ESSENTIALS OF ISCHEMIC OPTIC NEURITIS

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ABSTRACT

Since neurology implies often a multidisciplinary approach, and some specific of neurological entities implies the creation of subgroups of sub-specialties, such as neuroophtalmology and neurootorinolaringology, it is therefore important for the neurologist to approach pathologies being at frontier of specialties. Ischemic optic neuritis is the most often optic neuropathy in patients above 50. The aim of this short review is to focus on some aspects of ischemic optic neuritis, an entity frequently encountered in clinical practice but less known by the general neurologist.
Key words: optic neuritis, ischemic, optic nerve

Neurology is a specialty with a broad spectrum of pathologies, which often implies a multidisciplinary approach. The specific of neurological diseases implies the creation of subgroups of sub-specialties, such as neuroophtalmology and neurootorinolaringology. Often, in clinical settings, is difficult to have an accurate and competent opinion in these fields, because one can be a good specialist in his own field, without having the knowledge for interference pathologies.

Thus, it is important for neurologists to know entities that are at the frontier between specializations, as optic neuropathies. In patients with ages older than 50 years, ischemic optic neuritis (nevrita optica ischemica, NOI) is the most frequent acute optic neuropathy (1).

The aim of this short review is to focus on some aspects of ischemic optic neuritis, frequently encountered in clinical practice but less known by the general neurologist.

SHORT ANATOMY RECALL OF THE VASCULARISATION OF THE EYE

We can not understand NOI without an anatomical recall of the vascular supply of the eye.

a. The retina has a dual vascular blood supply feeding: from the choroidal and central retinal circulations, both occurring from the ophthalmic artery, the very known branch of the internal carotid artery.
b. The optic nerve head is supplied by the short posterior ciliary arteries and an anastomotic circle known as the circle of Zinn-Haller (2). The circle of Zinn-Haller is made of short posterior ciliary arteries, branches of the pial arterial network, and choroidal vessels.
c. The posterior optic nerve has a blood supply that can be divided into intraorbital, intracanalicular, and intracranial groups of vessels.
d. The intraorbital optic nerve is subdivided into anterior and posterior segments by the point of entry of the central retinal artery. The anterior segment has two vascular systems: a peripheral, centripetal vascular system formed by the pial vascular plexus and an axial, centrifugal vascular system supplied by branches of the central retinal artery. The posterior segment is supplied by the pial plexus, as the intracanalicular optic nerve and the intracranial portion of optic nerve, formed by branches of the ophthalmic artery. The pial plexus is arising from variable and inconsistent branches of surrounding arteries, mainly for the intracranial part.

CLASSIFICATION

NOI can be classified in accordance with the location of the optical nerve ischemic damage into anterior and posterior. Anterior ischemic optic neuritis (NOIA) implies the optic nerve head and ophthalmoscopically there is observable optic disc edema. On the other hand, posterior ischemic optic neuritis (NOIP) involves the retrobulbar optic nerve, and in this case ophthalmoscopy can reveal a normal-appearing optic disc (3).

In accordance with the type of arteries implied in the etiology of NOI, these entities can also be categorized varying with the presence or absence of temporal arteritis as an underlying etiology. It is very important to differentiate the nonarteritic anterior ischemic optic neuropathy (NOIANA) from the arteritic anterior ischemic optic neuropathy (NOIAA) not only because they show differences in their presentation, course, and management, but also because NOIAA is due to temporal arteritis and, thus, is an ophthalmological emergency. The under recognition of NOIAA and the lack of appropriate treatment may be followed by devastating blindness.

TYPES OF ISCHEMIC OPTICAL NEURITIS

1. Anterior Ischemic Optic Neuritis (NOIA)

Clinical presentation

NOIA is characterized by painless vision loss developing over hours to days. On examination, findings include decreased visual acuity, color vision loss, and a visual field defect. The pupil in the affected eye is slowly reactive with a relative afferent pupillary defect. At the onset, the papila is edematous, becoming pale as the edema subsides. The severity and characteristics of these findings vary depending on whether the patient has NOIAA or an NOINA.

Arteritic anterior ischemic optic neuritis (NOIAA)

NOIAA accounts for 6% of cases of NOIA, and white female patients have a higher risk. The most frequent pathology causing AION is temporal arteritis (giant cell arteritis, that affects mainly white women older than 65 years (annual incidence 2/10.000) (4). It is important to emphasize that NOIAA may be seen in vasculitic conditions other than giant cell arteritis, including herpes zoster, polychondritis, rheumatoid arteritis, and Churg-Strauss syndrome (3).

Giant cell arteritis is a granulomatous vasculitis that affects medium and large arteries (5). In NOIAA, there is granulomatous vasculitis of the short posterior ciliary vessels in addition to variable involvement of the superficial temporal, ophthalmic, central retinal, and choroidal arteries. Ischemic necrosis is observed in the laminar and retrolaminar portions of the optic nerve supplied by the vasculitic vessels (3). The etiology of temporal arteritis is unknown. Genetic susceptibly, antigen-driven autoimmunity, and hormonal changes have all been proposed as factors in the development of temporal arteritis (3, 8). NOIAA is the most common cause of vision loss in temporal arteritis, but other less frequent causes of vision loss in temporal arteritis patients are central retinal artery occlusion, branch retinal artery occlusion, and NOIP (5). The mean age of onset for NOIAA is 70 years, but it can occur from ago of 60 years (6, 7).

From a clinical point of view, NOIAA presents with rapid onset of severe visual loss, associated with pallid optic disc edema. A context of systemic symptoms of headache, jaw claudication, and scalp tenderness are suggestive of temporal arteritis. Visual acuity is worse than 1/10 in 57-76% of patients (3, 9, 10). Severe loss of visual acuity (between counting fingers and no light perception) is initially present in 54% of patients, versus 26% of NOIANA patients (3). In this respect, severe visual loss at presentation is extremely suggestive of NOIAA. Although vision loss is typically unilateral, bilateral vision loss occurs and is more common in NOIAA than in NOIANA. Transient vision loss (amaurosis fugax) precedes sustained vision loss in 30% of cases and is highly suggestive of temporal arteritis (3). Transient diplopia, secondary to ischemia of the muscles or cranial nerves, may precede vision loss in 5 to 10% of cases (11).

Edema of the optic disc is typically pallid and may be chalky white in severe cases, because of the diffuse nature of ischemic vasculitis (3, 12-14). Cilioretinal artery occlusion may occur simultaneously in 21% of patients (12). If concurrent retinal ischemia with cotton-wool spots and retinal arterial occlusion is encountered in a NOIA patient, it is highly suggestive of temporal artentis (16). The multifocal nature NOIAA often leads to involvement of posterior ciliary and choroidal circulations, as shown by fluorescein angiography who reveal generalized choroidal filling delay with involvement of the short posterior ciliary arteries (15, 16). When extensive choroidal hypoperfusion is identified, an arteritic etiology should be suspected (17, 18).

Even that NOIAA may present with only visual complaints (more that 20% of patients present without any systemic symptoms or signs), it typically occurs in association with systemic manifestations like

headache (often severe, is the most common symptom, encountered in 55.7% of patients with positive temporal artery biopsies) (3). Jaw claudication is also frequent and very specific for NOIAA, affecting also the neck muscles and tongue as well (4). Other signs as scalp tenderness, anorexia, weight loss, malaise, anemia, and fever may precede visual loss. Local signs such as nodularity of the temporal artery, induration of the temporal region, and absence of the temporal pulse may be observed (3). Polymyalgia rheumatica is reported in association with AAION with some frequency (19).

Temporal arteritis is an ophthalmic emergency because it is associated with a high risk of severe vision loss in the fellow eye and early aggressive treatment may prevent it (3). The hematological indicators useful in the diagnosis of temporal arteritis include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, and platelets. It is well established that the ESR is elevated in temporal arteritis, and its value is an important diagnostic test (3). The normal ESR increases with age, and women tend to have a higher ESR than men. Most cases of NOIAA present with an ESR more than 70 mm/h and often more than 100 mm/h. Interpretation of the significance of the ESR is more challenging when the level is not clearly elevated. Miller et al derived an empiric formula for calculating the upper normal level: age in years divided by 2 in men and age in years plus 10 divided by 2 in women (21). Interestingly, NOIAA associated with normal or low ESR and positive biopsy has been reported in 30% of cases (3, 21). The ESR may be affected by a variety of other causes like anemia, inflammatory disease, malignancy, infection, connective tissue disease, hypercholesterolemia, and other conditions and is considered to be a nonspecific indicator of disease (22). Elevation of CRP has been also proposed as another good indicator of the NOIAA, and C-reactive protein levels may become elevated within 4 to 6 hours after an injury (23). Unlike ESR, CRP levels are not influenced by hematological factors or age.

These characteristics make the CRP more sensitive but nonspecific as well (3). CRP have a specificity of 97% in patients with levels above 2.45 mg/dL (23). Fibrinogen and platelet levels are also elevated in temporal arteritis. Thrombocytosis has been shown to be a marker for positive temporal artery biopsy and may be a predictor of visual loss (24). The risk of permanent visual loss is high in patients with platelet counts > 600 x 109/L (3).

Biopsy of the temporal artery is the definitive diagnostic test in temporal arteritis. Biopsy confirmation is essential because long-term immunosuppressive therapy is the standard treatment (3). A negative biopsy does not rule out the diagnosis because false-negative results are possible. Because temporal arteritis may affect arteries discontinuously („skip lesion“) it is recommended to perform a biopsy of 3-to-6 cm length (25). Another reason for a false-negative biopsy is unilateral involvement with biopsy of the normal side (25). The false-negative error for unilateral biopsy has been estimated to be as high as 5 to 11% (3, 25). Controversy exists with regard to unilateral versus bilateral biopsy, but it is advocated that bilateral simultaneous biopsy is unnecessary and biopsy of the second side is done when the first biopsy is negative and high clinical suspicion persists (3).

In the differential diagnosis of NOIAA, acute optic neuropathy secondary to optic neuritis or infiltrative optic neuropathy should be considered and neuroimaging studies may be important to rule out an orbital mass in atypical cases (3).

In what concerns the management, initiation of therapy should not be delayed by waiting the performing of the biopsy. When temporal arteritis is suspected, treatment should start immediately to diminish the risk of further vision loss in the affected eye as well as involvement of the fellow eye. The histopathological changes in affected arteries may remain beyond 2 weeks after steroid initiation (26, 27). Systemic corticosteroids should be promptly started in the setting of vision loss: high-dose (1-2 g/d) intravenous methylprednisolone for 2 to 3 days followed by high-dose oral prednisone (1-2 mg/kg/d) (26, 27). Maintenance therapy with high-dose steroids should continue for 4 to 6 weeks until normalization of the systemic symptoms and laboratory findings (26, 27). The steroids should be tapered slowly, ~10 mg/mo initially, decreasing 5 mg/mo until reaching 10 to 15 mg/d. This low dose is maintained for 6 to 12 months (26, 27). The response of systemic symptoms to steroids is typically rapid: in 24 hours, the patient may experience relief of headache and malaise (26, 27). There is recovery of some degree of the visual function in the affected eye (in 4-34% of patients), although the visual field may remain severely constricted (26, 27). The main objective of treatment is prevention of systemic complications and contralateral vision loss (3). Without treatment, second eve involvement occurs in 50 to 95% patients (28, 29). The risk of recurrent or contralateral optic nerve involvement

during steroid taper has been reported at 7% (28, 29). If it is the case, the dose of steroids should be elevated immediately, as with the relapse in the same eye (28, 29). Methotrexate as adjunct therapy or a steroid-sparing agent has been evaluated, with conflicting results (30, 31). Because thrombocytosis is often present in temporal arteritis, the use of antiplatelet therapy has been suggested to be beneficial (32).

Nonarteritic Anterior Ischemic Optic Neuritis (NOIANA)

NOIANA means an infarction of the optic nerve head caused by inadequate perfusion through the posterior ciliary arteries in the absence of vasculitis (3). The typical patient tends to be younger than those with arteritis, and the visual loss is usually less severe. Diabetes mellitus and hypertension are present in many of these patients (3). NOIANA accounts for 94% of NOIA patients (3). The annual frequency is 2-10/100.000 for persons older than 50 and 0.5/100.000 for all ages (33, 34). NOIANA occurs usually between the ages of 57-65 years, but cases in children, young adults, and older patients are reported, with a mean age for all patients of 66 years, with a peak range of 60 to 70, and mainly in white people (35).

As clinical presentation, NOIANA can be manifested by blurred central vision, peripheral scotoma, or both. Loss of vision loss is unilateral, painless, occurring over hours to days and associated with optic disc edema (3). The vision loss is reported as a blurring or cloudiness in the affected visual field, and it is infrequent to see transient visual loss as premonitory sign (36). The NOIANA visual acuity loss is usually less severe than NOIAA, even it may range from 10/10 to light perception (3). 58-61% of patients have a visual acuity of 1/100 or better, and visual acuity is better than 1/3 in 30-50% of patients (3). The color vision is diminished in almost all patients on the affected side (more than 55%) and seems to correlate with the degree of vision loss (3). In contrast, inflammatory optic neuritis patients may have profound color vision loss with relatively good visual acuity. Also, every eye with NOIANA has a relative afferent pupillary defect unless an optic neuropathy or significant retinopathy is present in the fellow eye (3).

Disc edema may be diffuse or segmental, encountered diffuse in 75% of cases and segmental in 25% of patients, and usually involves the superior portion of the optic disc (3). Segmental disc edema has been attributed to the anatomic division of the circle of Zinn-Haller (3, 37). Another findings are the presence of a small optic nerve with a small or absent physiological cup in the unaffected eye and flame hemorrhages in 72% of patients and arteriolar narrowing adjacent to the optic disc in almost 20% of cases (3).

An altitudinal visual field defect is seen in 58-80% of patients (46% inferior), but central visual field defects are also encountered in 20% (3). A combination of relative inferior altitudinal defect and absolute inferior nasal defect is, apparently, the most common pattern in patients with NOIANA, and an absolute inferior nasal visual field defect is more common than an absolute inferior altitudinal defect (38).

Fluorescein angiography shows delayed filling of the prelaminar layers of an edematous optic disc in 76% of NOIANA patients. This observation was not present in patients with nonischemic optic disc edema, suggesting that the delayed filling represents a primary ischemic event rather than a mechanical process secondary to obstruction from the disc edema (3). In some NOIANA patients, the overlying disc surface vasculature that derives from the retinal arterial circulation, shows sector dilatation and early fluorescein filling, maybe representing a manifestation of shunting to relatively spared regions of the optic disc (3).

As prognosis, NOIANA generally remains stable, showing no significant improvement or deterioration over time, but within 4 to 6 weeks, the optic disc becomes atrophic, and persistent edema beyond 6 weeks should point to an alternative diagnosis. Recovery of at least three lines of visual acuity has been reported in 43% of the patients, but also 12% lost three or more lines of vision at 6 months of follow-up (3, 39, 40). After stabilization of vision, progressive vision loss in an affected eye is unusual, unless there is a recurrence, reported in 3.6 - 6.4% of patients (3, 41). The risk of sequential NAION in the second eye is 15% within 5 years (40, 41).

Concerning the etiology and the risk factors of NOIANA, the mechanism of development of the optic disc ischemia is unclear. Several factors are thought to play a role, including a small optic disc, nocturnal hypotension, sleep apnea, systemic or local vascular disease, some medications, and a combination of these conditions. 60% of patients have risk factors associated with small-vessel occlusive cerebrovascular disease including hypertension, diabetes mellitus, and cigarette use.

Absence of the optic cup or a small optic disc is consistently associated with NAION (3). It is a key finding noted by examination of the optic nerve in the unaffected eye (3). The physiological cup

corresponds to the size of the scleral canal, and „crowding“ of the optic nerve in this canal is thought to lead to a vicious cycle where swelling of the nerve leads to further compression of the vasculature and worsening ischemia (3, 42).

Some authors have proposed that nocturnal hypotension may be a risk factor for development of NOIANA (43). They suggested that patients with significant nocturnal hypotension those with systemic hypertension whose autonomic regulatory mechanism is impaired by antihypertensive therapy may have a compromise in the optic circulation (43). Patients with NOIANA have a lower daytime mean blood pressure and lag in the usual rise blood pressure in the morning (44). In this spirit, abnormal vascular autoregulation or over treated hypertension may lead to chronic hypoperfusion that predisposes to NOIANA (3). Also, a relationship of sleep apnea with NOIANA has been reported but is not well understood (3, 45).

Systemic diseases associated with an increased risk NOIANA include hypertension (34-49%) and diabetes (5-25%) (3). Ischemic heart disease, hypercholesterolemia, stroke, tobacco use, and systemic atherosclerosis have also been associated with the disease, mainly for patients younger than 50 years old. Even unclear until now, apparently there is an increased risk of cerebrovascular disease in patients with NOIANA who also have hypertension and diabetes (3). On the other hand, even NOIANA may be caused by internal carotid artery disease, it is important to consider carotid artery stenosis to be a sign of widespread atherosclerosis affecting the vascular system (3). NOIANA is associated with intraocular surgery, and thought to be caused by increased intraocular pressure with decrease optic nerve head perfusion (45).

The medications implicated in the pathogenesis of NOIANA include sumatriptan, sildenafil, and nasal decongestants, but it is important to note that most NOIANA patients taking such medications have concurrent vascular risk factors and a small optic nerve (47, 48, 49, 50).

Apparently, plasma levels of homocysteine are significantly elevated in some of the NOIANA patients, but this is not confirmed (51). Isolated reports have documented prothrombotic risk factors in patients with NOIANA, but larger scale studies have not confirmed an association with lupus anticoagulant, anti cardiolipin antibodies, prothrombotic polymorphisms (factor V Leiden), and deficiencies of proteins C and S and antithrombin III. Even these associations are not widespread, it is possible that they contribute to individual cases (3).

Even that the NOIANA pathogenesis is not clear, it is generally accepted that it involves hypoperfusion with ischemia of the retrolaminar optic nerve. Vasospasm and impaired autoregulation of blood flow in the optic disc vasculature may play a role (3). The autoregulatory mechanisms may be reduced by vasospasm, medications, or vascular disease, leading to hypoperfusion of the disc circulation (3).

Differential Diagnosis. The main differential diagnosis in patients younger than 50 years of age is inflammatory optic neuritis. Other important conditions are infiltrative optic neuropathy and compressive anterior orbital lesions. In patients older than 50 years, the main differential consideration is NOIAA, as shown before. In this respect, patients older than 60 years with NOIA and without symptoms or signs of giant cell arteritis should have an ESR and CRP measured, and evaluation of the patient for management of vascular risk factors is desired (3).

Treatment. Aside from correction of any acute problems (anemia, hypotension etc.), there is no proven treatment. Surgical decompression and medical therapies have been proposed, but none has been shown to be effective (3). Surgical decompression for NAION is not recommended (3). Medical therapies have been studied without definitive beneficial results (phenylhydantoin, subtenon vasodilators, intravenous norepinephrine, levodopa, aspirine, anticoagulation, corticosteroids) (3). Contradictory data emerged from various studies, suggesting but still not confirming some benefit for levodopa (3).

Aspirin is beneficial in the general prevention of vaso-occlusive disease, and can decrease incidence and relative risk of second eye involvement with NOIANA, regardless of the usual risk factors. Studies suggested a possible short-term benefit but little or no long-term benefit with aspirin in reducing the risk of NOIANA in the fellow eye (3). There is a report of transvitreal optic neurotomy performed in seven cases of NOIANA with severe vision loss, with improvement of visual acuity noted in six patients, but the authors emphasized the experimental nature of the technique (52). Megadose steroid treatment may have a neuroprotective effect of the NOIANA affected optic nerve, but has not been well studied (53). Recently, the use of intravitreal triamcinolone (Kenalog) for the treatment of acute NOIANA, was not sustained as markedly effective in such patients (54).

2. Posterior Ischemic Optic Neuropathy (NOIP)

NOIP is characterized by acute vision loss, initially associated with a normal optic disc that later becomes atrophic. Sometimes, a small amount of disc edema can be observed as a result of migration of the swelling forward along the course of the optic nerve from the original point of ischemia (3).

Ischemia of the retrobulbar portions of the optic nerve may occur in both arteritic and nonarteritic settings.

There is a classification of patients into three groups: the arteritic group, the nonarteritic group, and a related-to-surgery group (including coronary bypass and lumbar spine procedures) (55).

Clinical Manifestations

Both arteritic and nonarteritic NOIP typically present with acute, painless vision loss in one or both eyes (3). Patients with surgical NOIP note vision loss when they are alert following surgery. Vision loss in postsurgical NOIP is usually bilateral, severe, and, many times, irreversible. Vision loss in nonarteritic cases is less severe than in the other two forms, and 34% of patients are showing some improvement.

Important, no optic disc or fundus abnormality is present at the onset of symptoms, but the disc develops pallor within a few weeks (56). Fluorescein angyography is also normal. A central defect is the most common visual field defect in NOIP patients (56). Vision loss may be related to the anatomy of the optic nerve (3). Optic nerve fibers become realigned as they project into the posterior optic nerve. In the optic nerve head, macular fibers are located temporally (3). In the posterior optic nerve, the retinal ganglion cell axons from the macula are located in the central region of the optic nerve (3). The implication of this arrangement is that segmental ischemia of the optic nerve head is likely to produce a visual field defect different from the ischemia of the posterior optic nerve (3). The axial region in the posterior part of the optic nerve is considered to be a watershed zone, which makes it more susceptible to ischemic damage than the peripheral optic nerve (3). This is a possible explanation for the common occurrence of a central visual field defect in NOIP (3).

Pathogenesis

Arteritic NOIP. Temporal arteritis is the most common etiology of arteritic NOIP (57). This etiology should be considered in any elderly patient who loses vision acutely with a normal-appearing fundus in the affected eye (3). It was already disscused the management of this etiology, identically as for NOIAA.

Nonarteritic NOIP. The pathogenesis of nonarteritic NOIP, like NOIA, is multifactorial, with a wide variety of systemic disease and vascular risk factors involved (3). There is an increase in the prevalence of arterial hypertension, diabetes mellitus, ischemic heart disease, carotid artery disease, peripheral vascular disease, and vasospastic diseases (migraine) in patients with nonarteritic NOIP (57). This association does not necessarily imply a cause-and-effect relationship, but they constitute risk factors for the development of the NOIP (3). There is no known therapy for nonarteritic NOIP (3). Some authors suggested a possible beneficial effect on visual function of aggressive systemic steroid therapy during the very early stages of the disease (56).

Surgical NOIP is multifactorial (3). The main risk factors are thought to include severe prolonged arterial hypotension, hemodilution, orbital edema, and orbital compression (3). A large number of surgical PION cases have been published, most of them associated with prolonged systemic surgical procedures such as orthopedic and spinal surgeries, radical neck dissection, coronary artery bypass, and hip surgery (58, 59). The perfusion pressure in a tissue depends on the difference between the arterial and venous pressures, and it is speculated that in NOIP patients, increased orbital venous pressure caused by marked increased orbital edema and consequent increased intraorbital pressure along with simultaneous arterial hypotension is thought to result in reduced blood flow to the optic nerve (3, 58, 59).

Although no treatment has been found to be effective to recover or improve the lost vision after a surgical NOIP, anemia and hypotension should be identified and corrected (3). During surgery, efforts should be made to prevent hypotension, hemodilution, pressure over the eye, and prolonged surgical time (3).

Concluding, we had seen that various types of NOI can differ in their clinical presentation, diagnosis, course, and management. The vigilance of the neurologist should be combined with the presence of an ophthalmologist in the management and evaluation of these patients. It is important to note that usually, the ophthalmologist only suggests the ischemic character of optic neuritis, but doesn't classifies the NOI as a subtype. The differences between subtypes of NOI are important not only in the settings of management, but also considering the expectance of the patient, who should be informed according to the known prognosis of specific NOI subtype.

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