Title: Ischemic Optic Neuropathy: A Review **Author:** Dr. Naida Jakirlic

Learning Objectives

1. Review the anatomy and vascular supply of the optic nerve.
2. Identify cardinal signs of optic nerve dysfunction.
3. Identify key clinical considerations related to non-arteritic anterior ischemic optic neuropathy.
4. Identify key clinical consideration related to arteritic anterior ischemic optic neuropathy.
5. Review important laboratory tests necessary for the appropriate workup of non-arteritic and arteritic ischemic optic neuropathy.

Introduction

The optic nerve is the anterior-most component of the visual pathway. It is composed of approximately 1.2 million axons whose cell bodies are located in the ganglion cell layer of the retina[9,11]. The ganglion cell axons of the optic nerve synapse in the lateral geniculate body, pretectum, superior colliculus, accessory optic nuclei, and the suprachiasmatic nuclei of the hypothalamus[9]. Four anatomic sections of the optic nerve are recognized, including the intraocular, intraorbital, intracanalicular, and intracranial sections[9,11].

The intraocular section of the optic nerve is approximately 1mm in length[9]. It is the part of the optic nerve that can be visualized and photographed clinically during a routine eye exam. Most diseases of the optic nerve will result in characteristic changes of the intraocular optic nerve that can be observed clinically without any specialized equipment. This positions the primary care optometrist at the forefront of recognizing pathologies of the optic nerve during a routine eye exam and initiating the appropriate workup when warranted. Changes of the intraocular optic nerve that may be observed clinically include disc hemorrhages, swelling, pallor, and cupping of the optic nerve.

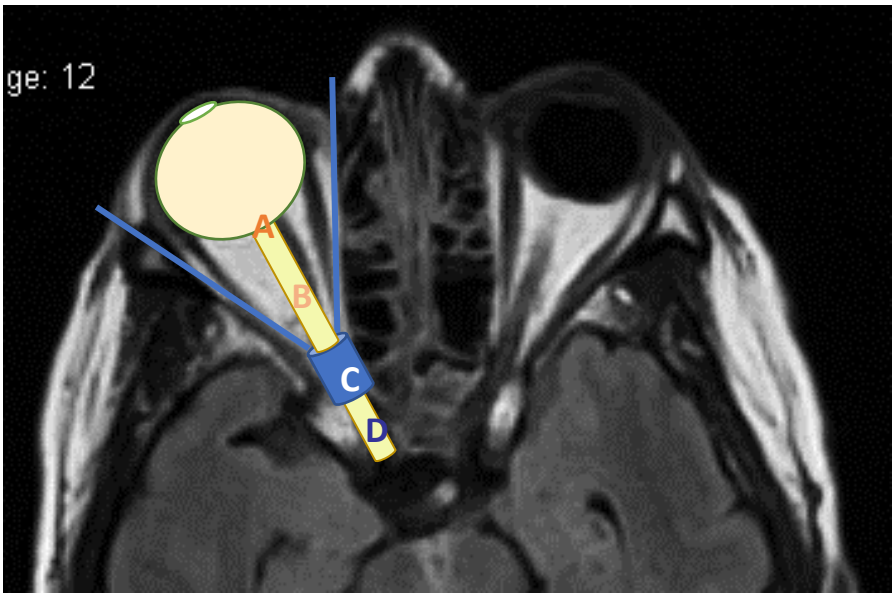
The intraorbital section of the optic nerve begins once the optic nerve axons pass through the lamina cribrosa. The intraorbital section of the optic nerve is approximately 25mm in length, allowing for the optic nerve to take on an “S” shape to prevent stretching during extraocular motilities[9]. The optic nerve becomes myelinated posterior to the lamina cribrosa, which is an important anatomic feature that makes the nerve vulnerable to changes in intracranial pressure and demyelinating disorders of the central nervous system. Due to limited space within the orbit, the intraorbital optic nerve can also suffer damage from muscle engorgement that can occur in thyroid orbitopathy.

The intracanalicular section of the optic nerve is approximately 10mm in length[9]. This portion of the optic nerve lies within the optic canal and is particularly vulnerable to fractures resulting from trauma and damage from adjacent sinus inflammation.

The intracranial section of the optic nerve is about 10mm long and spans the distance between the intracranial opening of the optic canal and the optic chiasm[9]. The intracranial section of the optic nerve is vulnerable to ischemia, compression, and demyelination, all of which can result in retrograde changes that are visualized in the intraocular section of the optic nerve.

Figure 1 provides a schematic of the four sections of the optic nerve superimposed over an MRI of the orbits.

Figure 1: MRI of orbits with superimposed schematic demonstrating the four anatomic sections of the optic nerve. A: intraocular, B: intraorbital, C: intracanalicular, D: intracranial



The vascular supply of the optic nerve varies throughout the length of the nerve. The surface retinal nerve fiber layer (RNFL) is supplied by branches of the retinal arterioles[7,11]. The prelaminar optic nerve is supplied by branches of the posterior ciliary arteries (PCAs)[7,11]. There are typically two to three PCAs that lie medial and lateral to the optic nerve[7]. The PCAs branch into about 20 short PCAs (sPCAs) that provide vascular supply to the prelaminar optic nerve and the choroid[7]. The sPCAs form a collateral circle, known as the Circle of Zinn Haller, to supply optic nerve axons as they pass through the lamina cribrosa[7]. The retrolaminar optic nerve is supplied by pial vasculature, branches from the ophthalmic artery, and branches from the central retinal artery[7].

When discussing the vasculature of the optic nerve, it is important to consider the phenomenon of watershed zones. A watershed zone is the border between the territories of any two end-arteries[6,7]. This zone is critical because in the event of a drop in perfusion pressure in the vascular bed of any end-artery, the watershed zone is the most vulnerable to ischemia[7]. In most individuals, at least one watershed zone passes through the optic nerve. However, there is significant variability in the location of the optic nerve watershed zones, thus leading to a wide range of clinical presentations caused by the same pathologic process of decreased vascular perfusion to the optic nerve[7].

Signs of Optic Nerve Dysfunction

Optic nerve dysfunction will typically result in clearly recognizable clinical findings. Patients who present with an optic neuropathy of any etiology will have a variable degree of visual acuity loss, dyschromatopsia, reduced contrast sensitivity, visual field (VF) loss, and abnormal Visually Evoked Potentials (VEP)[9,11]. If the optic neuropathy is unilateral or asymmetric, there will be a relative afferent pupillary defect (RAPD) present in the affected eye[9]. Any combination of the above findings should make one highly suspicious for a pathologic process of one or both optic nerves. The severity and rate of onset of each clinical finding will help clinicians narrow their differential diagnosis to a manageable list of potential causes that should result in a targeted workup of each patient.

The clinical findings will differ according to the etiology of each optic neuropathy. The onset of visual acuity and visual field loss is typically acute in cases of optic neuritis and ischemia, while it is usually gradual in cases of compressive and toxic/nutritional insults to the optic nerve[2]. Unilateral vision loss is more commonly seen in typical optic neuritis and non-arteritic anterior ischemic optic neuropathy (NAION). Bilateral vision loss is typically seen in toxic/nutritional optic neuropathy, hereditary optic neuropathy, and arteritic anterior ischemic optic neuropathy (A-AION).

The pattern of VF loss will also help guide the clinician to the most probable etiology. NAION typically results in altitudinal VF loss while toxic/nutritional and hereditary optic neuropathies often result in centro-cecal VF loss[2]. Compressive lesions of the optic chiasm typically result in bitemporal VF loss. Homonymous hemianopic VF defects point to compressive or ischemic lesions of the visual pathway posterior to the optic chiasm.

Figure 2: Examples of VF loss. A: centro-cecal VF defect caused by dominant optic atrophy; B: bitemporal VF defect caused by a compressive lesion of the optic chiasm; C: altitudinal VF defect caused by NAION.

Figure 2, Example A:

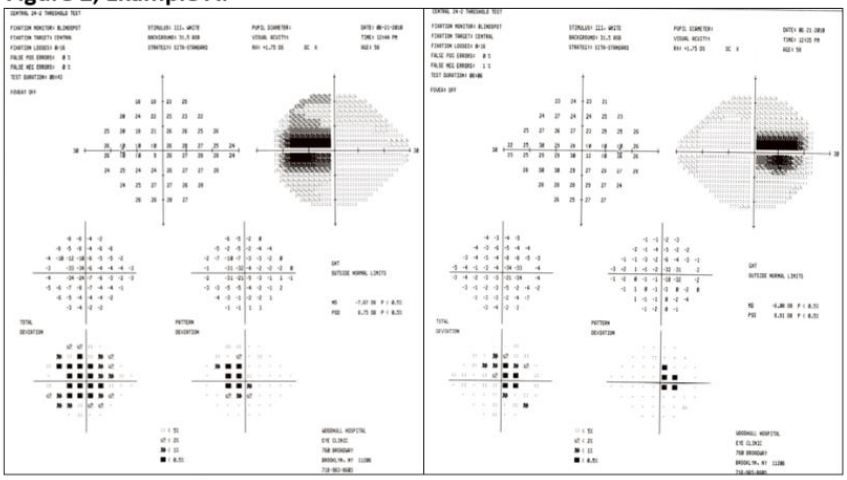


Figure 2, Example B:

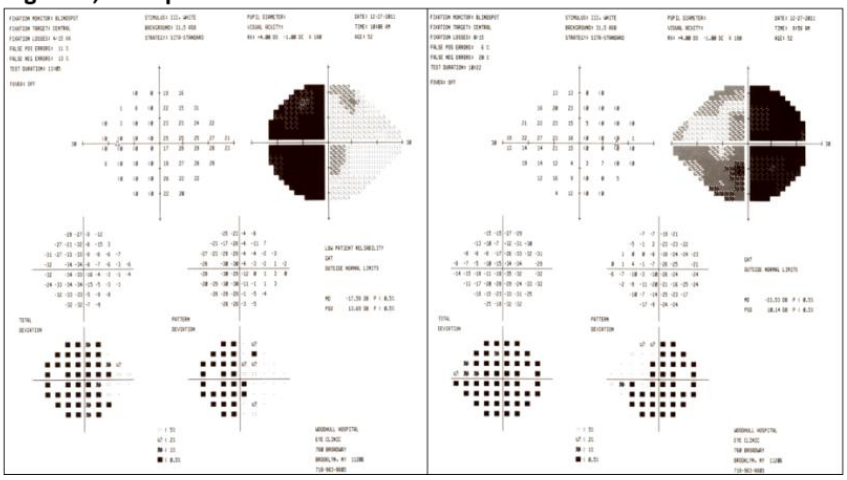
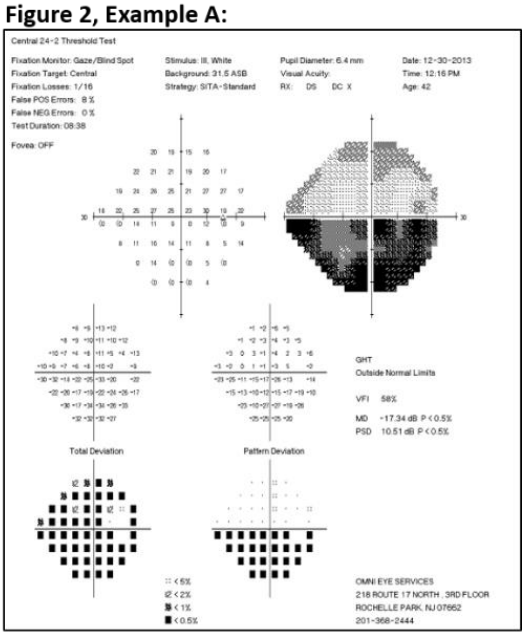


Figure 2, Example A:



Bloodwork Review

To prepare for the discussion that follows, it is important to briefly review the most common blood tests that are ordered in the workup of certain optic neuropathies.

Complete blood count (CBC) with differential gives the clinician a comprehensive overview of the patient's general health. It provides specific information about red blood cells, white blood cells, and platelets. It can detect underlying bacterial and/or viral etiology if leukocytosis and/or lymphocytosis is present. The platelet count is useful in the diagnosis and management of blood clotting disorders and is usually elevated in the presence of giant cell arteritis[1].

The glycosylated hemoglobin test (HbA1c) gives the percentage of free glucose bound to hemoglobin in red blood cells. The average lifespan of a red blood cell is three months, therefore the HbA1c is a relatively accurate estimate of a patient's average blood glucose over a 90-day period. Normal HbA1c values are 5.7% or lower.

Erythrocyte sedimentation rate (ESR) is a measurement of the rate at which erythrocytes settle in a standard tube in 1 hour. Elevated ESR values indicate general inflammatory activity in the body. All

laboratories will provide their normal ranges with the bloodwork results; however, a simple formula for normal ESR values that is widely utilized is: age/2 for men, age+10/2 for women[11]. The use of statin medications and non-steroidal anti-inflammatory medications may lower the ESR values, therefore caution must be exercised when ESR laboratory values are normal in patients with high clinical suspicion for any inflammatory conditions, particularly giant cell arteritis[5].

C-reactive protein (CRP) is a non-specific marker for inflammation within the body. It is an acute-phase protein that is produced by the liver during acute and chronic inflammation and infection[1]. Unlike ESR, CRP is not influenced by a patient's age or hematologic factors, therefore it is a more sensitive and reproducible laboratory value in giant cell arteritis than ESR[1]. The CRP value should be < 1 mg/dL regardless of the patient's age and gender. When ordered with ESR, there is 97% specificity for diagnosis of giant cell arteritis[11].

Ischemic Optic Neuropathies

I. Non-Arteritic Anterior Ischemic Optic Neuropathy (NAION)

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common cause of unilateral optic nerve swelling in patients over 50 years of age[9,11]. It is caused by a vascular insult to the pre-laminar and retro-laminar optic nerve[3]. The typical clinical presentation is that of acute painless vision loss in one eye upon waking due to insufficient perfusion to the optic nerve[11].

NAION results from vascular changes in patients with cardiovascular risk factors. Chronic hypertension causes alteration in the autoregulatory response of the optic nerve vasculature[6]. Vasodilation fails to occur during periods of decreased blood pressure, which typically occurs at night due to the phenomenon of nocturnal hypotension. This leads to decreased perfusion of the sPCAs that supply the pre-laminar and retro-laminar optic nerve, leading to ischemic damage of the optic nerve axons[6]. The ischemic axons swell as a response to the vascular insult, which is seen clinically as hyperemic optic disc edema. The severity of ischemic damage depends on the amount and duration of optic nerve ischemia and location of the watershed zones that were discussed earlier.

Risk factors for NAION are numerous. They include cardiovascular risk factors such as HTN, diabetes mellitus, atherosclerosis, arteriosclerosis, hypercholesterolemia, and nocturnal arterial hypotension[3,6,11]. Sleep apnea has also been recognized as a risk factor for NAION[3,11]. NAION is extremely uncommon in patients under 50 years of age, therefore advancing age is also considered a risk factor[3]. The anatomic risk factor for NAION is a small scleral canal, also known as a "disc at risk"[3,6,11]. A small scleral canal causes crowding of optic nerve fibers, leading to stasis of axoplasmic flow that is exacerbated by poor perfusion during nocturnal hours.

NAION is more common in males and patients of Caucasian ancestry[11]. Visual acuity can range from 20/20 to 20/200 depending on the severity of ischemia and location of watershed zones. Acutely, patients present with hyperemic disc swelling and variable disc hemorrhages[3]. The optic disc swelling subsides within 6-11 weeks after the acute insult, after which the nerve takes on a pale appearance due to loss of pre-laminar capillaries[3]. The optic nerve pallor that develops is commonly referred to as "optic

atrophy," which is an umbrella term used to describe a pale optic nerve without specifying the etiology of the optic nerve insult. Though the VA and VF can potentially improve up to 6 months after the initial insult, the final VA and VF will usually mirror the amount of loss seen during the acute phase of the disease. The most common VF defect is a relative inferior altitudinal defect, but other patterns of unilateral VF loss can be present as well[11].

All patients who suffer an NAION should be monitored within 2-4 weeks after the initial presentation. If the VA or VF is still worsening at the follow-up visit, the diagnosis of NAION is questionable and the patient needs a full workup with bloodwork and neuroimaging. If the VA and VF are stable or improving, then the patient can be seen again in 3-4 months. Important tests to conduct at follow-up visits include distance VA, monocular color vision, threshold VF, pupils, and RNFL OCT. The prognosis of NAION is generally favorable, with 50% of patients having 20/60 or better VA. Only 3-5% of patients will have a recurrence of NAION in the same eye, while 12-15% of patients will have suffer an episode of NAION in the fellow eye[3,7].

There is no proven treatment for NAION. The most important intervention is the reduction of modifiable risk factors through lifestyle alteration. Systemic corticosteroids, aspirin, intravitreal steroids and anti-VEGF have been tried in the past with minimal success[10]. The optometrist therefore plays an essential role in the evaluation and education of patients with NAION in order to decrease the risk of disease recurrence and further VA and VF loss.

In patients over 50 years of age with at least one cardiovascular risk factor, NAION is usually a clinical diagnosis without the need for additional laboratory testing[11]. However, if an older patient does not have any cardiovascular risk factors, the patient needs to be worked up with a basic bloodwork panel including CBC with differential, ESR, CRP, and HbA1C. Additional blood tests may be warranted depending on any accompanying clinical findings (anterior/posterior uveitis, macular exudates, etc.).

In patients younger than 50 years of age with apparent NAION, a hypercoagulable state must be ruled out with the appropriate bloodwork in addition to the basic bloodwork mentioned above[3]. Additionally, patients should be evaluated for elevated homocysteine as elevated levels can cause vascular endothelial cell injury, leading to inflammation of blood vessel walls. Systemic disorders such as systemic lupus erythematosus and Wegener's granulomatosis should be considered if the standard bloodwork for diabetes mellitus, hyperlipidemia, elevated homocysteine, and hypercoagulable states are negative. Lastly, all patients should have bloodwork to rule out syphilis and Lyme disease if the standard workup is negative. Neuroimaging may also be warranted if bloodwork is non-contributory.

Figure 3: Example of sequential NAION in a 64 year old Caucasian male with HTN and hypercholesterolemia. OD with acute findings of hyperemic disc edema, OS with longstanding pallor and disc at risk.

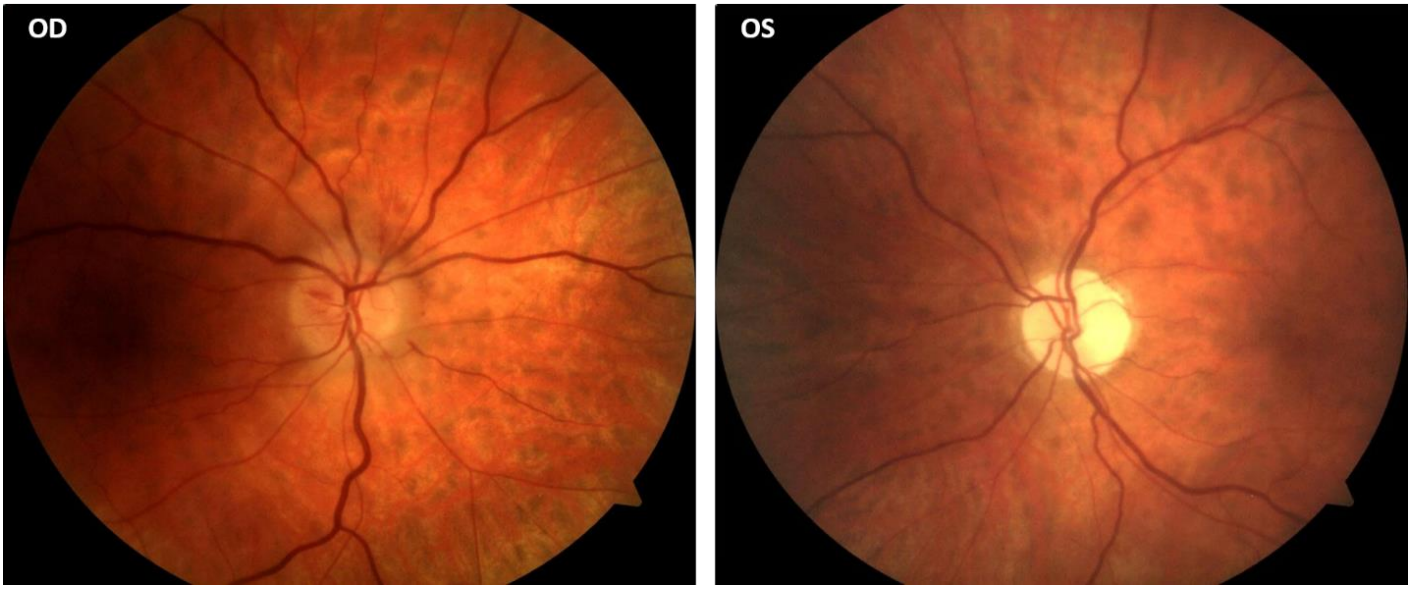
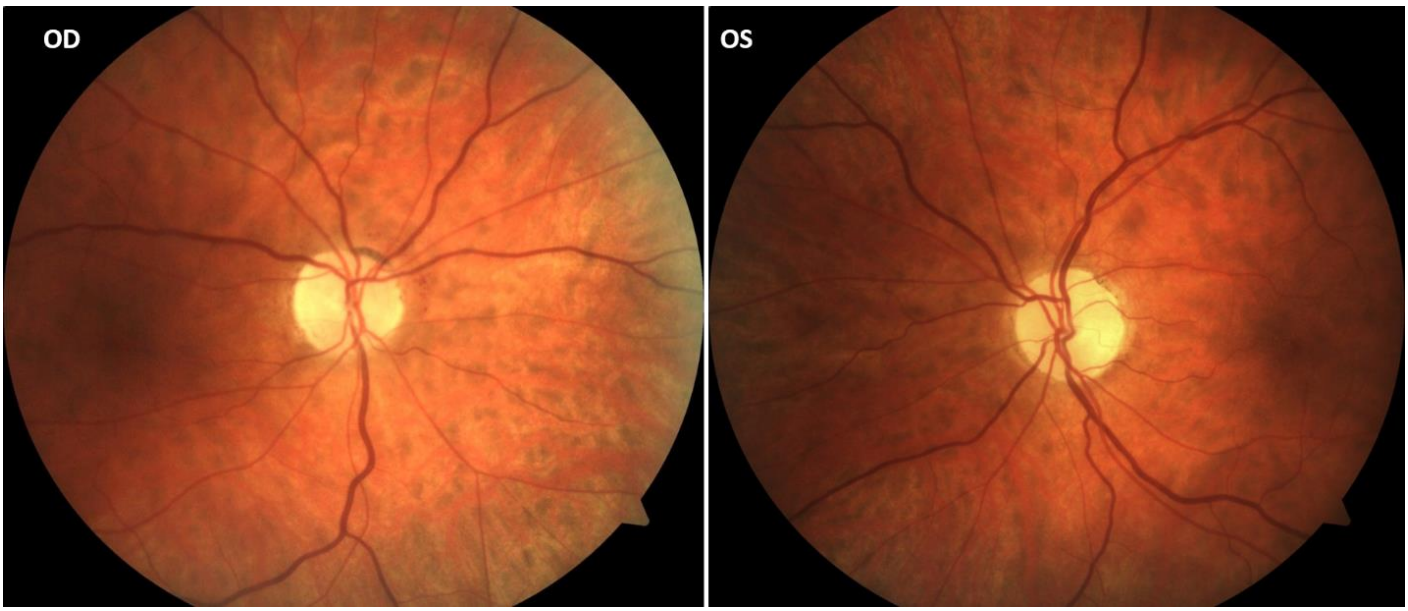


Figure 4: 6 weeks after initial presentation, patient from Figure 3 demonstrates resolution of optic disc edema and new onset optic nerve pallor OD.



II. Arteritic Anterior Ischemic Optic Neuropathy (A-AION)

Arteritic anterior ischemic optic neuropathy is caused by giant cell arteritis (GCA), also known as temporal arteritis (TA), which is a systemic vasculitis of medium and large-sized arteries[11]. GCA has a predilection for the ophthalmic and posterior ciliary arteries of the eye, resulting in thrombotic occlusion and severe ischemia of various ocular tissues including the optic nerve[6,8]. A-AION has a predilection for patients of Caucasian ancestry and is rare prior to age 50[6]. It is far more common in women, with men being affected only 29% of the time[6]. Systemic symptoms of GCA include anorexia, weight loss, headache, jaw claudication, scalp tenderness, neck pain, myalgia, fatigue, and anemia[3]. However, occult GCA can occur in up to 25% of patients who will suffer vision loss from A-AION without experiencing any preceding systemic symptoms[3].

A-AION is a devastating result of GCA that results in severe vision loss that can progress to the fellow eye within days if left untreated[11]. Amaurosis fugax is a frequent sign of impending vision loss in GCA from A-AION[14]. Patients with GCA may also present with cranial nerve palsies due to ischemic insults to the third, fourth, and/or sixth cranial nerves[3,14].

A-AION presents clinically as sudden, severe, painless vision loss in one eye.[3] The optic nerve will demonstrate pallid edema, also described as chalky pallor of the optic nerve[11]. Cotton wool spots and choroidal non-perfusion are often present due to thrombotic occlusion of a posterior ciliary artery[11]. Optic nerve and intra-retinal hemorrhages are rare due to severe ischemia to the ocular tissues. Up to 75% of cases will progress to bilateral involvement within 1-2 days of the initial insult if left untreated[11]. Even with appropriate treatment, it is highly unlikely that the vision in the affected eye will be restored[14].

If there is high level of suspicion for A-AION, clinicians should not wait for bloodwork results to initiate steroid therapy[7]. The patient must be started on high-dose corticosteroids immediately, and bloodwork can be ordered concurrently. There is a lack of consensus whether the initial steroid therapy should be administered via intravenous infusion or oral administration[5]. Traditionally, patients were referred to the Emergency Department for immediate IV steroid therapy. However, it is argued that high-dose oral steroids with bioequivalent doses of the IV alternative can be used to manage acute cases of A-AION[5]. This alleviates the burden of hospital admission and IV administration of steroid treatment in the acute phase for many patients, thereby increasing patient compliance and improving disease outcomes.

The most important blood tests to order if GCA is suspected include CBC with platelets, ESR, and CRP[3,8]. Though the bloodwork will typically be abnormal, a temporal artery biopsy (TAB) is still the gold standard for diagnosing GCA as it confirms granulomatous inflammation of the blood vessel walls[5,8]. The TAB should be performed within 3 days of starting steroid therapy and the biopsy should be at least 2 centimeters long to avoid skip lesions[5]. There is evidence that the TAB will remain positive for weeks and even months after initiation of steroid therapy, therefore steroid treatment should not be delayed in favor of obtaining a biopsy first[5]. If the biopsy results are normal for the ipsilateral temporal artery, the contralateral temporal artery should be biopsied[11].

GCA is a disease that requires long-term immunosuppressive treatment. High-dose oral steroid treatment must be maintained for at least two to three weeks until the CRP and ESR levels become stable and low, and there is typically a very slow steroid taper over months to years to ensure adequate disease remission. However, long-term steroid therapy can have significant adverse effects, including diabetes mellitus, infection, cataract formation, hypertension, gastrointestinal bleeding, aseptic bone necrosis, adrenal insufficiency, and osteoporosis[4,5]. In 2017, the FDA approved the first steroid-sparing

agent for the treatment of A-AION[10,13]. Tocilizumab (trade name: Actemra) is an interleukin-6 receptor inhibitor that maintains sustained remission after a 26-week steroid taper[4,5,10,13]. The medication is administered via weekly or bi-weekly injections[10,12,13]. It is a tremendous advancement in the treatment of GCA and A-AION as it allows much earlier cessation of oral steroid therapy that can wreak havoc on various body systems in patients with GCA. There are clinical trials currently underway assessing the safety and efficacy of additional biologic agents in treating GCA, the results of which will hopefully add to the very limited therapeutic armament that is currently available.

Conclusion

Non-arteritic and arteritic anterior ischemic optic neuropathies are relatively common causes of vision loss encountered by the primary eyecare provider. The optometrist must therefore be very adept in identifying and discriminating between the two entities as the management and visual outcomes are dramatically different. Unlike NAION, A-AION is a true ophthalmic emergency due to the severity of vision loss and frequency of involvement of the fellow eye if treatment is delayed. The optometrist must be equipped with the knowledge to discriminate between the two disease processes and must initiate timely and appropriate care to prevent further vision loss in cases of A-AION. The optometrist should also play a key role in long-term monitoring of visual function in both groups of patients via periodic assessment of visual acuity, contrast sensitivity, color vision, visual fields, and RNFL OCT to monitor for any signs of recurrence or progression.

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