Continued from Part 1:

Case 5

Our next clinical case involves a 47 YO African-American male who presented with complaints of blur in the right eye for the past 48 hours. He had also reported mild pain with eye movements. Systemically, he described numbness of the left arm three weeks previous, and a history of hypertension, which was controlled with an unknown medication.

Visual acuities were 20/20-2 in the right eye, and 20/20 in the left eye. There was slight pain of the right eye when testing EOM movements, but both pursuits and saccades were full. Pupils were equal, and briskly reactive to light with a moderate right RAPD. Anterior segment examination was unremarkable. IOP’s were 18 mmHg in the right eye and 20 mmHg in the left. A dilated fundus examination revealed Grade 3 Disc edema with flame-shaped hemorrhages and cotton wool spots (CWS) in the right eye. (Fig 1) The left optic nerve head was flat and pink with distinct margins.

Figure 1: DFE showing disc edema with flame hemorrhages and CWS

Figure 2: Visual Field results
Visual field testing showed a diffuse depression in the right eye and a slight inferior nasal depression in the left eye. (Fig 2)

The patient was diagnosed with probable optic neuritis. He was referred for an MRI of the brain and orbits with contrast. He was asked to return for follow-up care in one week, at which time IV steroid treatment would be considered depending on the results of the MRI.

At the one week follow-up visit, the patient reported that his vision was “sore” in the right eye for the last four days. Visual acuities at this visit were No Light Perception (NLP) in the right eye, and 20/20 in the left. The patient reported moderate pain with eye movements in the right eye. Pupils were reactive to light with a right RAPD. Anterior segment was unremarkable, and IOP’s were 17mmHg in the right eye and 19 mmHg in the left eye.

Results of the dilated exam of the right eye are shown in Figure 3 (top). No change was seen in the left eye. MRI (Figure 3, bottom) revealed diffuse longitudinal inflammation with a chunky appearance of the right optic nerve sheath. The optic nerve enhanced from the orbit to the chiasm. There was no evidence of demyelination or other brain abnormalities.

Figure 3: Top: DFE at 1 week follow-up exam. Bottom: MRI with contrast.
At this time, the patient was sent for laboratory testing to rule out Sarcoidosis, Syphilis, or other inflammatory or infectious disease, as well as a chest X-ray and CT. He was prescribed Prednisone, three 20mg tablets to be taken every morning, and told to return for follow-up care in two days.

Table 1

<table>
<thead>
<tr>
<th>Blood Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>18</td>
<td>0-15 mm/hr</td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>RPR</td>
<td>Non-reactive</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>ACE</td>
<td>19</td>
<td>9-67 U/L</td>
</tr>
<tr>
<td>Monocytes (CBC)</td>
<td>11</td>
<td>0-10%</td>
</tr>
<tr>
<td>Glucose</td>
<td>90</td>
<td>65-99 mg/dL</td>
</tr>
</tbody>
</table>

At the next follow-up visit, visual acuities remained NLP in the right eye, and 20/20 in the left eye. The results of blood testing are shown in Table 1. The chest X-ray and CT of the thorax with contrast were unremarkable. PPD for tuberculosis was non-reactive. The patient was told to decrease the Prednisone to 30 mg every morning and return for follow-up care in two weeks.

One month after the initial visit, the patient reported that some vision was returning in the right eye. Visual acuities were finger counting at 4 feet in the right eye and 20/20 in the left eye. The patient experienced no pain with eye movements. Pupils were equal, reactive to light, with a right RAPD. IOP’s were 16 mmHg in the right eye and 17 mmHg in the left. Optic nerve edema was significantly improved.

He was diagnosed with optic neuropathy due to presumed neurosarcoidosis and told to continue tapering the steroid to 30 mg per day for two weeks, followed by 30 mg per day for two weeks. A follow-up appointment was made in one month.

Approximately two months after the initial attack, the patient still had some trouble making out letters. Visual acuities were 20/200 in the right eye and 20/20 in the left. The right RAPD was still present, and IOPs were 16 mmHg in both eyes.

Dilated fundus exam revealed diffuse pallor of the right optic nerve head. (Fig 4) Three months following the initial attack, visual acuities stabilized at 20/70 in the right eye.

The optic nerve can be affected by inflammation or infection. The most common cause of inflammatory infiltrative optic neuropathy is sarcoidosis. The inflammatory optic neuritis results from granulomatous infiltration of the optic nerve. Sarcoidosis is most common in women and African-Americans. Between 53 and 90% of patients do not know they...
have Sarcoid at the time of neurologic involvement. Progressive vision loss occurs with Sarcoidosis affecting the optic nerve. Most patients report headache or ocular pain. The condition is bilateral in 40-75% of cases.

Visual loss is usually severe when Sarcoidosis affects the optic nerve. If Sarcoidosis affects the anterior optic nerve, the disc will either be diffusely or sectorially elevated. In many cases the findings may be identical to demyelinating optic neuritis. However, occasionally a white, lumpy, nodular appearance of the optic nerve will suggest a granulomatous process. The vessels overlying the disc may be dilated. Other evidence of intraocular inflammation is usually present. There may be inflammation involving the vitreous or anterior chamber.

MRI of the brain or orbits with contrast should be performed in patients suspected of Sarcoidosis with optic nerve involvement. Diffuse enlargement or enhancement of the optic nerve is seen on MRI. Sarcoidosis should be suspected if the optic nerve enhances from the globe to the chiasm, especially if the involvement is nodular. Enlargement or enhancement of the lacrimal gland, in addition to optic nerve involvement is also suggestive of Sarcoidosis.

Elevated Angiotensin Converting Enzyme (ACE) levels and a chest radiograph or chest CT are helpful in making the diagnosis of Sarcoidosis. However, ACE levels are not specific for Sarcoidosis and are not reliably elevated in Neurosarcoidosis. 25-80% of Neurosarcoidosis patients have normal ACE levels and 28-40% have normal chest radiography. Gallium scanning is consistent with Sarcoidosis in 71-93% of Neurosarcoidosis patients. Conjunctival or lacrimal gland biopsy can confirm the diagnosis. Occasionally a biopsy of the nerve is necessary to make the diagnosis, however this should only be performed if visual recovery is not expected.

Treatment of Sarcoidosis involves corticosteroids. Other immunosuppressive agents have also been used with variable success.

Neurologic manifestations of Sarcoidosis, including optic neuritis, respond quickly to corticosteroid treatment, but may worsen when the steroids are tapered. Complete resolution or stabilization of neurological deficits occur in 70-92% of patients.

Optic neuritis can occur with a large number of infectious conditions.

Common viral and bacterial causes associated with optic neuritis are shown in Table 2. Toxoplasmosis can also result in optic neuritis. The various causes result in similar clinical signs and symptoms.

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Bacteria</th>
</tr>
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<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Hepatitis A virus</td>
<td>Cat-scratch disease</td>
</tr>
<tr>
<td>Herpes Simplex virus</td>
<td>Lyme disease</td>
</tr>
<tr>
<td>Human Immunodeficiency virus</td>
<td>Anthrax</td>
</tr>
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<td>Influenza</td>
<td>Streptococcal infection</td>
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<tr>
<td>Measles</td>
<td>Meningococcal infection</td>
</tr>
<tr>
<td>Mumps</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Varicella-zoster</td>
<td>Typhoid fever</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Whipple’s disease</td>
</tr>
</tbody>
</table>

- **Parasite: Toxoplasmosis**
Visual loss associated with Syphilis-related optic neuritis occurs quickly and is typically severe. Optic neuritis associated with Syphilis can be unilateral or bilateral, anterior or retrobulbar. It is common to see cells in the vitreous, helping to distinguish this from typical demyelinating optic neuritis.

A test specific for Syphilis, such as T. Pallidum hemagglutination assay (TPHA) or Fluorescent treponemal antibody absorption (FTA-ABS), and a lipid antigen test, such as Venereal disease Research Laboratory (VDRL) or Rapid plasma reagin (RPR), should be performed together. All patients with Syphilis should be evaluated for HIV.

Treatment of Neurosyphilis with IV penicillin usually results in visual recovery.

Cat-scratch disease is the most common infection associated with neuroretinitis. Patients have a history of a scratch or bite from a cat one week to three months prior to signs or symptoms. Up to 5% of cases result in neuroretinitis. Vision loss is painless, disc edema is more common unilaterally, and a stellate pattern of infiltrates surround the macula to form a macular star 2-4 weeks after the disc edema. (Fig 5) Serologic tests show an increased antibody titer.

Cat-scratch disease is a self-limiting infection. A 1-6 week course of ciprofloxacin or doxycycline may speed recovery when ocular tissue is involved. The papillitis will resolve within 3-6 weeks but the exudates will take 6-12 months to completely resolve. Most regain normal visual acuity.

Lyme disease is transmitted through an infected tick bite. (Fig 6) Patients have typically been exposed to an endemic area. Ocular involvement is rare, but can present with anterior or retrobulbar optic neuritis as well as papilledema secondary to Lyme disease meningitis. Serologic testing such as ELISA and Western blot can aid in the diagnosis. This condition is effectively treated with antibiotics such as IV ceftriaxone.

Parainfectious optic neuritis usually occurs 1-3 weeks after a viral, and sometimes a bacterial, infection. The neuritis is most common in children, and often occurs bilaterally. It is common to present with no neurologic signs other than optic neuritis. Visual prognosis is excellent even without treatment.

Bilateral optic neuritis can occur 1-3 weeks after viral or bacterial vaccination. Spontaneous visual recovery usually occurs over several months.

Vasculotides, such as Systemic lupus erythematosus, Polyarteritis nodosa and Rheumatoid arthritis can produce optic neuritis. This neuritis can cause either sudden or slowly progressive vision loss. The
neuritis is more often bilateral with painless vision loss. This type of optic neuritis may show rapid improvement with steroid treatment, but the prognosis is generally poor.

**Case 6**

Our next clinical case involves a 21 YO white male who presented with gradual loss of vision in the right eye over a 2 year period. When the vision loss first started, he noticed transient visual obscurations (TVO’s) in the right eye that lasted for a couple of minutes. At that time, he was being followed by a neurologist in a different state. Notes from the neurologist noted no relative afferent pupillary defect (RAPD), a normal fundus examination, and an unremarkable MRI and MRV. He recommended a neuro-ophthalmic examination and lumbar puncture, but neither were performed.

Over the subsequent year, the TVO’s subsided and he noticed a fading of the vision in the right eye. He also began noticing retro-orbital tenderness with slight pain with eye movements.

At the time of the exam, vision was stable, and the periocular pain had resolved. The patient reported no problems with the left eye, and no other neurologic symptoms. He was on no medications and had an unremarkable family history.

Visual acuities at the examination were 20/80 in the right eye, and 20/20 in the left eye. Color vision was decreased, and minimal limitation of abduction and 25% limitation of supraduction was found in the right eye. There was slight proptosis with resistance to retropulsion. No eyelid retraction or ptosis was noted. Pupils were equal and briskly reactive to light with a right RAPD.

Anterior segment was unremarkable. Intra-ocular pressures were 12 mmHg in the right eye, and 14 mmHg in the left eye.

On dilated fundus exam, the disc appeared pale, edematous, and elevated in the right eye. (Fig 7) An optociliary shunt vessel was present. The left optic disc appeared normal. There were no hemorrhages or exudates in either eye, and the macula appeared unremarkable in both eyes.

Visual field testing revealed diffuse loss of vision in all quadrants of the right eye. (Fig 8 Top) The patient was referred for an orbital MRI with contrast. The results show longitudinal enlargement and enhancement of the right optic nerve sheath. (Fig 8 Bottom) The optic nerve is still visible in the center, which is characteristic for an optic nerve sheath meningioma.

The patient was referred for a neurosurgical consultation, and the decision was made to follow the patient due to the stability of the vision over the past year.
Figure 8: Top: 30-2 SITA Fast visual field showing diffuse loss of vision OD. Bottom: MRI with contrast showing enlargement and enhancement of the right optic nerve sheath.
Lesions in the orbit, including tumors, infections and inflammation, can compress the optic nerve. Compression of the optic nerve can also be caused by idiopathic inflammatory orbital pseudotumor or by enlargement of orbital structures as seen in thyroid eye disease. Resulting compression can cause swelling of the optic nerve.

Atrophy of the optic nerve is more likely to occur with lesions involving the intracranial and intracanalicular optic nerve.

Optic nerve sheath meningiomas account for 1/3 of optic nerve tumors. They are typically unilateral, occurring most commonly in middle-aged women. Although they may have no complaints, as many as 96% of patients with optic nerve sheath meningiomas present with painless progressive visual acuity or visual field loss. Headache and diplopia may also be present. The majority of optic nerve meningioma patients do not report proptosis until more than a year after initial visual symptoms. Due to pressure on the optic nerve, or decreased blood supply, transient vision loss in certain positions of gaze can occur with orbital lesions. The vision improves quickly when the gaze changes.

Optic nerve meningiomas can be differentiated from idiopathic inflammatory orbital pseudotumor (IIOP) based on symptoms. Patients with idiopathic inflammatory disease complain of visual loss, as well as pain, proptosis, as well as congestion.

Visual acuity with optic nerve sheath meningiomas may be 20/20 or 20/25, but patients will read the line with difficulty compared to the other eye. With careful scrutiny, a mild RAPD and color vision deficiency is usually found despite normal visual acuities. These patients are commonly misdiagnosed as having macular degeneration, cataract, or glaucoma. However, the presence of color vision deficiency in the affected eye and an APD would rule out these conditions.

Compressive optic neuropathy will cause proptosis, congestion, and EOM limitations. These patients often have an enlarged blind spot on visual field testing. A reduced mean deviation, or generalized constriction may also be present.

Disc swelling occurs, even if the patient is asymptomatic. Optic disc swelling is generally mild or moderate. Peripapillary hemorrhages are not usually present. Horizontal or vertical chorioretinal striae adjacent to the optic disc may be present when the lesion is pressing on the globe. Optociliary shunt veins and optic atrophy also become apparent.

<table>
<thead>
<tr>
<th>Table 3</th>
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<tbody>
<tr>
<td><strong>Causes of Compressive Optic Neuropathy</strong></td>
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<tr>
<td><strong>Tumor</strong></td>
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<tr>
<td><strong>Infection</strong></td>
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<tr>
<td><strong>Inflammation</strong></td>
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Patients suspected of compressive optic neuropathy should undergo neuroimaging. An optic nerve sheath meningioma is best demarcated with use of fat saturation in a contrast-enhanced MRI. A focal or diffuse tubular optic nerve enlargement that enhances with gadolinium is seen. (Fig 9) MRI is also helpful in determining intracanalicular and intracranial extension.

The optic nerve can be seen as separate from the tumor, creating a classic Tram-track sign that helps to distinguish an optic nerve sheath meningioma from a glioma. The Tram-track sign can also be seen in other orbital diseases including Sarcoidosis, orbital pseudotumor, optic neuritis, leukemia, lymphoma, and metastasis.

The diagnosis of optic nerve sheath meningioma is made clinically with neuro imaging. Biopsy is only recommended in uncertain cases when lumbar puncture has excluded neoplasm and inflammation, and when vision does not improve with steroid treatment. Biopsy should only be performed in cases of poor vision.

If good, functional vision remains, or visual decline is negligible, optic nerve sheath meningiomas are often observed without treatment. These patients should be examined every 6 months looking for progressive loss of visual acuity, color vision, or visual fields. Imaging should be performed every 6 months as well. If the vision remains stable for 2-3 years, the patient can be seen annually.

If the lesion is extending intracranially, threatens the vision of the other eye, causes disfiguring proptosis, or is causing progressive vision loss, treatment may be warranted. Due to the involvement of the blood supply, surgical excision is not possible without damaging the optic nerve. Radiotherapy is effective in improving or stabilizing remaining vision in up to 80% of patients.

Compressive optic neuropathy occurs in 5-6% of patients with Thyroid Eye Disease (TED). Women are much more likely to develop severe orbital involvement. Enlarged extraocular muscles (EOM’s) compress the optic nerve at the apex of the orbit. A relationship exists between the EOM size and motility, and the development of compressive optic neuropathy. Proptosis may be a protective factor, allowing the total orbital volume to expand.

Vision loss with TED is usually gradual onset, bilateral, and symmetrical. Tearing, irritation, photophobia, and eyelid puffiness are common occurrences prior to vision loss. Transient diplopia that is worse in the morning due to EOM fluid accumulation during the night is very common.

Compressive optic neuropathy with TED results in visual acuities that are usually worse than 20/60. Visual field testing shows central scotomas or arcuate defects, and a RAPD will be present only if the condition is asymmetric.
Conjunctival hyperemia over the horizontal rectus muscle insertions, punctate epithelial erosions, superior limbic keratoconjunctivitis, swelling of the eyelids, eyelid retraction, and lid lag are commonly but not always seen with TED. Restriction of the EOM’s, most commonly the inferior and medial recti, is likely.

Optic nerve compression with TED can present with swelling, hyperemia, pallor, or increased cupping of the optic nerve. Up to half of eyes will have normal appearing optic discs.

CT remains the imaging method of choice for patients with optic nerve compression secondary to TED. Neuroimaging with compressive optic neuropathy secondary to TED shows moderate to severe enlargement of the extraocular muscles with sparing of the tendons. (Fig 11) Optic nerve compression occurs with enlargement of the muscles at the orbital apex.

Serum tests for thyroid function should be performed if TED is suspected. Antibody titers against thyroid hormones are useful when thyroid function tests are normal. (Table 4)

Treatment of compressive optic neuropathy due to TED includes the use of corticosteroids, immunosuppressive therapies, orbital decompression, and radiation. Tight thyroid control and cessation of smoking is also beneficial.

The most common tumor to infiltrate the optic nerve is an optic nerve glioma. 70% of gliomas are found in the first decade of life, and 90% are found by the end of the second decade. These children will often have signs of Neurofibromatosis type 1. Although optic nerve gliomas are rare in adults, when they do occur, they usually result in blindness and death within a short period.

Patients with optic nerve gliomas commonly present with complaints of diplopia and/or proptosis. Vision loss is typically present and may be due to the tumor itself, or to strabismic amblyopia.

A glioma within the orbit causes proptosis (94%) and a swollen (35%) or atrophic (59%) optic disc. Patients can develop optociliary shunt vessels. Increased volume of the optic nerve can cause retinal striae and increased hyperopia.

Table 4

<table>
<thead>
<tr>
<th>Serum laboratory tests for TED</th>
</tr>
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<tbody>
<tr>
<td>Triiodothyronine (T3)</td>
</tr>
<tr>
<td>Thyroxine (T4)</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Thyrotropin releasing hormone (TRH)</td>
</tr>
<tr>
<td>Antibody titers</td>
</tr>
<tr>
<td>- TSH receptor</td>
</tr>
<tr>
<td>- Thyroperoxidase</td>
</tr>
<tr>
<td>- Thyroglobulin</td>
</tr>
</tbody>
</table>

Figure 11: Conjunctival hyperemia in TED

Figure 10: CT showing enlarged EOM's due to Thyroid Eye Disease
With neuroimaging, optic nerve gliomas are seen as a fusiform enlargement of the optic nerve. (Fig 12) There is no clear distinction between the tumor and the nerve. The lesion may enhance but the enhancement is not as pronounced as that seen with a meningioma. Two other distinguishing features are kinking of the optic nerve and the Pseudo-CSF signal surrounding the optic nerve.

Optic nerve gliomas can generally be observed. Neuroimaging and neuro-ophthalmic examination should be repeated regularly to insure the stability of the lesion. Chemotherapy or radiation treatment is not warranted unless the optic nerve glioma is progressing to the chiasm, hypothalamus, or other optic nerve. Surgical resection is only used if the patient is already blind or has severe proptosis.

Optic nerve gliomas in children are generally benign lesions that result in few long-term complications. The size of the glioma typically does not increase, and vision remains stable or improves in up to 91% of patients. Optic nerve gliomas found in adults are almost always malignant with rapid unilateral or bilateral vision loss or optic atrophy. These patients typically go blind within several months after the onset of symptoms, and most die within 6-12 months.

Astrocytic hamartomas (Fig 13 top) infiltrate the optic disc. The lesion becomes glistening and yellow with a mulberry appearance composed of calcific concretions. The appearance must be differentiated from optic nerve head drusen. Drusen are within the substance of the nerve, whereas astrocytic hamartomas overly the disk.

Melanocytomas (Fig 13 bottom) are elevated, grey or black intraocular tumors that occur within the substance of the optic nerve. The majority are less than 2 disc diameters. Good visual acuity is maintained, but an enlarged blind spot, generalized constriction, or arcuate scotomas can often be seen with visual field testing. These tumors are benign. Slight growth may occur, but malignant transformation is rare.

Secondary tumors may also infiltrate the optic nerve. These include metastasis, carcinomas, lymphoma and leukemia. In patients with a history of cancer, the cause of an acquired optic neuropathy should be considered cancer until proven otherwise.
**Case 7**

The next clinical case involves a 47 YO black male who presented with loss of vision in both eyes three months previously. He came into the office at that time, but missed all follow-up visits. The patients had a history of excessive alcohol abuse, and came to the first examination drunk.

The visual acuities were 20/200 in both eyes, and color vision was reduced in both eyes (1/8 OD, 1/8 OS). Pupils were briskly reactive to light, with no RAPD. Visual field testing showed a cecocentral scotoma which was more prominent temporally in both eyes. (Fig 14) Dilated fundus examination revealed temporal pallor in both optic nerves. There were no hemorrhages or exudates in either eye, and the maculae were unremarkable.

Laboratory testing was remarkable for a positive RPR, high ACE, and decreased folate and vitamin B12 levels. An MRI with contrast was unremarkable. Due to the positive RPR, the patient was treated with doxycycline for syphilis. Because the ACE was high, steroids were given for sarcoidosis. Despite these treatments, the vision did not improve.

A diagnosis of toxic amblyopia was made, and intramuscular injections of vitamin B12 were instituted. It was also recommended that the patient stop alcohol use. Unfortunately, this patient’s vision is not likely to improve, because atrophy had already occurred by the time he returned for follow-up visits.

The characteristics of optic neuropathy resulting from toxicity or metabolic problems are similar to other optic neuropathies, especially those that are bilateral and simultaneous. Nutritional deficiency over a period of months can cause optic neuropathy. Nutritional optic neuropathy is more likely in times of war, famine, or economic challenge. Most patients will have other signs of malnutrition including weight loss, peripheral neuropathy, keratitis, or skin and mucous membrane lesions. However, pernicious anemia, or vitamin B12 deficiency, can occur without observable signs of nutritional deficiency.

Vitamin B12 deficiency can result in neurologic dysfunction. The vitamin must be obtained through diet, and is found in meat and dairy products. Because it is stored in the liver, and distributed slowly, a person must have a deficiency lasting several years to cause the disease. Pernicious anemia is the most common cause of complications due to vitamin B12 deficiency. This presumable autoimmune disorder occurs due to poor absorption of the vitamin in the ilium. The condition is found most commonly in middle-aged and elderly Caucasians of northern European descent. Without treatment, most patients develop neurological complications, most commonly paresthesias and weakness of the extremities.

Optic neuropathy can occur after acute or prolonged exposure to toxic substances. Certain people are at higher risk for toxic and metabolic optic neuropathy. These include those who smoke or consume...
alcohol, those with high risk of exposure to toxins at their occupation, and those on certain medications. Optic neuropathy due to tobacco use usually occurs in middle-aged or elderly men. It is more common in pipe and cigar smokers. The mechanism of damage is unclear, but may be related to concurrent malnutrition. Tobacco may also interfere with vitamin B12 absorption.

Many drugs can cause toxic optic neuropathy. (Table 5) Ethambutol, and antibacterial drug used to treat tuberculosis, and Amiodarone, an antiarrhythmic medication, are among the most common medications that can cause optic neuropathy.

Methanol causes severe irreversible vision loss, as well as life-threatening systemic complications. It is used as an antifreeze solvent or fuel. The odor is very similar to that of ethanol, or drinking alcohol and it is usually consumed by accident. Another cause of toxic optic neuropathy is ethylene glycol, an ingredient in automobile antifreeze. Vision loss is not as common, but can be severe.

A thorough history covering dietary intake, exposure to drugs, tobacco or alcohol use, and occupational background is critical. Loss of vision will be bilateral with both toxic and metabolic optic neuropathy. Symptoms will occur shortly after exposure to the toxic substance. Patients with toxic or metabolic disorders affecting the optic nerve will generally report slowly progressing vision loss over weeks or months, but vision loss can occur rapidly. Initially a blur, fog or cloud may be reported in the central vision. This is followed by a general loss of acuity. Either a loss of color vision or a report that colors are not as bright or vivid as usual may be the initial symptom in these patients. The patient should not report pain associated with the vision loss. Initial symptoms of methanol or ethylene glycol poisoning include nausea and vomiting. Respiratory distress, headache, and vision loss occur within 24-48 hours. Drowsiness, abdominal pain, weakness and confusion, followed by coma and death due to respiratory failure may occur.

Most patients with toxic optic neuropathy have visual acuity better than 20/400. One exception, methanol, can produce complete or nearly complete blindness. Color vision is decreased, and visual field defects are either central or cecocentral in nature with sparing of the peripheral visual fields. A RAPD is uncommon in these patients due to the bilateral nature of the condition. Pupils will react normally to light and near stimulation, unless there is complete loss of vision as occurs with methanol ingestion.

Toxic or metabolic optic neuropathy causes mild, bilateral disc swelling. Early stages may have a normal disc

<table>
<thead>
<tr>
<th>Medications that can cause toxic optic neuropathy</th>
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</thead>
<tbody>
<tr>
<td>Ethambutol (tuberculosis) &gt;25 mg/kg/day</td>
</tr>
<tr>
<td>Amiodarone (antiarrhythmic)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Ergot</td>
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<tr>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td>Chemotherapy agents</td>
</tr>
</tbody>
</table>

Figure 15: Temporal disc pallor and atrophy
appearance. Disc hemorrhages may be present. Optic atrophy, most commonly of the temporal disc, occurs in later stages. (Fig 15)

Other ocular signs may aid in the diagnosis. Nystagmus and ophthalmoplegia occur with ethylene glycol ingestion. Pigmented, whorl-shaped corneal epithelial deposits (Fig 16 top) occur with Amiodarone use. Keratopathy may be present in cases of nutritional deficiency (Fig 16 bottom).

Laboratory testing, including vitamin assays, serum protein concentrations, and antioxidant levels lend support for a nutritional cause of optic neuropathy. Vitamin B12 levels should be obtained to rule out pernicious anemia. Red blood cell folate levels provide evidence of general nutritional status.

Insufficient nutrition does not prove that the optic neuropathy is a result of the deficiency. MRI with contrast and special attention to the optic nerves and chiasm should be performed to rule out compressive or infiltrative lesions. In some cases, it may be necessary to evaluate the cerebrospinal fluid for infections or inflammatory causes of optic neuritis.

Vision loss due to nutritional abnormalities can often be reversed with improved nutrition. Optic neuropathy due to vitamin B12 deficiency or tobacco use is improved with intramuscular injections of hydroxocobalamin. Removal of the toxic substance, as well as cessation of smoking is critical. Drugs that may be responsible for the optic neuropathy should be discontinued and alternative drug forms should be considered.

Patients generally have partial or complete recovery of visual acuity, color vision, and visual field once the toxic agent is eliminated, or the metabolic abnormality is corrected. However, if optic atrophy or loss of the nerve fiber layer has occurred, prognosis is not as good. Therefore early detection and treatment is important.

**Hereditary optic neuropathies**

Hereditary optic neuropathies have different inheritance patterns. Autosomal dominant, autosomal recessive and mitochondrial are the most common patterns. The same genetic defect can result in a different clinical expression.

Vision loss with Leber’s Hereditary Optic Neuropathy (LHON) typically occurs between age 15 and 35, but can occur in both younger and older individuals. Males are much more likely to acquire the disease, and to be symptomatic.

LHON has a maternal inheritance pattern. Only females can pass on the trait, and all offspring will inherit the trait. Females with vision loss from LHON are more likely to have affected children than females who are only carriers.
Several mitochondrial DNA mutations have been shown to cause LHON. (Mutations 3460, 14484, and 11778) Other factors, including other genetic mutations and environmental variables may play a role in the expression of the disease. In addition, a small crowded optic nerve head may put the patient at risk for developing blindness due to LHON.

Painless vision loss typically occurs in one eye first, with the second eye becoming involved weeks to months later. It is rare for the condition to remain monocular for years. The loss of vision may be acute and sub-acute, and usually stabilizes after 3-4 months. Patients generally don’t have symptoms other than vision loss, but they may experience pain on eye movements or Uhtoff’s phenomenon.

Hereditary optic neuropathies are typically bilateral and symmetric with central vision loss. Visual acuity is usually worse than 20/200 but may range from 20/20 to no light perception (NLP). Color vision is decreased, and pupillary responses remain relatively intact despite vision loss. The papillomacular bundle is affected, resulting in a central or cecocentral visual field defect, with preservation of peripheral visual field. The visual field defect often begins prior to acuity loss. It starts as a relative scotoma, but rapidly becomes absolute.

During the acute phase, the optic nerve head will be hyperemic with obscuration of the disc margins. (Fig 17) Retinal blood vessels become tortuous and dilated. In many cases, a classic triad is seen of circumpapillary telangiectasia, swelling of the nerve fiber layer around the disc, and absence of leakage from the disc on fluorescein angiography. The absence of fluorescein dye leakage distinguishes LHON from true optic nerve edema. The classic triad can be seen in both symptomatic and pre-symptomatic patients. Interestingly, telangiectatic vessels and nerve fiber layer swelling can also be seen in carriers. Some patients have completely normal appearing discs, despite being symptomatic for LHON.

Despite continued vision loss, the telangiectasia and nerve fiber layer swelling resolve. The optic nerve head does not become pale for some time, but eventually optic atrophy ensues. The pallor is most pronounced in the temporal area with co-existent damage of the papillomacular bundle. Attenuation of

Figure 17: Dilated, tortuous vessels in LHON. Left: acute phase with hyperemic disc and obscured disc margins. Right: post-acute atrophy and optic disc pallor
retinal arteries and non-glaucomatous cupping may also be evident. Genetic testing should be performed looking for LHON mutations.

There is no proven treatment for vision loss associated with LHON. Avoidance of environmental triggers such as tobacco, excessive alcohol, and environmental toxins has no proven benefit, but is a reasonable recommendation. Genetic counselling is important with LHON. It should be explained that males will not pass on the mutation to their children. Women, whether symptomatic or not, will pass on the mutation to all children both male and female. However, all offspring may or may not become symptomatic. 20-60% of men and 4-32% of women at risk for LHON experience vision loss. Consultation with a low-vision specialist is also critical.

Occasionally, patients experience gradual improvement of vision 6-12 months after the initial vision loss. However, vision loss is most often profound and permanent. If improvement occurs, it is usually bilateral and symmetric. It may be an overall improvement or may be restricted to a small area within a large scotoma. Patients with mutation 14484 have the best prognosis for recovery.

Autosomal dominant optic atrophy is the most common hereditary optic neuropathy. It occurs in the first decade of life, with an average onset of 4-6 years of age. Patients have mutations, deletions or insertions within the OPA1 gene. Patients with autosomal dominant optic atrophy often do not have symptoms – they are found due to routine vision examinations or because of a known family history.

Visual acuity ranges from 20/20 to 20/800. It is better than 20/60 in 40% of cases. If present, the vision loss is typically bilateral and symmetric. Loss of color vision that does not necessarily correlate with the acuity loss is present. Visual fields show central, paracentral, or cecocentral scotomas with sparing of the peripheral field. Nystagmus may be present due to early visual deprivation.

Optic atrophy may be subtle. The pattern of pallor can be either temporal or diffuse. A wedge-shaped excavation of the temporal disc is characteristic for autosomal dominant optic atrophy. (Fig 18) Peripapillary atrophy, absent foveal light reflex, arterial attenuation, and non-glaucomatous cupping may also be present.

Due to the number of different mutations, there is no simple DNA test for autosomal dominant optic atrophy. There is currently no treatment. Visual acuity has been shown to deteriorate by 1 line per decade. The prognosis is not correlated with initial VA’s or acuity loss in family members. Spontaneous recovery does not occur in autosomal dominant optic atrophy.

Traumatic optic neuropathy occurs in 4% of patients after head trauma. The most common cause of injury to the optic nerve, motor vehicle and bicycle accidents, account for up to 60% of optic nerve injuries. Between 10-32% are the result of motorcycle accidents. Damage to the posterior optic nerve usually occurs at the optic canal. Deceleration injury to the ipsilateral forehead region will commonly
result in traumatic optic neuropathy because the force is transmitted to, and becomes concentrated in, the area of the optic canal.

It is important to obtain a complete history from the patient, as well as witnesses. The patient will have a history of blunt or penetrating trauma. The injury may be severe enough to cause loss of consciousness, or be relatively trivial. There may or may not be other ocular evidence of injury such as periorbital hemorrhage, ecchymosis or lacerations. (Fig 19)

Visual acuity will vary from 20/20 to NLP. Vision loss is most likely in those with a fracture in the optic canal. Color vision will be decreased with traumatic optic neuropathy, and an RAPD will be present on the side of the injury. Examination of ocular structures may reveal other evidence of trauma including orbital rim fractures, hyphema, angle recession, or dislocated lens (Fig 20 left). Resistance to retropulsion of the globe is indicative of retrobulbar hemorrhage. Blood in the vitreous may obscure the retinal view. Commotio retinae (Fig 20 right), or a choroidal rupture, may also be responsible for vision loss.

The location of damage causes distinct optic nerve appearances. Optic nerve evulsion produces a partial ring hemorrhage at the optic nerve head. Damage to the optic nerve within 10 mm of the globe, where the central retinal artery and vein reside, result in retinopathy consistent with retinal vein occlusion (CRVO), retinal artery occlusion (CRAO, BRAO), or anterior ischemic optic neuropathy (AION). Hemorrhages of the optic nerve sheath can result in optic disc edema. This should be differentiated from true papilledema due to raised intracranial pressure. After an injury to the posterior optic nerve, the disc will remain normal for 3-5 weeks, followed by pallor. Nearly all patients will develop pallor after injury to the optic nerve.

The images in Fig 21 show the disc appearances of a 37 year old white male with a history of a bike injury involving the left eye at age 6. Note the pallor of the remaining neuroretinal rim.
Neuroimaging with CT is useful with traumatic optic neuropathy. It permits visualization of the bony anatomy, including that of the optic canal and paranasal sinuses. Currently there is no standard approach to treatment of traumatic optic neuropathy. Some advocate the use of steroids, but evidence does not show that treatment with corticosteroids, surgical decompression, or a combination of the two is more effective than no treatment. However, surgery can be helpful to remove bone fragments that are impinging on the optic nerve.

There is reduced chance of visual recovery after optic nerve injury when blood is present in the posterior ethmoidal cells, the patient is over the age of 40, there is loss of consciousness, there is no recovery after 48 hours, or the initial visual loss is severe.

**Congenital optic nerve anomalies**

Congenital optic nerve anomalies are commonly encountered in the ophthalmic practice. Optic nerve hypoplasia is bilateral in 75% of cases. Patients with optic nerve hypoplasia have visual acuity ranging from 20/20 to NLP. Vision should remain stable throughout life. Patients with optic nerve hypoplasia commonly have astigmatism and often develop amblyopia. Visual fields show a generalized constriction or localized defects.

With optic nerve hypoplasia, the optic nerve head appears abnormally small due to a low number of axons. (Fig 22) The disc may appear grey or pale, and is surrounded by a light colored peripapillary halo.

There is another change in pigmentation creating a double ring sign that is associated with optic nerve hypoplasia. Retinal blood vessels are normal size, but retinal veins may appear tortuous.

The relative size of the optic nerve can be determined by measuring the distance from the center of the disc to the macula and dividing this by the size of the disc. (Fig 23) Patients with optic nerve hypoplasia have a ratio that is greater than 3.

Occasionally, the hypoplasia is segmental. (Fig 24) Superior hypoplasia with an inferior visual defect is seen more frequently in children born of mothers with insulin-dependent diabetes.

Optic nerve hypoplasia can occur in isolation or in combination with central nervous system abnormalities. (Table 6) Optic nerve hypoplasia is associated with other neurologic conditions including developmental delay, seizures, and cerebral palsy. Endocrine deficiency can
be associated with optic nerve hypoplasia.

Megalopapilla, an abnormally large optic disc, usually occurs bilaterally and is associated with a large cup-to-disc ratio. (Fig 25) The round, or horizontally elongated cup, as well as the lack of notching of the rim, helps to distinguish megalopapilla from normal-tension glaucoma. The neuroretinal rim may be pale due to axons being spread over the larger disc area.

Morning Glory Disc Anomaly is typically unilateral, with at least half of patients having visual acuity between 20/200 and finger counting. It is more common in females and rarely found in African American patients.

Morning Glory Disc Anomaly is evidenced by a congenital funnel shaped excavation of the posterior pole. The disc appears enlarged and may be recessed or elevated centrally. A white tuft of glial tissue covers the central portion of the cup. Blood vessels appear to be increased in number and emanate from the edge of the disc. After arising from the disc, the vessels turn sharply at the edge of the cup, and have an abnormally straight pattern in the peripapillary region. (Fig 26)

With Peripapillary Staphyloma, the area around the disc is deeply excavated with atrophic changes in the Retinal Pigment Epithelium (RPE). It is generally unilateral and the disc may be normal or appear pale. In contrast to that in Morning Glory Disc Anomaly, the blood vessels have a normal pattern.

These eyes are normally emmetropic or slightly myopic, but can be highly myopic. Visual acuity is markedly reduced, but can vary from 20/30 to NLP. Conventional occlusion therapy can improve acuity if amblyopia is present. Patients typically have cecocentral scotoma. Other congenital abnormalities are common in patients with Peripapillary Staphyloma. Figure 27 shows a Peripapillary Staphyloma in a patient whose prescription is -1.25D with 1.75D cylinder. Best corrected visual acuity is 20/30.
Colobomas result from an incomplete closure of the embryonic fissure. They can be either unilateral or bilateral and are often familial. Visual acuity can vary depending on the nerve fiber layer integrity.

A coloboma of the optic disc appears as a white bowl-shaped excavation of the inferior optic nerve head. (Fig 28) The optic disc is typically enlarged. The inferior neuroretinal rim is thin or absent, and the superior neuroretinal rim is relatively normal. The coloboma may involve the choroid and retina. Iris and ciliary body colobomas may also be present.

An optic pit appears as a round or oval, grey or white, depression in the optic disc. (Fig 29) They are most commonly found temporally, but can be found in any area of the disc. Optic pits are thought to have an autosomal dominant transmission. They are most commonly unilateral, but can be bilateral. Unless macular edema occurs, visual acuity is usually normal. Visual field defects are variable, but include arcuate defects and an enlarged blind spot.

Typically the optic nerve exits the sclera at a 90 degree angle. A tilted optic nerve occurs when the optic nerve exits the eye at an oblique angle. Tilted disc is usually a bilateral condition in which the superior temporal disc is raised simulating disc swelling, while the inferior nasal disc is flat or depressed. This results in an oval-shaped disc with the long axis at an oblique angle. The blood vessels also enter the globe at an oblique angle. There is thinning of the RPE and choroid in the inferior nasal quadrant. (Fig 30)

Patients with tilted disc typically have a bitemporal hemianopic visual field defect that does not respect the vertical midline. The visual field defect is usually confined to the superior temporal quadrant, and may be reduced by performing the visual field with -1.00 to -2.00D over the expected correction. Because patients with tilted discs may also have chiasm defects, neuroimaging is warranted if a bitemporal hemianopsia respects the vertical midline.

Normally, myelination does not extend past the lamina cribrosa. However, in 0.6-1.0% of the population, myelinated nerve fiber layer occurs. The myelination is bilateral in only 8% of cases, and is
continuous with the optic nerve head in only 33% of eyes.

Myelinated nerve fibers manifest as white, feathery patches that follow the nerve fiber bundles, and have a striated appearance. The peripheral edges will appear to be fanned out. The myelination can simulate papilledema due to the elevation of the optic nerve and obscuration of the disc margins and retinal vasculature. Visual acuity is usually not affected in patients with myelinated nerve fiber layer. However, extensive myelination is associated with high myopia and amblyopia. Visual field testing may reveal scotomas or an enlarged blind spot. Myelinated nerve fiber layer is typically static, but reports of progression have occurred. Also, regression has occurred after damage to the nerve fiber layer.

**Conclusion**

Prior to diagnosing optic neuropathy, a detailed history is critical. With a careful history, a cause of the neuropathy, such as demyelinating disease, drugs that cause optic neuropathy, history of neoplasm, or undiagnosed systemic disease may be found. A vaccination history or recent illness can indicate a cause of the optic neuropathy. Also, inquire about symptoms of collagen vascular disease, inflammation, chronic cough, fever, or skin lesions.

The age of the patient should be the first feature to differentiate the cause of optic neuropathy. If the patient is under the age of 40, look for signs of typical demyelinating optic neuritis. Anterior ischemic optic neuropathy (AION) should be suspected in patients over the age of 40. If signs are not consistent with typical demyelinating optic neuritis or AION, perform neuroimaging, serologic testing or lumbar puncture to rule out compressive, infiltrative, infectious or inflammatory optic neuritis. Also look for evidence of current or past uveitis that may indicate an inflammatory or infectious cause. Toxic, nutritional and hereditary optic neuropathy should also be considered in the differential diagnosis. Occasionally, only time will tell the cause of the optic neuritis.

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