Optic Nerve: Anatomy, Function, and Common Disorders

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Optic nerve diseases and disorders affect millions of people worldwide. These small nerves act as cables to form the essential link connecting the eye to the brain. At any point along this trajectory, damage to these nerves will result in visual impairment; further, due to the crossing over of nerve fibres at the optic chiasm, various distinct patterns of visual loss can occur. This issue of Ophthalmology Rounds reviews the various diseases and disorders of the optic nerve pathway based on anatomy and function, and offers the practicing clinician suggestions for diagnosis and treatment.

Anatomy of the optic nerve

The optic nerve is about 4 cm in length and extends from the ganglion cell layer of the retina to the optic chiasm. It is divided into intraocular, intraorbital, intracanalicular, and intracranial parts. Clinically, a good understanding of anatomical correlations with clinical examination findings can allow a prediction of the pathology location.1-3 Any pathology, trauma, or change in blood supply that deprives the nerve cells of energy for metabolism can result in cell damage, loss and, subsequently, vision disturbance.

Intraocular (optic disc)

Almost 1.2 million axons extend from the cell bodies of the ganglion cell layer to the optic disc. As the axons enter the optic nerve head, they maintain their retinal organization: those from the upper retina enter superiorly and those from the lower retina inferiorly. Axons originating from the papillomacular nerve fibre layer (NFL) bundle enter centrally, temporal ones enter inferiorly and superiorly, and the nasal fibres enter nasally (Figure 1). This corresponds to the configuration of nerve fibre bundle defects on visual fields – central and cecocentral, arcuate, and temporal wedges.

The optic disc, the portion of the disc visible on a fundoscopic examination, is usually a vertical oval 1.5 mm × 1.75 mm in size. Behind the disc, the nerve travels through the lamina cribrosa to the orbit and behind the lamina cribrosa, the nerve fibres are myelinated and surrounded by meningeal sheaths (pia, arachnoid, dura).

The blood supply to the optic nerve head is mostly via the circle of Zinn-Haller, composed of 2 often not connected semicircles of the short posterior ciliary arteries. In nonarteritic ischemic optic neuropathy (NAION), a drop in the perfusion pressure in the short posterior ciliary arteries is the presumed culprit. Optic-disc territory perfused by these arteries demonstrates segmental disc edema corresponding to the semicircle that has been compromised.

Intraorbital

The intraorbital portion of the optic nerve lies within the muscle cone. Before entering the optic canal, the nerve is surrounded by the annulus of Zinn formed by the origins of the rectus muscles. Both the superior and medial recti partially originate from...
the sheath of the optic nerve, which perhaps explains the pain on eye movement felt by patients with retrobulbar optic neuritis. The length of the intraorbital portion is greater than the length of the orbit, allowing for greater mobility and providing some protection from trauma and mass lesions in the orbit. The blood supply to this portion of the optic nerve is via the pial vascular plexus and branches of the ophthalmic artery; distally, the central retinal artery also contributes intraneural branches.

**Intracanalicular**

The optic nerve passes into the cranium through the optic canal, which is about 1.2 cm in length, and is located in the lesser wing of the sphenoid bone. At the entrance to the canal, the dural sheath of the nerve fuses to the periosteum, thus immobilizing the nerve. Trauma, particularly to the brow area, may transmit forces to the optic canal causing traumatic optic neuropathy due to shearing between the dura and the periosteum; the medial wall of the canal, the thinnest part, is most likely to exhibit trauma damage. The blood supply for this portion of the nerve is from the ophthalmic artery.

**Intracranial**

In the cranium, optic nerves travel 12-16 mm to the optic chiasm. In this pathway, they are associated with neighbouring blood vessels: ophthalmic arteries above, internal carotid arteries superiorly and medially, and the anterior cerebral arteries that cross over the optic nerves and are connected by the anterior communicating artery. Posterio to the cavernous sinus, both nerves join together to form the optic chiasm; the blood supply to this portion of the optic nerve is from branches of the internal carotid and ophthalmic arteries. This close proximity to large blood vessels makes this segment vulnerable to aneurysms.

**Testing optic nerve function**

Central visual acuity is an important indication of optic nerve function; however, it may remain normal even in the presence of significant optic nerve dysfunction. Further, it should be recognized that this is a subjective measurement and depends entirely on patient cooperation.

The presence of a relative afferent pupillary defect (RAPD) is one of the most important tests in evaluating optic nerve function. In the case of asymmetric optic neuropathy, it is an invaluable tool for providing an objective confirmation of optic nerve dysfunction. An ophthalmologist should always record the presence or absence of an RAPD if optic neuropathy is part of the differential diagnosis.

To test for an RAPD, a light is shone into a pupil and then quickly switched to the other one. Because of the decussation of the papillary light pathways, the size of the pupils should remain the same. If one pupil dilates, even slightly, when the light is switched to it, RAPD is present in that eye.

Colour vision is another test that provides a gross subjective assessment of optic nerve function; however, even in the presence of significant optic neuropathy, colour vision may remain normal. Again, this subjective test is dependent on patient cooperation.

Contrast sensitivity is a much more sensitive indicator of optic nerve function, but because the testing chart is not widely available and both patients’ understanding of the test and their co-operation are crucial, it is not commonly used.

Formal visual-field testing is an invaluable tool in evaluating patients with suspected optic neuropathies. The presence of nerve fibre bundle defects (arcuate defects, central or cecocentral scotomas, and temporal wedges) indicates optic nerve dysfunction. Here as well, the subjective nature of this test must be kept in mind.

Examination of the optic nerves by ophthalmoscopy provides invaluable objective information for evaluating patients with suspected optic neuropathies. Four alterations in optic disc appearance could be found on examination: optic nerve pallor, elevation, cupping (excavation), and hypoplasia.

- **Optic nerve pallor** develops within 4-6 weeks after the onset of the insult; subtle unilateral pallor is best appreciated by comparing the colour with the fellow eye on fundus photographs.
- **Elevation** is either a result of axonal swelling or a congenital anomaly. Axonal swelling is secondary to the reduction of the axoplasmic flow from the retinal ganglion cell bodies toward the lateral geniculate nucleus. The most prominent barrier to effective axonal flow occurs at the scleral lamina cribrosa. Conditions resulting in an increase in intracranial pressure, as well as inflammatory/ischemic/compressive insults to the intraocular,
Intraorbital, and intracanalicular portions of the optic nerve will result in swelling visible through ophthalmoscopy.

- Optic nerve cupping (excavation) is characteristic of glucomatous optic neuropathy. This can also be seen in high myopia and the colour of the rim is characteristically preserved.
- Hypoplasia is characteristically hard to recognize because of the wide variation in the size of optic nerves and usually it reflects a congenital anomaly.

Visual evoked potential is an objective test of optic nerve function that measures the time required for the retinal response to the light stimulus to travel to the occipital cortex. It is a sensitive indicator of dysfunction in the retinocortical pathway that is mediated by cones. The utility of this test is limited, though, because the test is not widely available. With this test as well, attention and deliberate noncompliance may lead to abnormal test results.

Neuroimaging is a very important adjunct to the standard tests employed by clinicians. The anatomy of the optic nerves can be evaluated either by computed tomography (CT) or by magnetic resonance imaging (MRI) scans of the brain and orbits. CT scans can be used as an initial test in ruling out compressive lesions in the orbit, as well as in the evaluation of optic nerves in thyroid eye disease. MRI provides more detailed information on the intracranial optic nerve. It is invaluable for determining inflammatory optic neuropathies that frequently cause the breakdown of the blood-brain barrier and, thus, the enhancement of the optic nerve on T1-weighted MRI sequences with gadolinium.

**Optic neuropathies**

Categorizing optic neuropathies into several large subgroups based on etiology improves the process of forming a differential diagnosis.

**Inflammatory optic neuropathies**

- **Infectious:** In infectious neuropathies, the patient is either immunocompromised or has evidence of systemic infection. The most common infections are due to spirochetes (syphilis), mycobacteria (tuberculosis and atypical mycobacteria), protozoa (toxoplasmosis), or viruses (cytomegalovirus [CMV], herpes simplex, or herpes zoster).
- **Noninfectious:** This type of inflammatory neuropathy can include demyelinating and nondemyelinating disorders. Demyelinating disorders are discussed in more detail under “Optic neuritis.” Nondemyelinating neuropathies include optic neuritis secondary to such entities as sarcoidosis, Wegener granulomatosis, Behçet disease, and other connective tissue diseases (systemic lupus erythematosus, relapsing polychondritis, mixed connective tissue disease, etc).

**Ischemic optic neuropathies**

- **Nonarteritic anterior ischemic optic neuropathy** and arteritic ischemic optic neuropathy (temporal arteritis) are discussed later in this paper.
- **Hypertensive optic neuropathy** is usually found in the setting of malignant hypertension; many cotton wool spots (small areas of yellowish-white colour on the retina fundus indicating nerve fibre layer infarcts), are usually present. To rule out this potentially life-threatening entity, all patients with bilateral optic nerve swelling must have their blood pressure measured.
- **Hypotensive optic neuropathy** usually follows intraoperative hypotension, severe blood loss, or renal dialysis, and is usually irreversible. The prevention of hypotension is key, especially in renal-dialysis patients, to preventing disease in the other eye.
- **Radiation optic neuropathy** usually occurs on average 1.5-2 years after radiation exposure, generally following treatment of malignancies in paranasal sinuses, nasopharynx, orbit, and anterior/middle cranial fossa. The total radiation dose is usually ≥ 6000 cGy. The visual loss is abrupt and no treatment is available. An MRI usually demonstrates an enhancement of the affected area.
- **Chronic low perfusion of the optic nerves** is observed in increased intracranial pressure states. An increased cerebrospinal fluid pressure in the dural sheath of the optic nerve leads to hypoperfusion of the ciliary arteries supplying the optic nerve head and thus to chronic axoplasmatic stasis.

**Compressive optic neuropathies**

Generally, compression of the intraocular, intraorbital, and intracanalicular portions of the optic nerve will cause edema of the optic nerve head, but compression of the intracranial portion will not. Central or cecocentral scotomas are common visual-field defects. Neuroimaging must be performed in all cases where compression is suspected. Several common entities can compress optic nerves, such as:

- optic nerve sheath meningiomas
- optic nerve gliomas
- thyroid orbitopathy
- metastasis
- sphenoid wing meningiomas
- aneurysms: in these cases, ophthalmic artery or supraclinoid carotid-artery aneurysms are the most common causes.

**Infiltrative optic neuropathies**

These neuropathies are usually secondary to leukemia, lymphoma, multiple myeloma, or carcinomatous meningitis. Malignant cells directly infiltrate the tissue of the optic nerve, and prognosis for survival in these patients is usually dismal.
Toxic/nutritional optic neuropathies

These are usually bilateral and symmetric, with central/ceccocentral scotomas and a gradual onset of optic nerve pallor, but no edema. Common culprits that trigger this neuropathy are methanol, ethylene glycol, and B12/folate deficiencies. Some medications can also be implicated (eg, ethambutol is commonly reported).

Hereditary optic neuropathies

Dominant optic atrophy is the most common entity, but Leber hereditary optic neuropathy is another cause. The hereditary optic neuropathies are bilateral, symmetric, and reveal central/ceccocentral scotomas on visual-field testing.

Traumatic optic neuropathies

This condition usually results from indirect injury to the optic nerve from blunt trauma, commonly to the brow area, where the force is transmitted to the optic canal. Treatment with a pulse dose of intravenous steroids has been advocated, but no benefit was demonstrated in a recent trial; moreover, a harmful effect was observed in patients with spinal-cord injury.

Optic neuritis

Optic neuritis denotes inflammation of the optic nerve caused by demyelination, which is primary in most cases, but in rare instances can be secondary to a variety of inflammatory disorders, such as sarcoidosis, autoimmune disorders, uveitis, infectious retinitis, meningitis, and idiopathic inflammation. This is usually a disorder of young adults (third decade of life) and is at least twice as common in women. The typical presentation is of a patient with acute or subacute monocular visual loss and pericentral pain that is made worse by eye movements (pain on eye movement was present in ~90% of patients enrolled in an optic neuritis treatment trial). On objective examination, the presence of RAPD in the affected eye (unless the disease is bilateral or there was previous damage to the optic nerve in the other eye) is often the only finding. In most cases, this defect is accompanied by decreased central visual acuity and colour vision, as well as the presence of a nerve fibre bundle defect on visual-field testing (although any visual-field defect can be seen, including hemianopic defects). In up to two-thirds of cases, the optic nerve appears normal on fundoscopy; in the remaining one-third, there is unequivocal disc edema. No ancillary tests are required for the diagnosis; however, MRI demonstrates enhancement of the optic nerve on the affected side in >75% cases and, in about 50% of cases, focal white matter high-intensity T2-weighted signal abnormalities are seen. Optic neuritis will recur in up to 35% of patients.

Important aspects of optic neuritis

A thorough clinical examination is adequate for the diagnosis of optic neuritis. Patients should be counseled on the results of the Optic Neuritis Treatment Trial (ONTT); ie, treatment with high-dose intravenous methylprednisolone (1 g/day for 3 days) will hasten the resolution of visual symptoms and reduce the incidence of developing multiple sclerosis (MS) in the next 2 years, but has no long-term benefit. Spontaneous visual recovery will occur in up to 85% of patients. Reasons for ordering an MRI are twofold: prognostication and possible eligibility for treatment. Ten-year follow-up results of ONTT revealed that, if only 1 lesion is seen on brain MRI, the probability of developing MS in 10 years is 56%, if no lesions are seen this risk is reduced to 22%. Overall, 38% of patients will develop MS in 10 years and 30% will have a recurrence of optic neuritis within 5 years of diagnosis. In patients with a “high-risk” MRI (≥2 lesions on MRI), treatment with glatiramer acetate or beta-interferon reduced accumulation of MRI signal abnormalities and clinical relapses; however, no solid evidence exists that this regimen improves long-term disability resulting from MS. Patients in whom optic neuritis is the first manifestation of MS have a low rate of disability compared with other MS patients.

Nonarteritic anterior ischemic optic neuropathy (NAION)

NAION is one of the most common causes of optic neuropathies in adults over the age of 40 years; patients present with an acute painless monocular visual loss. Patients often report noticing decreased vision when waking up in the morning. In a small subgroup of patients, visual loss can be progressive over the course of 1-3 weeks. Impaired perfusion of the short ciliary arteries supplying the optic nerve head is generally accepted as an etiology. Objectionly, decreased visual acuity, RAPD, and visual-field defects (commonly an altitudinal nerve-fibre bundle defect) are present. Risk factors include hypertension, hypotension, hyperlipidemia, diabetes, smoking, obesity, and crowded optic nerves (nerves with cup to disc ratio ≤0.2, termed a “disc at risk”). Recently, a randomized clinical trial produced data on the visual recovery and natural history of the disease: at 6 months, 45% of patients demonstrated 3 lines of improvement.
Anatomy and physiology of optic nerves are in visual acuity on the Snellen chart, 12% lost ≥3 lines, and the rest remained stable. Some postulate that the recovery of vision is secondary to the learned new fixation preference and that most patients do not notice an improvement. Over the course of 5 years, involvement of the second eye occurred in 15% of patients. No treatment has been shown to be beneficial for this condition and there is no evidence that any measure reduces the risk of second eye involvement. The same trial demonstrated that optic nerve sheath fenestration has not improved the visual outcome; moreover, patients who have undergone this procedure had worse visual outcomes than patients in the controlled arm. This procedure, therefore, should not be performed in patients with NAION.

It is important for the clinician examining patients with NAION to ask them about any recent addition of antihypertensive medications to their regimen, since this can cause a dip in blood pressure, particularly in the morning. It is essential that all patients with NAION have their blood pressure measured. When indicated, a complete medical history and measurements of serum inflammatory markers must be performed to exclude arteritic ischemic optic neuropathy (temporal arteritis). An MRI in NAION does not demonstrate any abnormalities; as a result, it can be used to differentiate this entity from demyelinating optic neuritis, since optic nerve enhances in up to 75% of these cases. Finally, control of atherosclerotic risk factors should be emphasized.

**Arteritic ischemic optic neuropathy (giant-cell arteritis)**

This neuropathy is a chronic granulomatous vasculitis that affects the cranial branches of the aortic arch arteries. This entity, although rare, should be considered by every ophthalmologist in their daily clinical practice, since the onset of the disease is usually sudden and unexpected, and a misdiagnosis can lead to severe bilateral visual loss. The disease affects patients over the age of 50 years, with the incidence rising dramatically after the age of 70 years. It is 3 times more common in women and is more common in whites. It is at least 10 times less common than NAION, but because the risk of second eye involvement is around 30% and the visual loss is very profound, it must always be excluded. If untreated, visual loss in the second eye occurs in up to 75% of patients, usually within 3 weeks of first eye involvement. Most patients present with symptoms of polymyalgia rheumatica (headaches, proximal muscle aches, fatigue, fever, weight loss), or they have inflammation of the cranial tissues (headaches, jaw claudication, scalp tenderness). Jaw claudication is the most sensitive symptom, however, in some patients (8%-38% in different studies), optic neuropathy is the first evidence and is an isolated manifestation. Findings are similar to those with NAION, but visual loss is usually much more profound and there is “pallid swelling” of the optic nerve head. Other manifestations of retinal ischemia, such as cotton wool spots and occlusion of the cilioretinal or central retinal artery, are occasionally present. Occasionally, there are clinical manifestations of anterior segment ischemia due to proximal involvement of the long ciliary arteries by vasculitis (anterior chamber cell and flare, hypotony).

Elevated inflammatory markers are present in a majority of cases with laboratory testing. In a recent study of 119 biopsy-positive cases of temporal arteritis, 99% of patients had either elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP); in only 1 patient were both markers normal. Elevated CRP by itself has a sensitivity of 97.5%; ie, only 2.5% of patients with biopsy-proven disease had a normal CRP. The presence of choroidal infarcts can often be seen on fluorescein angiography. If giant-cell arteritis is suspected, treatment with steroids should commence immediately. Some authors recommend a 3-day course of intravenous methylprednisolone (1 g/day) followed by a very slow oral taper, as opposed to initial high-dose oral steroids. If visual loss has occurred, steroid use is geared towards decreasing the risk of second eye involvement. Temporal artery biopsy should be performed on every patient in whom the disease is strongly suspected. Biopsy findings remain positive even in patients who have been on steroids for several weeks (giant cells may not be present in the vessel wall, but macrophages will). Steroid tapering should be slow and most experts recommend at least a 6-month to 1-year course of withdrawal.

**Conclusions**

- Anatomy and physiology of optic nerves are complex. Familiarity with them will help an ophthalmologist in busy practice to recognize optic nerve disorders and formulate a differential diagnosis.
- Visual acuity and presence of relative afferent papillary defect should be documented in all patients in whom optic neuropathy is a possibility.
- Optic neuritis is a common entity and familiarity with results of the optic neuritis treatment trial is paramount.
The most important contribution of ophthalmologists to the management of patients with NAION is measuring patients’ blood pressure, as prevention of hypo- and hypertension is the key.

Giant-cell arteritis should be suspected in every elderly patient with polymyalgia rheumatica symptoms and/or visual disturbances.

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