Review Article

Ischemic optic neuropathies—update

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Abstract: This submission will briefly review the anatomy and physiology of the optic nerve, and highlight various ischemic optic neuropathies including anterior ischemic optic neuropathies (non-arteritis and arteritic), diabetic papillopathy, posterior ischemic optic neuropathies, and ischemic optic neuropathies in the setting of hemodynamic compromise.

Keywords: Ischemic optic neuropathy; anterior ischemic optic neuropathy; posterior ischemic optic neuropathy (PION); diabetic papillitis

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Optic nerve anatomy and physiology

The optic nerve is part of the central nervous system. As such, the 1.2 million axons are myelinated by oligodendrocytes, not Schwann cells, as are peripheral nerves (1,2). These optic nerve axons originate from retinal ganglion cell bodies. The optic nerve is divided into four parts: (I) the intraocular portion, (II) the intraorbital portion, (III) the intraosseous intracanalicular portion in the optic canal, and (IV) the intracranial portion.

The optic nerve head is about 1 mm in anterior-posterior dimension, becomes slightly wider in the retro-laminar space. Myelination occurs at the posterior end of the optic nerve head. The ONH is supplied by two independent arterial sources. Its surface nerve fiber layer is supplied by the central retinal artery circulation and its deeper part by the posterior ciliary artery circulation. The central retinal artery and central retinal vein pass through the nerve head to supply the retina. Capillaries form the pial plexus provides blood supply to the intraorbital portion of the optic nerve. All of the blood supply to the optic nerve is ultimately derived from the ophthalmic artery (3,4).

History and examination

In a patient with afferent visual dysfunction, a complete history of the chief complaint must be obtained. This includes detailing if the vision loss is bilateral or unilateral, and the quality of the vision loss. It is important to define the temporal nature of the problem (e.g., details of onset, duration of symptoms, chronicity of symptoms); any associated pattern to the symptoms; and systemic and neurological symptoms that are associated with the vision loss. For example, in elderly patients suspected of temporal arteritis, it is important to ask about a history of headaches, malaise, jaw claudication, fevers, and unintentional weight loss. It is also highly relevant to obtain a detailed past medical and surgical history from the patient, as many neuro-ophthalmic disorders are manifestations of systemic disease states. A specific focus should be placed on systemic hypertension, diabetes, hypercholesterolemia, obstructive sleep apnea, history of migraines, prior cerebral vascular accidents, and any prior rheumatologic conditions. In addition, a detailed family history and social history should be obtained, as the afferent visual system can be affected by illicit drug use, smoking, alcohol consumption in certain cases.

A complete neuro-ophthalmic assessment requires detailed examination of both the afferent and efferent visual systems. This includes visual acuity, color perception, visual field testing, pupillary assessment, external adnexal examination, cranial nerve examination, extraocular motility, slit lamp examination, and dilated funduscopic examination. Ancillary testing may also be useful (e.g., optical coherence

tomography).

Visual acuity should be tested with the patient's best corrected vision. Refraction should be performed when necessary. It is important to note that although visual acuity is commonly reduced in optic neuropathies, this can be highly variable. Color vision should be tested (e.g., Ishihara color plates, or Hardy-Rand-Ritter plates). Color vision should be obtained one eye at a time. Any mismatch between visual acuity and color vision can be a good indication of optic nerve dysfunction. Confrontation visual fields are diagramed in circles representing the patient's point of view. The pupillary examination should include pupillary size, reactivity to light, shape of pupils, and the results of the swinging flash light test [i.e., testing for a relative afferent pupillary defect (RAPD)]. The presence of an RAPD documents a lesion in the afferent pupillary pathway anterior to the lateral geniculate nucleus (i.e., a lesion from the retinal ganglion cell to the optic nerve chiasm, tract, or pretectal interneurons to the dorsal midbrain. Special attention should be paid to the appearance of the optic disc, including cup-to-disc ratio, disc swelling, and disc pallor. The most common causes of optic neuropathies that present with swollen optic nerves include ischemic optic neuropathies and optic neuritis. In selected patients, automated perimetry testing and ocular coherence tomography (OCT) examination of the retinal nerve fiber layer (RNFL) of the optic nerves can add valuable diagnostic information.

Anterior ischemic optic neuropathy

Ischemic optic neuropathies typically cause sudden, acute vision loss, which is vascular in nature. Anterior ischemic optic neuropathies are broadly categorized into non-arteritic anterior ischemic optic neuropathy (NAION) and arteritic anterior ischemic optic neuropathy (AAION).

NAION

The majority (up to 95%) of anterior ischemic optic neuropathies are non-arteritic (NAION). In patients over 50 years old, NAION is the most common cause of optic neuropathy with unilateral optic nerve swelling, an ipsilateral RAPD, and vision loss (5,6).

The typical age range of patients with NAION is from 57–80 years old, with a less common presentation in patients younger than 50 (5). NAION of the young may be more common than previously thought. Arnold and associates reviewed 848 patients with NAION and found 108 (12.7%) were younger than 50 years (6). Caucasians are more likely to be affected than are African American or Hispanic patients, and there is no gender predilection (5,7). Hypertension, diabetes mellitus, hypercholesterolemia and ischemic heart disease are all proposed risk factors for NAION (8,9). In one study, the Ischemic Optic Neuropathy Decompression Trial (IONDT), 47% of patients had hypertension and 24% had diabetes (10). Other risk factors include nocturnal hypotension, which can be exacerbated by some anti-hypertensive medications when taken at bedtime (11,12). This could account for the common symptom of vision loss upon awakening (11). A small crowed disc, "disc at risk," is also believed to be predisposing structural risk factor for NAION (13,14). Interestingly, ipsilateral carotid occlusive disease has not been proven to be a risk factor (15). Obstructive sleep apnea has been demonstrated to be a separate and independent risk factor in the development of NAION (16). Pomeranz *et al.* has demonstrated the association between phoshodiesterase-5 (PDE-5) inhibitors used to treat erectile dysfunction, and NAION (17). Campbell and associates used a case-crossover study design in 43 patients with exposure to PDE5 inhibitors with 30 days of onset of NAION (18). They found the odds ratio for developing NAION within 5 half-lives of PDE5 use was 2.15 normal. There are two principle mechanisms proposed by which PDE-5 inhibitors may cause NAION: first, they cause systemic hypotension and second, they cause impaired local autoregulation at the optic nerve head in the short posterior ciliary arteries (19,20). It is common practice that patients who have had ION in one eye should be cautioned against the use of PDE-5 inhibitors, particularly if they have systemic risk factors and a crowded disc.

NAION, in most patients, presents with painless vision loss upon awakening that is maximal on onset. Prodromal symptoms such as amaurosis, headache, or diplopia are not seen with NAION, and should raise suspicion for giant cell arteritis (GCA) (i.e., arteritic AION). The level of vision loss in NAION versus AION is usually much less profound. NAION usually presents with altitudinal visual field defects but any nerve fiber layer type defect can occur (21). The minority of patients will present with central scotomas. Additionally, patients will present with dyschromatopsia and an RAPD if unilateral or if bilateral but asymmetric. Commonly, there is an absence of severe pain, but mild pain can be seen in 10% of patients (22). The disc appearance in NAION is quite characteristic. The typical appearance is that of a disc at risk (a small crowded nerve head), segmental

disc edema, and splinter disc hemorrhages (23). Initially, the disc edema may only be mild, and this segmental edema progresses to pallor, usually after 2 months from onset. Within weeks of onset, telangiectatic vessels may appear on the surface of the ischemic disc, in a phenomenon called "luxury of perfusion" (24). In typical NAION cases, no further diagnostic work-up is necessary but the patient should be evaluated for the vasculopathic risk factors listed above. Checking an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and complete blood count (CBC) with platelets could be helpful to screen for temporal arteritis (A-AION). Automated perimetry can be useful in following the stability of the visual field defect as the disc edema improves. RNFL OCT testing can demonstrate subtle subretinal fluid acutely, and subsequent thinning. MRI scanning does not have a diagnostic role in NAION but could be considered in atypical cases (e.g., bilateral, lack of disc edema at onset, progression). Clinically, most patients demonstrate a vision loss that is fixed, but during the first month, visual improvement can occur (25). In the IONDT, the 5-year risk of second eye involvement was approximately 15% (26). The risk of second eye involvement was higher in older patients, and in patients with hypertension and diabetes (27).

The pathogenesis of the ischemia in NAION remains unclear. Hypoperfusion to the posterior ciliary arteries has been postulated (28). It is unknown how local atherosclerosis of the optic nerve head circulation with or without thrombosis, hypoperfusion, nocturnal hypotension, or a crowded optic nerve head culminates in an a NAION (29). It has also been postulated that the crowded disc configuration leads to a compartment syndrome that contributes to ischemia (30).

NAION has also been infrequently associated with antiphospholipid syndrome in younger patients, as well as uremia in patients on hemodialysis (31,32). Additionally, other factors that might interfere with optic disc perfusion or disc architecture such as migraine, disc drusen, hyperopia, and cataract surgery have also been associated with NAION.

No known proven therapy exists for the treatment of NAION. The use of steroids has not been proven to be an effective treatment, although their use is on occasion employed in clinic practice. The IONDT concluded that optic nerve sheath decompression was not helpful, and sometimes harmful, in the treatment of patients with NAION (33). Aspirin and hyperbaric oxygen were not proven to be effective treatments (34,35), as were intravitreal bevacizumab (36) and triamcinolone (37). The occurrence of prior NAION seems to confer a protective effect against the same eye, but this does not confer protection against second eye involvement (38). Most recently, the QRK207 NAION study, sponsored by Quark Pharmaceuticals Inc., in collaboration with NORDIC, is the first clinic trial designed to test therapy with potential to provide neuroprotection for acute optic nerve injury due to NAION. The study agent is QPI-1007, which is an interfering ribonucleic acid that resists apoptosis in cells by temporarily blocking caspase 2 (39). Patients that have met study criteria are currently being enrolled.

Diabetic papillopathy

Diabetic papillopathy usually presents in young type 1 diabetics (40). This represents an atypical form of NAION that presents with unilateral or bilateral disc swelling that results in minimal visual dysfunction and resolves spontaneously within weeks to longer than 18 months of onset. The mechanism behind this atypical disc swelling is unknown, but is thought to be due to poor perfusion of the optic nerve head. If the vision is affected, it typically improves with the resolution of the disc edema. Enlarged blind spots or arcuate defects can be seen on visual field examination. The disc edema presents with prominent telangiectatic vessels without neovascularization, and does not correlate with the degree of diabetic retinopathy. Visual recovery can be hastened by intravitreal or periocular steroid injection (41,42) but we do not recommend this. The pathogenesis of diabetic papillopathy is poorly understood, but is thought to represent a NAION variant.

AAION

GCA, also known as temporal arteritis, is the most common primary vasculitis of the elderly in the Western world (43). Visual symptoms due to GCA are a neuro-ophthalmic emergency. In up to 60% of patients, acute vision loss occurs (44). There is an increased prevalence in Caucasian women over 50 years old but it can affect individuals of either gender and other races (45). Prompt diagnosis and intervention with corticosteroids are of paramount importance to prevent blindness and stroke.

GCA affects large and mid-sized arteries, with a preferential effect on branches of the internal and external carotid arteries (46). Headache, the most common symptom in patients with GCA, is believed to be due to inflammation of branches of the external carotid artery (47).

Jaw claudication, which has been shown to be the most specific symptom of GCA, is a consequence of ischemia to the masseter muscle supplied by the maxillary artery (48). Ischemia of the retrolaminar portion of the optic nerve occurs at a watershed zone supplied by the posterior ciliary arteries and the ophthalmic artery (49). On pathology, necrosis of the internal elastic lamina of the vessel wall with granulomas containing multinucleated histiocytes and lymphocytes are seen. This marked inflammation causes direct occlusion or thrombotic occlusion of the affected vessels (50).

In AAION visual loss is usually acute and profound. Patients may also complain of prodromal symptoms of amaurosis fugax, pain, or diplopia. These symptoms would not be expected in NAION. Second eye involvement can occur in up to 75% of untreated patients within days (51). Many patients may have polymyalgia rheumatica, headache, jaw claudication, scalp tenderness, fever, malaise, and unintentional weight loss (52). Up to a fourth of patients with vision loss from GCA will have visual complaints only, without systemic symptoms (53). Because of its varied presentation, establishment of a diagnosis can be difficult and a high level of suspicion must be maintained.

On neuro-ophthalmic examination, AAION is the most common cause of visual loss due to GCA (54). Other causes of visual loss include posterior ischemic optic neuropathy (PION), non-embolic central retinal or cilioretinal artery occlusion, and choroidal infarction (55). In contrast to NAION, in AAION, the visual loss is often profound (56). Disc edema may be present or absent (AION *vs.* PION). When present, its classic appearance is one of chalky pallor, oftentimes associated with cotton-wool spots due to ocular ischemia. Additionally, the intraocular pressure may be reduced, and strabismus may be seen secondary to extraocular muscle or ocular motor cranial nerve ischemia (57,58).

The probability of GCA in patient over 50 years old can be established by the presence of the following criteria: (I) evidence of extracranial circulation ischemia (AION, PION, CRAO, ophthalmic artery occlusion); (II) new onset headache; (III) abnormal laboratory results (ESR, CRP, platelets); (IV) jaw claudication; (V) abnormal superficial temporal artery (pulseless, localized pain); (VI) constitutional symptoms (fatigue, malaise, fever, weight loss); and (VII) polymyalgia rheumatica (59). Patients who have one positive finding have low clinical suspicion, and an alternative diagnosis must be sought. Patients with at least two positive findings have moderate clinical suspicion and should be started on 1 mg/kg/d oral prednisone, and a temporal artery biopsy should be pursued within 2 weeks of steroid administration. Patient with 2 or more positive clinical findings have a high clinic suspicion, and should be started on IV steroids 1 g/day or oral steroids, and a temporal artery biopsy should be obtained. If the temporal artery biopsy is negative in patients with high clinical suspicion for GCA, a contralateral biopsy should be pursued (59). In most cases, a unilateral biopsy is sufficient in suspected cases of GCA (60), but in 3–5% of cases, there can be significant differences in the pathologic grade of disease from one side to the other (61). To emphasize, temporal artery biopsies should be pursued if there is even a moderate suspicion of GCA, and contralateral biopsies should be pursued if clinical suspicion is high. In an editorial review of the subject, Miller discussed the lower risk of the procedure compared with the significant risk of vision loss due to a missed diagnosis of GCA and concluded that bilateral simultaneous or sequential biopsies should be considered (62). Clinical judgment is also important, and not every patient with a low suspicion of GCA needs bilateral biopsies (63). Because of skip-lesions (portions of artery not affected by inflammation), a biopsy length of 3 cm or more is recommended (64). Of note, normal ESRs can be estimated as (age ×0.5) for men, and [(age +10) ×0.5] for women. An elevated ESR is a non-specific test, and can be found to be elevated in the setting of renal disease, lowered in patients taking non-steroidal anti-inflammatory agents and statins, and can be found to be normal in GCA (65). An elevated CRP is more sensitive test than ESR in the diagnosis of GCA (66), and when both CRP and ESR are elevated, there is a 97% specificity for the diagnosis of GCA (67). Fluorescein angiography may be used as an adjunctive test, as it can reveal delayed choroidal filling in GCA (68). Non-invasive vascular studies such as carotid Doppler of the superficial temporal artery are not sensitive and specific enough to be considered as providing significant diagnostic yield in the setting of GCA, and should not be employed as standard of care (69).

Corticosteroids remain the mainstay of treatment in patients with GCA, and should be initiated prior to temporal artery biopsy. Evidence has shown that prompt initiation of corticosteroids retards visual loss and may prevent second eye involvement in GCA. Some studies have demonstrated an improvement in vision with corticosteroid treatment, and this was found to be more significant in patients treated initially with intravenous corticosteroids versus oral steroids (70). The debate continues with some authors arguing that immediate administration of intravenous

steroids show no greater benefit than do oral steroids in the treatment of GCA (71,72). Controversy continues on whether patients with GCA should be treated with immediate high-dose oral versus intravenous steroids, with some consensus that a patient presenting with severe vision loss should be given at least 1 dose of intravenous steroids (73). If intravenous steroids are initiated, it should be at a dose of 1 gm/d, with elderly patients being hospitalized to minimize the risk of gastrointestinal (GI) and cardiac complications. In patients with risk factors for GI bleeding (e.g., ulcer disease), GI prophylaxis could be used. After IV administration for 3–5 days, an oral steroid taper should be employed at a dose of 1 mg/kg/d, and should be tapered over the next 10–12 months, and should remain high during the first month of treatment. Rheumatologic consultation for the management of prednisone sided effects, including osteoporosis and glucose monitoring, is of vital importance in this patient population. When tapering the corticosteroids, before the dose is dropped, the ESR level and systemic symptoms should be confirmed as stable. Despite careful corticosteroid tapering, there are cases of GCA that are refractory to treatment (74,75). Additionally, recurrence of ION was observed in patients on maintenance doses of prednisone, up to 3 years after initial GCA diagnosis (76,77). These cases present a therapeutic challenge. The immunopathology of GCA is under investigation for the consideration of future targeted therapies (78). Stone and associates reported the results of a Phase III study known as GiACTA (79) that evaluated tocilizumab, an IL-6 receptor antagonist, in people with GCA. The study met its primary and secondary endpoints, showing tocilizumab, initially combined with a six-month corticosteroid regimen, more effectively sustained remission through one year compared to a 6- or 12-month steroid-only regimen in people with newly diagnosed and relapsing GCA. However, their corticosteroid dosing regimen (80) was not typical high dose treatment for GCA with ocular symptoms or signs. Only 14% and 18% of their patient treated with prednisone alone for 26 and 52 weeks respectively achieved remission at 52 weeks. The question also remains as to the long-term efficacy of this regimen in preventing GCA relapse and whether there is adequate justification to use this extremely expensive medication.

Visual recovery for patients with GCA is poor (81), and progression can occur despite treatment with corticosteroids (82). Despite the devastating visual consequences, a recent review of visual performance and quality of life measures in GCA patients showed no significant difference in disability between patients with and without vision loss when only one eye was affected (83).

PION

PION is far less common than AION, and should prompt systemic investigation. PION patients can be broken down into two main groups: (I) secondary to GCA and (II) perioperative vision loss (84). PION due to just vascular risk factors (hypertension, diabetes) is very and extreme caution should be taken if considering this as a diagnosis. PION presents with acute vision loss secondary to an optic neuropathy of the retrolaminar optic nerve, without disc edema, which progresses to optic atrophy. In the diagnosis of PION, neuro-imaging is required to exclude compressive or infiltrative lesions. In elderly patients with PION, investigations for GCA must be pursued (85). Additionally, infectious and inflammatory causes of PION have been elucidated including herpes, varicella, lupus, and polyarteritis nodosa (86,87). In patients with perioperative PION, coronary artery bypass and lumbar spine procedures were most commonly associated (88,89), as well as episodes of hypotension or severe bleeding (further detail given in section below).

Ischemic optic neuropathy in the setting of hemodynamic compromise

Optic nerve infarction can incur under the combined effects of severe blood loss, hypotension, and anemia. Under these circumstances, the vision loss is usually bilateral, and severe. The vision loss can present acutely after the event, or may present days later. Perioperative vision loss is most commonly associated with spine surgery and cardiac surgery (88,89), and has also been reported with radical neck dissection (90). This disorder may occur in an anterior ischemic or a posterior ischemic form, disc swelling versus no disc swelling, respectively. Predisposing risk factors include vasculopathic risk profile, crowded disc, long operative time, prone positioning, the use of the Wilson frame, anemia, and hypotension. There has been no identifiable blood pressure threshold associated with this condition, but once recognized, correction of hemoglobin less than 8 mg/dL, although unproven could be undertaken. Similar vision loss can present in patients with renal failure with chronic anemia and dialysis (91). While normalization of volume status and anemia is a reasonable therapeutic approach, no treatment has been proven effective, and

visual prognosis is poor.

Summary

NAION is by far the most common type of ischemic optic neuropathy encountered. Unfortunately, no proven treatment for NAION exists. One must always consider GCA if AION occurs. Detailed questioning regarding symptoms of GCA and blood tests (ESR, CRP, CBC with platelets) should be considered. If temporal artery biopsy is scheduled, always start corticosteroids immediately. PION usually occurs in either the setting of GCA or perioperatively. One should be very cautious in making this diagnosis in any other setting.

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