical. At present, there is no proven treatment for the non-arteritic subtype; however, the devastating bilateral visual loss that can occur in the arteritic subtype warrants careful investigation and prompt treatment with high-dose steroids if suspected.

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Conflicts of interest

There are no conflicts of interest.

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