Title: Inflammatory Optic Neuropathies: Distinguishing Optic Neuritis from Potential Mimics

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Objectives:

1. To review optic neuritis as a clinical entity versus the spectrum of diagnostic considerations
2. To discuss potential “red flags” which herald an optic neuritis mimic, and review ways to avoid clinical pitfalls in misdiagnosis
3. To outline an approach to the investigation and management of different inflammatory optic neuropathies

Introduction

Many potential causes of optic nerve inflammation exist. Idiopathic optic neuritis (ON) is the most common inflammatory optic neuropathy. This entity is heralded by pain, and often has a self-limited course. While ON may be a sporadic event for some patients, one in every 5 individuals affected by multiple sclerosis (MS) will present with ON as the first manifestation of their disease. Therefore, recognizing the cardinal clinical features of ON is important, because the diagnosis may have potential long-term implications. By extension, it is also crucial that clinicians be aware of the red flags that may indicate the presence of an alternative diagnosis, including age of onset greater than 45 years, absence of pain, atypical systemic symptoms and signs, and poor recovery. Alternatively, conditions mimicking ON may require a different course of management. Therefore, an in-depth understanding of inflammatory optic neuropathies is paramount, because it can help reduce the morbidity associated with these conditions.

Optic Neuritis

Optic neuritis is an inflammatory injury of the optic nerve, which can manifest as an isolated syndrome, or in some cases, represent a harbinger for the diagnosis of MS. With an incidence of 1 to 5 per 100,000 per year, ON is a common cause of acquired vision loss in young adults. Despite the fact that it is a well-described clinically isolated syndrome (CIS), the cause of ON is often unknown. Moreover, it is unclear why women are more likely to be affected than men. Much of what we have come to understand about the clinical presentation of typical ON in patients at risk for MS has been based on the initial experience and long-term follow-up from the Optic Neuritis Treatment Trial (ONTT). This randomized, multicenter study was initially designed to compare the benefits of treatment with either intravenous methylprednisolone (IVMP) (250 mg administered every 6 h for 3 days followed by oral prednisone [1 mg/kg/day] for 11 days); oral prednisone (1 mg/kg/day); or oral placebo in 457 patients with acute ON. From the ONTT, we learned that most ON patients are Caucasian (85%) women (77%),
with a mean age of 32 years. In adults, the majority of ON cases are unilateral, but occasionally bilateral simultaneous vision loss is observed. Yet, in this setting, ON mimics need to be considered including: neuromyelitis optica (NMO) toxic-metabolic optic neuropathies and Leber’s hereditary optic neuropathy (LHON). Patients with typical ON often report sub-acute onset vision loss that worsens over hours to days. Ninety two percent of ON patients experience pain within the first week of symptom onset, which is frequently provoked by eye movements. Approximately one-third of typical ON patients will note flashes of light in the affected eye, known as photopsias or phosphenes albeit they may not divulge this information without prompting.

Optic Neuritis: Approach to the Examination

In patients with suspected ON, there are several localizing features on initial examination, which are key to securing the diagnosis. Initially, the severity of vision loss in the affected eye (ON eye) may range from mild (Snellen visual acuity equivalent of 20/20) to no light perception. In patients with unilateral optic nerve involvement, a relative afferent pupil defect (RAPD) will be apparent in the ON eye. Visual field defects follow the topography of the retinal nerve fiber layer (RNFL). Cecocentral, altitudinal and arcuate patterns of vision loss are often observed. Dyschromatopsia, or decreased color vision is also common. This finding can be particularly helpful in localizing the diagnosis in patients with mild central vision loss, who have disproportionate deficits in color vision function. In cases of retrobulbar ON, the fundus examination is initially normal, whereas patients with anterior ON (sometimes referred to as ‘papillitis’) manifest mild to moderate optic disc swelling acutely. The ONTT demonstrated that severe optic disc edema, vitreous cell, and hemorrhage are relatively uncommon findings in typical ON patients and may herald a mimic (Table 1) such as neuroretinitis. Not surprisingly, these atypical fundus features are associated with a reduced risk of developing MS, potentially because the patient does not in fact have ON. Our understanding regarding the clinical presentation, diagnosis and treatment of these alternate conditions has evolved since the inception of the ONTT study.

Optic Neuritis: Considering the Mimics

While the diagnosis of typical ON is often apparent, misdiagnoses in clinical trials have occurred. Of 457 patients enrolled in the ONTT, three patients were later diagnosed with anterior ischemic optic neuropathy, two had compressive lesions, and two had ON associated with connective tissue diseases. The realization of an alternate diagnosis may arise after the initial cranial imaging study reveals an unexpected finding, such as a mass lesion, or when clinical recovery is worse than expected over the course of follow-up. Yet, in a typical patient, with a classic history and a compatible examination, the diagnosis of ON can be made with a high degree of certainty on clinical grounds alone. Even in patients with uncommon features, an atypical presentation of a common diagnosis is still more apt to occur than an uncommon diagnosis. Yet, there are several
clinical ‘red flags’, which should prompt concern for a potential diagnosis of an ON mimic, which may indicate the need for additional investigations (Table 1). Patients, particularly young men, who present with painless, bilateral sequential (or simultaneous) optic nerve dysfunction should be investigated for LHON. While LHON is considered to be a mitochondrial disorder predominantly affecting young males, the risk of women becoming symptomatic if they are carriers of a primary mutation is one-fifth of that in males. Therefore, female gender should not preclude investigations for LHON mutation testing in appropriate circumstances. When affected, women are at increased risk of having children with LHON, and may wish to seek further genetic advice. Individuals who are older than average for ON, who present without pain and manifest prominent optic disc edema may harbor a diagnosis of anterior ischemic optic neuropathy (AION). Young adults, particularly women, with photopsias and evidence of an enlarged blind spot on visual field testing may have one of the ‘Big Blind Spot’ syndromes (including multiple evanescent white dot syndrome [MEWDS] and the acute idiopathic blind spot enlargement syndrome [AIBSE]). Young to middle-aged women, especially those of Asian descent, presenting with unilateral or bilateral ON should be evaluated for NMO, because the visual outcome in these individuals tends to be poor, and the management of ON in NMO patients is different from that of MS patients. On occasion, young patients are mistakenly diagnosed with ON when they report acute onset awareness of a more longstanding problem, particularly in the setting of compressive optic nerve lesions.

**Optic Neuritis: Making the Diagnosis**

With a classic history and a compatible examination, the diagnosis of ON can be made with a high degree of certainty on clinical grounds alone. Cranial MR imaging is performed because it is the best predictor of the patient’s future or current risk of MS, not because it is necessary to confirm the diagnosis of ON. In the original ONTT cohort, the 10-year risk of developing clinically definite MS was 22% in patients with no brain lesions on baseline MRI, as compared to 56% in patients with one or more lesions. After 15 years, 72% of patients with ON who had one or more white matter lesions on their initial MRI scan developed MS as compared with only 25% of patients with no baseline MRI lesions. With the benefit of 15 years of hindsight, the ONTT investigators concluded that the risk of developing MS was highest in the first 5 years after ON. Yet, a substantial risk persisted throughout the 15 years of follow-up in patients with ON who had initial brain MRI lesions. Among patients who were not diagnosed with MS at the 10-year examination, the probability of developing MS by the 15-year follow-up point was 32% when one or more baseline lesions were present versus 2% when there were no such lesions. It is noteworthy that, since the adoption of the revised McDonald criteria, the diagnosis of MS can be confirmed as early as the first clinical presentation with cranial MRI.

In the ONTT, the predictive value of other baseline factors for the development of MS varied depending on presence or absence of brain lesions on MRI at presentation. When MRI showed one or more lesions were present at study entry, no demographic or clinical characteristics were predictive of MS development. In contrast, among patients without
baseline lesions on MRI, the risk of MS was higher for women, when there was a history of a viral syndrome before ON onset, and when the optic disc appeared normal at the time of visual loss. MS was more than twice as likely to develop in ON patients when the retrobulbar part of the optic nerve was affected (31%) as opposed to the anterior optic nerve (14%), consistent with the belief that retrobulbar neuritis is the typical form of ON in MS. In the final 15-year ONTT follow-up, among patients with monofocal ON at study entry (no baseline brain lesions on MRI, no prior contralateral eye ON, and no prior neurologic symptoms or signs), the diagnosis of MS was not observed in any patient when initial ophthalmoscopy showed: severe optic disc swelling (n = 21), disc or peripapillary hemorrhages (n = 16), retinal macular exudates (n = 8), lack of pain (n = 18), or when presenting visual acuity was reduced to no light perception (n = 6). Thus, in addition to highlighting the predictive value of the baseline MRI scan, the ONTT also demonstrated the importance of the initial fundus findings in determining the future risk of MS in patients with ON.

**Optic Neuritis: Investigations**

When the diagnosis of ON is not clear, other ancillary tests can be useful in the investigative process, although the role of these investigations has been diminished since the introduction of the revised McDonald criteria. Cerebrospinal fluid (CSF) analysis can be used to detect evidence of CNS infection, characterized by hypercellularity and a raised protein concentration. Finding oligoclonal bands of immunoglobulins in the CSF can help differentiate between demyelinating ON and other causes of inflammatory optic neuropathy. Patients with ON may have no oligoclonal bands or local intrathecal synthesis of immunoglobulins (unmatched bands compared with serum). In other demyelinating optic neuropathies, sarcoidosis, or vasculitis, there may be no oligoclonal bands or systemic production of immunoglobulins (matched oligoclonal bands in both CSF and serum). The CSF analysis can also play a role in establishing a link with MS in patients with ON who have atypical features at presentation (eg, older age), or have abnormal cranial MRI findings that are not classic for demyelination, including nonspecific punctate white matter lesions. In some cases, visual evoked potential (VEP) testing may also aid in establishing the mechanism of optic nerve injury. Patients with ON frequently manifest increased VEP latencies and reduced amplitudes consistent with demyelination. Previously, VEP findings have been used to show dissemination of lesions in the CNS of patients deemed to be at risk of developing MS. Yet, VEP testing is not routinely indicated in the evaluation of ON because abnormal findings may also occur in patients with other conditions, such as optic nerve compression, infiltration, and non-demyelinating inflammation.

**Optic Neuritis: Treatment**

The ONTT demonstrated that high-dose IVMP initiated within 8 days of initial presentation hastened the clinical recovery but did not change long-term visual outcomes
in ON patients. In the original ONTT study, IVMP was administered in divided doses, but for practical reasons 1000 mg IVMP is often given as a single dose (with or without an oral taper) in clinical practice. In some centers, the oral equivalent (prednisone or methylprednisolone) of the original ONTT IVMP dose is used in the outpatient setting. Previous studies have shown that the bioavailability of 1250 mg of oral prednisone is comparable with 1 g of IVMP, and that patients are highly compliant with oral corticosteroid treatment. Hence, for patients considering using high-dose corticosteroid therapy for the management of acute ON, we advise that it is likely the dose of drug, not the route by which it’s taken, that determines its efficacy.

The decision regarding what specific regimen of high-dose corticosteroid therapy to use for the management of acute ON is generally left to the discretion of the treating physician, and practice patterns vary from one region to the next. Suffice to say, there are conflicting opinions on this issue, probably because there has not been a large-scale, randomized, placebo-controlled trial since the ONTT designed to address some potential areas of ambiguity. More specifically, it is not known whether corticosteroid treatment is beneficial in patients whose symptom duration is longer than 8 days; whether larger doses of corticosteroids are more effective than lower doses; what the optimal corticosteroid regimen is; whether the observed increased ON recurrence rate associated with oral prednisone is also observed in MS attacks and whether high-dose methylprednisolone given periodically will improve the prognosis for patients with MS. In 2000, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) reviewed the role of high-dose corticosteroids in the treatment of acute ON, and concluded that: “Oral prednisone in doses of 1 mg/kg/day has no demonstrated efficacy in the recovery of visual function in acute monosymptomatic ON, and therefore is of no proven value in treating this disorder”. Furthermore, according to the AAN, “higher dose oral or parenteral methyl-prednisolone ACTH may hasten the speed and degree of recovery of visual function in persons with acute monosymptomatic ON. There is, however, no evidence of long-term benefit for visual function. The decision to use these medications to speed recovery but not to improve ultimate visual outcome should therefore be based on other non-evidence-based factors such as quality of life, risk to the patient, visual function in the fellow eye, or other factors that the clinician deems appropriate”. In accordance with AAN recommendations, we endorse a patient-centric philosophy, and tailor our treatment approach to the circumstances of the individual. In cases of typical ON with mild vision loss, we may not recommend steroids, because the ONTT showed that for patients presenting with a visual acuity of 6/12 (Snellen equivalent of 20/40) or better, steroids provided no benefit. Similarly, if the symptom onset was in excess of 2 weeks prior to clinical presentation and patients have already manifested visual recovery we may defer therapy because the benefit of steroids initiated outside this time window for acute ON is not known. By contrast, if a patient has pre-existing vision loss in the contralateral eye, we may offer corticosteroids to hasten visual recovery in the ON eye. We do not generally implement an oral prednisone taper, as there is no evidence that this improves visual outcomes or impacts the long-term risk of MS. Furthermore, an oral taper of corticosteroids is often not necessary because the short treatment course employed for typical ON is unlikely to suppress the hypothalamic–pituitary axis. In patients with co-morbidities such as poorly controlled diabetes or a known prior adverse response to corticosteroids we may defer therapy in cases of typical
ON. When we decide to treat, we offer typical ON patients 1000 mg/day of IVMP or an equivalent daily dose of oral prednisone (1250 mg) for 3–5 days with or without an oral taper. Appropriate precautions are taken before starting treatment, and we may provide a medication for sleep and/or gastric protection. Moreover, we advise patients of possible side effects related to corticosteroid use including: weight gain, headache, elevated blood sugars, avascular necrosis of the hip and bone density loss, gastritis or peptic ulcer disease, mood alteration (including psychosis), elevated blood pressure, elevated intraocular pressure, immunosuppression and accelerated cataract development, to name a few.

**Other Demyelinating Optic Neuropathies**

Several inflammatory forms of optic neuritis are not associated with MS but manifest as part of another demyelinating condition, including neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), chronic relapsing inflammatory optic neuropathy (CRION), anti-myelin oligodendrocyte glycoprotein (MOG) associated ON, and postvaccination-associated ON. These entities should be considered in patients who manifest atypical features, including pediatric or older age at onset, the presence of specific clinical signs (recurrent myelitis in NMO or encephalopathy in acute disseminated encephalomyelitis), or poor clinical recovery.

**Neuromyelitis Optica**

Neuromyelitis optical spectrum disorders (NMOSD) are typically characterized by a combination of ON and transverse myelitis; severe inflammation and necrosis of the optic nerves and spinal cord often lead to marked disability and a decreased life expectancy, especially if untreated. Within 5 years of onset, approximately 50% of patients with NMO are either blind in one or both eyes or require a walking aid, in sharp contrast to the relatively milder impact of MS on affected individuals with the same disease duration. Predictors of a worse prognosis in NMO include the number of relapses in the first 2 years of symptom onset, the severity of the first attack, and, having an associated autoimmune disorder such as systemic lupus erythematosus (SLE). While other potential mimics may manifest with atypical signs and symptoms at initial presentation, NMO associated ON can easily be overlooked if a high degree of suspicion is not present, since these patients often present with monocular involvement. Patients with poor visual recovery a month after symptom onset, a history of recurrent ON, bilateral ON, or symptoms of transverse myelitis should be investigated for NMO. Previously, the diagnosis of NMO was made predominantly on clinical grounds and with spinal MRI evidence showing extensive longitudinal cord lesions. Currently, 80% of NMO cases are associated with serum antibodies to aquaporin-4, the most abundant water channel protein in the CNS. Yet, anti-NMO-IgG antibodies are absent in 10% to 20% of patients with NMO, even with the most up-to-date assays. Thus, while this antibody has been incorporated into the diagnostic criteria for the disease, it is neither a necessary nor sufficient feature. Notably, patients with NMO are on average older than their MS
counterparts (the median age of onset is 40 years in NMO), with a strong female preponderance (female-to-male ratio is 9:1). In a recent retrospective study of 175 patients with NMO, isolated ON was the initial event in 58% of cases. Interestingly, bilateral ON was more likely to occur in sero-negative NMO cases. Furthermore, this study showed that there was a marked delay to diagnosis in patients with NMO, which ranged from 16 months if the disease started with myelitis and 55 months if ON was the initial clinical event. Classically, NMO attacks are treated with high-dose steroid therapy or plasma exchange treatments. Maintenance therapy may begin with prednisone and azathioprine, although mycophenolate mofetil can also be used. In recent years, rituximab has been shown to be a moderately effective agent, and tocilizumab, an interleukin-6 blocker, has been studied in patients with NMO with encouraging results.

Recurrent Optic Neuropathy

While ON is frequently limited to a single episode, 3% to 5% of patients experience recurrent episodes (affecting either or both eyes, sequentially or simultaneously) with negative preliminary investigations for MS, NMO, or other causes. A clinical entity referred to as recurrent (or relapsing) optic neuritis or (alternatively, neuropathy) has been described. Although the lexicon used to describe these entities varies slightly, reports to date reveal two main forms of recurrent demyelinating optic nerve injury. The first, termed chronic relapsing inflammatory optic neuritis (CRION), is a painful, progressive condition that relapses after steroid withdrawal. The second, commonly referred to as relapsing idiopathic optic neuritis (RION), is a non-progressive condition that is not associated with steroid dependence. Similar to typical ON, these recurrent demyelinating optic neuropathy subtypes have occasionally been linked to CNS diseases. In one study, the combined conversion rate to MS or NMO was 27% at 5 years and 42% at 10 years. Approximately 20% to 25% of patients with recurrent demyelinating optic neuropathy have been shown to convert to NMO within 5 years, with a higher rate (50%) in the NMO-IgG seropositive group than in the seronegative group (10%). Therefore, it is important to remember that many of these recurrent optic neuritis subtypes fall into the broad category of steroid-responsive optic neuropathies, which over time can be linked with other systemic diseases such as NMO, sarcoidosis, and Wegener granulomatosis, to name a few (Table 1). Therefore, rigorous and repeated efforts should be made to investigate for these conditions over time in cases of relapsing demyelinating optic nerve injury, particularly when symptoms recur during a steroid taper. Patients with steroid-responsive optic neuropathies, regardless of etiology, are often treated with long-term, tapering corticosteroid regimens, with or without adjuvant immunosuppressive therapy.

Infectious Optic Neuropathies

Optic neuritis is rarely infectious in nature. More commonly, optic nerve involvement can occur in the clinical setting of neuroretinitis, which is characterized by vision loss, optic disc swelling, and exudative maculopathy, commonly referred to as a “macular star”.
Despite the ever-growing list of infectious, neoplastic, and inflammatory conditions linked with neuroretinitis, approximately 50% of cases are idiopathic. A complete workup including cranial imaging, lumbar puncture, and serologic evaluation in patients presenting with acute neuroretinitis is often necessary because treatments are directed toward the underlying pathogen. The investigations involve testing for potential sources of infection, including syphilis, Lyme disease, histoplasmosis, brucellosis, chlamydia, HIV, West Nile virus, toxoplasmosis, Epstein-Barr virus, viral hepatitis B and C, and tuberculosis.

**Neuroretinitis**

Neuroretinitis typically affects young, healthy adults, and no sex predilection exists. In approximately two-thirds of cases, patients present with an antecedent viral prodrome. The presenting visual acuity deficit can be mild to severe, and usually a relative afferent pupillary defect in the affected eye is present. The most common visual field defects noted are of the cecocentral and central types. While the severity of the clinical presentation can vary, patients generally present with stellate maculopathy and disc edema, which may be associated with exudative detachment in the peripapillary region. Ophthalmoscopy reveals vitreous cells in 90% of cases, and multiple focal yellow-white retinal lesions may appear, which can induce further retinal vascular injury in the form of branch retinal artery or vein occlusions. Optic disc edema associated with neuroretinitis typically begins to abate in 2 weeks, and to resolve within 3 months. In contrast, the macular star may be present for up to a year. Visual recovery usually starts within several weeks of symptom onset. In cases of recurrent idiopathic neuroretinitis, however, visual recovery is limited and vision loss is cumulative with repeated attacks, often resulting in permanent impairment. In this setting, immunosuppressive treatment may lessen the attack frequency.

**Cat Scratch Disease**

Cat scratch disease, caused by Bartonella henselae, is a relatively common cause of neuroretinitis and represents one of several diseases caused by Bartonella species. It is a worldwide condition and typically affects children more often than adults. The majority of cases are caused by a cat scratch or bite, but the disease can also be transmitted to humans by dogs. Pain in or around the eye is a variable symptom, and vision loss may be mild to severe at onset. It is noteworthy that, in cases of cat scratch disease, a macular star may not be initially evident, but may evolve over days to weeks. MRI of the optic nerve is usually normal but CSF analysis may show lymphocytic pleocytosis. The diagnosis of cat scratch disease is confirmed by the detection of serum antibodies to B. henselae.

**Syphilis**
Syphilis is a bacterial infection caused by the spirochete Treponema pallidum. It is primarily a sexually transmitted disease, although vertical transmission can occur from mother to child. Optic neuropathy indicates evidence of active or clinically evident neurosyphilis, and usually manifests in later (secondary or tertiary) stages of the condition. Approximately 18% of secondary syphilis cases develop neurologic or ophthalmic manifestations. The type of vision loss in patients affected by syphilis largely depends on the mechanism of injury. Visual symptoms can manifest as part of a meningeal process and may be accompanied by features of raised intracranial pressure, including papilledema. Patients with syphilitic perineuritis present with inflammation of the optic nerve sheaths associated with optic disc swelling in the absence of increased CSF pressure, and visual impairment. In cases of optic neuropathy associated with syphilis, vision loss is often central and associated with dyschromatopsia. Pain may or may not be reported. The optic disc appearance may be normal (in cases of retrobulbar optic nerve involvement), atrophic, or edematous. Accompanying features of neuroretinitis may also be seen, including the manifestation of a macular star. The neuroimaging findings of syphilis are not particularly distinguishing, although meningeal enhancement may be observed. Similarly, CSF findings may include a normal cell count with differential, normal protein level, and normal Venereal Disease Research Laboratory (VDRL) results (diagnostic sensitivity is 27%). Specific testing with fluorescent treponemal antibody absorption (FTA-ABS) may be abnormal. Patients infected with HIV may have syphilis, even in the absence of positive VDRL or FTA-ABS serology. False negatives (32%) can occur in early primary, latent, or late syphilis and with concomitant HIV infection. Moreover, patients with concurrent HIV have a higher incidence of neurosyphilis, including ocular complications, which are more likely to be bilateral. Benzathine penicillin is the mainstay of therapy for primary and secondary syphilis but its CNS penetration is poor; therefore, in syphilitic optic neuropathy, long-term therapy with IV aqueous penicillin at a dose of 2 to 4 million units every 4 hours for 2 weeks is standard treatment. Corticosteroid therapy may also be used.

**Lyme Optic Neuropathy**

Lyme disease is caused by the spirochete Borrelia burgdorferi, which is a tick-borne pathogen. This condition is often characterized by a classic rash called erythema chronicum migrans. CNS involvement may occur days to weeks after the initial infection. Patients with Lyme disease may manifest inflammation of the ocular anterior segment, exudative retinal detachment, papilledema, and cranial neuropathies. Papilledema caused by raised intracranial pressure in Lyme meningitis occurs more frequently in children, although some adult cases have been reported. Occasionally, cases of retrobulbar optic neuritis, papillitis, neuroretinitis, and ischemic optic neuropathy have been associated with Lyme neuroborreliosis. In cases of Lyme associated optic neuritis, vision loss is typically acute, and pain may occur at initial presentation. Visual acuity deficits range from mild to severe in cases of optic neuritis, whereas, for patients with perineuritis, visual acuity is generally well preserved. Optic disc edema can be observed in in cases of papillitis and neuroretinitis. The MRI findings in Lyme disease are often not specific and may include meningeal involvement and cranial nerve enhancement. The CSF may show
a lymphocytic pleocytosis with or without protein elevation. The standard screening test is an ELISA, whereas the Western blot assay is used to distinguish false-positive ELISA results from true infection. In cases of optic neuritis associated with CSF lymphocytic pleocytosis and cranial neuropathies, neuroborreliosis should be strongly considered, particularly in Lyme-endemic areas. Detection of intrathecal antibody against Lyme is diagnostic. Treatment for neuroborreliosis typically involves 2 g/d of IV ceftriaxone for 1 month.

Tuberculosis

Tuberculosis (TB) is bacterial infection caused by Mycobacterium tuberculosis, which on rare occasions causes ON. Since the emergence of AIDS, TB has made a resurgence in the clinical arena, and is now considered a significant opportunistic infection in HIV patients. While TB typically presents with pulmonary involvement, extrapulmonary involvement is also relatively common in immunocompromised patients. As with syphilis, manifestations of vision loss in TB patients vary with the mechanism of optic nerve involvement. Tuberculomas can cause mass effect on the anterior visual pathway. Alternatively, there may be direct infiltration of the optic nerve or optic nerve inflammation caused by opticochiasmatic arachnoiditis. Pain is a variable finding, and vision loss may be mild to profound in TB-associated ON. The onset of visual symptoms may be rapid or gradual. The optic disc can be normal, edematous, or atrophic at presentation. In the setting of meningitis, multiple cranial neuropathies may be seen. MRI features may be nonspecific in TB, although skull-based dural disease is common, and optic nerve enhancement may or may not be evident. Similarly, the CSF findings may be difficult to distinguish from other entities, with elevated protein, mild pleocytosis, and low glucose being variably detected. The gold standard for diagnosis is the demonstration of tuberculous bacteria by smear or culture, yet recent studies have shown that PCR molecular assay testing of respiratory specimens can provide sensitive and rapid results. Treatment for TB-associated optic neuritis includes isonicotinic acid hydrazide (INH), ethambutol, rifampin, streptomycin, and pyrazinamide, and may vary between the immune-competent versus immune-compromised hosts.

Inflammatory Optic Neuropathies Associated with Systemic Disease

Rarely, optic neuritis may occur as part of a systemic disease such as SLE, sarcoidosis, or Sjogren syndrome. Given the multisystem nature of these conditions, early diagnosis and initiation of appropriate treatment can be paramount to reducing visual morbidity. To further complicate matters, medications including some of the anti-tumor necrosis factor agents and hydroxychloroquine can cause a demyelinating optic neuropathy and retinopathy, respectively. Thus, in patients presenting with vision loss secondary to systemic inflammatory conditions, it is important to distinguish the manifestations of the underlying disease from the effects of the therapies used to treat them.
Sarcoidosis

Sarcoidosis is a multisystem granulomatosis inflammatory condition that typically affects the lymphatic system, lungs, skin, and eyes. Like syphilis, sarcoidosis is a master mimicker, and sarcoid-associated optic neuropathy can present exactly like typical ON. Hence, the diagnosis can be missed unless there is an aberrant feature of the patient’s clinical presentation or course (including recurrent vision loss with steroid withdrawal) that prompts suspicion. Sarcoidosis affects all ethnic groups, although in the United States it is more prevalent in African Americans. Females are more commonly affected than males, and neurologic involvement occurs in 5% to 16% of cases. Ophthalmic involvement occurs in approximately 25% of patients, with a higher incidence noted in those with pulmonary disease. The optic nerve can be affected via several mechanisms in sarcoidosis, including nonspecific inflammation of the optic nerve similar to typical ON; infiltration of the optic nerve or sheaths mimicking mass lesions, such as optic nerve glioma or meningioma; mass effect due to direct compression of the nerve; and parachiasmal involvement. Patients may or may not present with pain, and the extent of vision loss can be variable. Visual field defects tend to reflect the region of involvement in the anterior visual pathway affected, and central scotomas, altitudinal defects, or homonymous field loss may be seen. The optic nerve may be normal, atrophic, or edematous in appearance. Other findings that may provide a clue to the diagnosis include the presence of conjunctival nodules, keratic precipitates, iris nodules, uveitis, and lacrimal gland enlargement. In many cases of neurosarcoidosis, the patient may not have pulmonary features or any other associated findings; therefore, establishing the diagnosis can be challenging. In these cases, recognizing the cardinal ocular symptoms and signs can be helpful. The cranial and orbital MRI features include intense optic nerve and meningeal enhancement, particularly at the base of the skull in close proximity to the chiasm. The CSF analysis may show lymphocytic pleocytosis and an elevated protein level. If clinical suspicion exists, additional investigations to consider include chest imaging, total body gallium scan, pulmonary function tests, an anergy panel, and 24-hour urine calcium levels. To diagnose sarcoidosis, potential sites to biopsy include the lacrimal glands, conjunctival lesions, or accessible lesions implicated on the gallium scan. Treatment regimens usually involve corticosteroids, sometimes in conjunction with other immunosuppressive agents.

Giant Cell Arteritis

Giant cell arteritis is also known as temporal arteritis, and represents a systemic, inflammatory, vascular syndrome that predominantly affects the temporal arteries. Giant cell arteritis is commonly associated with polymyalgia rheumatica (PMR). Approximately half of GCA patients have underlying PMR, whereas about 15% of PMR patients develop GCA. Giant cell arteritis affects individuals aged greater than 50 years, and occurs more often in women than men. It is more common in Caucasians relative to Asians, African or Americans. Vision loss tends to be severe (worse than 20/200), and
may affect one or both eyes at the same time. Patients may report episodic transient vision loss in advance of more permanent visual disturbances. Defects tend to involve the central and peripheral visual field regions. Patients may note pain with vision loss, and therefore new onset headaches in patients aged greater than 50 should prompt consideration for GCA. Other specific symptoms which may herald vision loss include jaw claudication, scalp tenderness, episodic diplopia, and neck pain. General constitutional complaints reported by GCA patients may include fever, weight loss, malaise, myalgias, and fatigue. The hallmark of GCA associated arteritic anterior ischemic optic neuropathy (AION) is pallid optic disc edema, which is often associated with vessel attenuation, hemorrhages, and cotton wool spots in the retina. On occasion, optic nerve involvement can occur in the absence of edema, in cases of posterior ischemic optic neuropathy (PION). Other associated ocular features of GCA include cilioretinal artery occlusion and choroidal ischemia. The diagnosis is made with the demonstration of elevated acute phase reactants [erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP)] in the serum, normochromic normocytic anemia, thrombocytosis, and elevated serum fibrinogen level. A temporal artery biopsy (aiming for a specimen length of at least 2 cm) demonstrating granulomatous infiltration by epithelioid cells and lymphocytes, with loss of the internal elastic lamina is considered the diagnostic gold standard for GCA. High-dose corticosteroids are the mainstay of therapy, and occasionally adjunctive treatment with immunosuppressive agents may be used. Because the recovery tends to be poor in eyes affected by arteritic AION, treatment is aimed at protecting vision in the clinically unaffected eye.

Wegener Granulomatosis

Wegener granulomatosis is characterized by necrotizing granulomatous vasculitis affecting vessels in the upper and lower respiratory tracts, paranasal sinuses, kidneys, and lungs. It can occur in a limited ocular form, namely without pulmonary or renal involvement. Ocular involvement is seen in approximately 50% of patients and is usually bilateral. A classic non-ocular feature is saddle-nose deformity. Orbital involvement can arise secondary to extension from the sinuses and may manifest with proptosis (45%), ocular motility deficits, and pain. Wegener granulomatosis generally affects patients 40 to 50 years of age, but has also been reported in children and younger adults. There is a predilection for male involvement, with a sex ratio (male to female) of 2:1. However, limited Wegener granulomatosis is more common in women. Investigations include cranial and orbital imaging to look for evidence of sinus inflammation, lacrimal gland enlargement, and orbital masses (with infiltration and obliteration of the fat planes, midline involvement, and bone erosion). Serologic testing includes cytoplasmic neutrophilic cytoplasmic antibodies (c-ANCA), which have good sensitivity and specificity for Wegener granulomatosis, resulting in positive results in 60% to 95% of patients with disseminated disease. The yield of testing decreases in cases of limited disease, however, and false-negative results can occur. Tissue diagnosis is ideal and may be obtained from the nasal sinuses or orbits. Treatment consists of high-dose corticosteroids, often in combination with cyclophosphamide or rituximab.
Sjogren Syndrome

Sjogren syndrome is a systemic autoimmune disease characterized by dry eyes (keratoconjunctivitis) and dry mouth (xerostomia). Primary Sjogren tends to be limited to the oral and lacrimal glands, causing sicca syndrome. Patients who manifest features of other conditions, including rheumatoid arthritis, vasculitis, scleroderma, polymyositis, primary biliary cirrhosis, or chronic active hepatitis, are characterized as having secondary Sjogren syndrome. This condition is usually seen in middle-aged adults, with a female-to-male sex ratio of 9:1. Thirty percent of patients with rheumatoid arthritis have associated Sjogren syndrome, and may carry the human leukocyte antigens (HLA) DQ*0501 allele, HLA-B8, HLA-DR3, and/or HLA-DRw52. CNS involvement occurs in 2% to 25% of people with Sjogren syndrome and is much less common than peripheral nervous system involvement in affected individuals. Sjogren syndrome has been associated with NMOSD and, accordingly, severe vision loss and optic atrophy can manifest in affected patients. Present studies indicate that ON in patients with Sjogren syndrome who are seropositive for NMO-IgG have two coexisting autoimmune diseases rather than a secondary vasculitic complication of the systemic disease. The diagnosis of Sjogren syndrome can be determined by testing for rheumatoid factor (50% of patients) and antibodies against antigens known as Ro (SSA) and La (SSB). Treatment commonly involves corticosteroids and immunosuppressive therapies.

Systemic Lupus Erythematosus

As in sarcoidosis, systemic lupus erythematosus (SLE) can present with a myriad of ocular manifestations that may be a harbinger of the disease, or a marker of disease activity in those with an established diagnosis. From a clinical perspective, patients with SLE and optic nerve involvement may be distinguished from patients presenting with typical ON because the former often have coexisting features of systemic disease, including rash, fever, weight loss, and other organ involvement. While relatively rare (affecting 1% of patients), optic nerve involvement in SLE may manifest as ON or ischemic optic neuropathy. The onset of vision loss is usually painless, sub-acute, progressive, and severe. Visual acuity in SLE-associated optic nerve injury is usually worse than 20/200, whereas in the ONTT only 36% of typical ON patients had similar visual dysfunction. In SLE, visual recovery is not as robust as typical optic neuritis, with only 50% of patients recovering better than 20/25, and 38% of patients having a postacute visual acuity worse than 20/200. The increased severity of disease in SLE-associated optic injury is believed to occur because the primary process is considered an ischemic injury to the nerve as opposed to a primary demyelinating insult. When SLE is suspected, the ANA level may be abnormal, with a speckled pattern most commonly seen. While ANA titers can be sensitive, this test is not specific for SLE, and serologic markers including anti-double-stranded DNA and anti-Smith antibodies can help confirm the diagnosis. Anti-phospholipid antibodies are also seen with increased frequency in patients with SLE who have manifestations of ophthalmic or neurologic disease. The
Inflammatory optic neuropathy associated with SLE can respond dramatically to corticosteroid therapy, and early treatment is associated with better visual outcomes. Standard therapy includes high-dose corticosteroids followed by an extended oral taper. Therapeutic benefits have also been shown with immunosuppressive agents such as cyclophosphamide, cyclosporine, methotrexate, and azathioprine.

Table 1:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical Features</th>
<th>Investigations to Consider</th>
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<tbody>
<tr>
<td>Nonarteritic anterior ischemic optic neuropathy (NAION)</td>
<td>Painless, altitudinal visual field defect is common, vision loss noted upon awakening, vascular risk factors, phosphodiesterase type 5 inhibitor use, nocturnal antihypertensive use, sleep apnea, physiological disc at risk, patients with NAION have optic disc edema acutely</td>
<td>Sleep study, 24-hour blood pressure monitoring, investigations for hypertension and diabetes</td>
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<tr>
<td>Compressive optic neuropathy (pituitary lesions, meningiomas, aneurysm)</td>
<td>Painless, progressive vision loss, color loss disproportionate to visual acuity deficit, non-glaucomatous optic disc cupping, temporal visual field cut, bilateral visual field involvement</td>
<td>Cranial and orbital MRI/MRA or CT/CTA</td>
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<tr>
<td>Infectious optic neuropathies (eg, tuberculosis, syphilis, Lyme disease, among others)</td>
<td>Associated uveitis, papillitis or retrobulbar optic neuropathy, macular star, infectious symptomatology</td>
<td>Serum/CSF culture/sensitivity; specific serological testing for syphilis, Lyme, Bartonella henselae, HIV, toxoplasmosis, viral hepatitis B and C; Epstein-Barr virus; histoplasmosis; tuberculin testing; chest imaging; serum sedimentation rate, C-reactive protein</td>
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<td>Inflammatory/de-myelinating optic neuropathies not associated with MS or an underlying systemic disorder: NMO, CRION, ADEM, anti-Myelin oligodendrocyte glycoprotein–associated (MOG) optic neuritis</td>
<td>Poor recovery, unilateral or bilateral optic neuritis, associated transverse myelitis, recurrent symptoms</td>
<td>Brain MRI, cervical spine MRI, anti-NMO antibody testing</td>
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<tr>
<td>Genetic optic neuropathies (LHON, autosomal-dominant optic neuropathy)</td>
<td>Bilateral vision loss, painless, poor recovery, family history</td>
<td>Genetics referral with specific mutation testing</td>
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<tr>
<td>Toxic/nutritional (tobacco-alcohol amblyopia and Cuban and Tanzanian epidemic optic neuropathies)</td>
<td>Bilateral optic nerve involvement, history of drug use (ethambutol, selenium, amiodarone), restricted nutritional intake, glue sniffing, methanol ingestion</td>
<td>Vitamin B12 levels, toxic screen</td>
</tr>
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</table>
Sarcoid optic neuropathy  Steroid responsive, poor recovery, systemic symptoms and signs  Chest imaging, serum ACE, Gallium scan, tissue diagnosis, bronchoalveolar lavage, soluble IL-2 receptor

Connective tissue/vasculitic optic neuropathy (lupus, Wegener granulomatosis, Sjögren syndrome, Behçet disease)  Steroid responsive, associated systemic symptoms and signs  Serum ESR, Sjögren specific antibodies, CRP, ANCA, ENA panel, ANA

Orbital inflammation/optic perineuritis/Grave disease  Orbital signs (proptosis)  MRI or CT orbital imaging, blood work including TSH ANCA, CRP, ESR, ACE

Raised ICP  Optic disc edema; pulsatile tinnitus, transient visual obscurations, headaches, elevated body mass index  MRI/MRV of brain and orbits, lumbar puncture with opening pressure, CSF analysis

Optic disc drusen  Visible disc drusen or optic disc elevation  B-scan ultrasonography of orbits, orbital CT

Uveitis/posterior scleritis  Severe pain, floaters, vitreous reaction  Fluorescein angiography, B-scan ultrasonography of orbits

Autoimmune optic neuropathy (Similar to CRION)  Steroid responsive  Skin biopsy for immunoglobulin deposition

Infiltrative optic neuropathy  Associated cancer or infection  Gadolinium-enhanced MRI, CSF analysis

Paraneoplastic  Associated cancer, prominent photopsias, often bilateral disease  Mammography, paraneoplastic antibody panel including CV2/CRMP5-IgG, scrotal ultrasound, CT chest/abdomen/pelvis, bone marrow aspirate, full-field ERG may be diagnostic

Big blind spot syndromes  Blind spot on visual field testing, painless, photopsias, bilateral ocular involvement  Full-field/multifocal ERG, fluorescein angiography

**Abbreviations:** NMO-IgG = neuromyelitis optica immunoglobulin G; MRI = magnetic resonance imaging; AON = autoimmune optic neuropathy; CRION = chronic relapsing inflammatory optic neuropathy; HIV = human immunodeficiency virus; CSF = cerebrospinal fluid; VDRL = Venereal Disease Research Laboratory; FTA-ABS = fluorescent treponemal antibody absorption; ESR = erythrocyte sedimentation rate; ANA = anti-nuclear antigen; ACE = angiotensin converting enzyme; anti-DS DNA = anti-double-stranded DNA; PCR = polymerase chain reaction

**Conclusion**

The inflammatory optic neuropathies represent a group of conditions often characterized
by sub-acute onset vision loss, pain, and variable visual recovery. Optic neuritis associated with MS is the most common inflammatory optic neuropathy encountered in clinical practice, and typically affects young Caucasian women. This syndrome is generally self-limited and carries a favorable prognosis for clinical recovery. Optic neuritis is a cause for concern as it may be the first clinical manifestation of MS. In cases of typical ON, the baseline MRI scan is the most potent predictor for the current or future risk of MS. Optic nerve involvement associated with other demyelinating conditions (including NMO) and other mimics must be distinguished from typical ON, because they can implicate underlying and potentially life-threatening systemic conditions. For this reason, an in-depth understanding of the presenting features, diagnostic evaluation, and treatment of inflammatory optic neuropathies is important in day-to-day clinical practice.

References: