

Treatment options for atypical optic neuritis

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Context: Optic neuritis (ON) is defined as inflammation of the optic nerve and can have various etiologies. The most common presentation in the US is demyelinating, or “typical” ON, usually associated with multiple sclerosis. This is in contrast to “atypical” causes of ON, which differ in their clinical presentation, management, and prognosis. These atypical cases are characterized by lack of eye pain, exudates, and hemorrhages on exam, very severe, bilateral or progressive visual loss, or with failure to recover vision.

Aims: The aim was to describe the clinical presentations of atypical ON and their treatments. **Settings and Design:** Review article. **Materials and Methods:** Literature review. **Results:** Types of atypical ON identified include neuromyelitis optica, autoimmune optic neuropathy, chronic relapsing inflammatory optic neuropathy, idiopathic recurrent neuroretinitis, and optic neuropathy associated with systemic diseases. Atypical ON usually requires corticosteroid treatment and often will require aggressive immunosuppression. **Conclusions:** Unlike demyelinating ON, atypical ON requires treatment to preserve vision.

Key words: Atypical optic neuritis, autoimmunity, multiple sclerosis, neuromyelitis optica, neuroretinitis, optic neuritis, optic neuropathy

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Optic neuritis (ON) is defined as inflammation of the optic nerve. This broad definition describes a common pathological phenotype, which may be due to a broad range of diseases, varying in their clinical presentation, natural history, treatment, and prognosis. In the United States, the most common presentation is acute, inflammatory, demyelinating ON that may be associated with multiple sclerosis (MS). This is often termed “typical” ON because it is so common. However, this may not be as common in other parts of the world. These patients generally present with acute onset of painful, unilateral vision loss, and usually have a good visual recovery. Though steroids can be used to speed visual recovery, the overall visual improvement is unaffected by treatment.^[1] This is in contrast to other atypical, inflammatory causes of ON, where the visual outcome may be poor if left untreated. These “atypical” cases of ON include neuromyelitis optica (NMO), autoimmune optic neuropathy, chronic relapsing inflammatory optic neuropathy (CRION), idiopathic recurrent neuroretinitis (NR), and optic neuropathy associated with systemic diseases. These entities can be distinguished from typical ON based on features listed in Table 1. Atypical ON can have devastating visual results if not treated in a timely fashion. Thus, it is critical that these atypical optic neuritides are recognized early to initiate proper treatment and preserve vision. Infectious optic neuropathy is sometimes referred to as ON but is beyond the scope of this review.

Neuromyelitis Optica

A unique variant of ON occurs in NMO, also known as Devic’s disease. NMO is a demyelinating autoimmune disease that in contrast to MS primarily affects the optic nerve and spinal cord.

The clinical presentation of ON in this disease often occurs bilaterally and recurrently, and visual loss is more severe with less improvement compared to typical ON.^[2] The definition of typical NMO phenotype has been defined as ON, acute myelitis, and at least two of the following: (1) Longitudinally extensive spinal cord lesions over 3 or more spinal cord segments; (2) lack of brain lesions in magnetic resonance imaging (MRI) fulfilling MS criteria at disease onset; and (3) serum positive for aquaporin-4 (AQP-4) antibodies.^[3] In addition, cerebrospinal fluid (CSF) oligoclonal bands are not present in contrast to patients with typical ON. Serum NMO immunoglobulin G antibodies that bind to AQP-4 are more than 90% specific and 60-70% sensitive. Identification of these antibodies has allowed us to diagnose NMO in patients who previously may not have been considered as candidates. Thus, patients with recurrent ON and/or visual loss that does not recover may have positive NMO antibodies in the absence of transverse myelitis. The differentiation of NMO from MS is important for long-term treatment, as the established disease-modifying drugs for MS are usually ineffective in NMO, and have been associated with a worsening of symptoms in patients with NMO.^[4,5] Current treatment guidelines include immunosuppression with azathioprine or rituximab as first line, with mitoxantrone, cyclophosphamide or mycophenolate mofetil as second line therapy.^[6] Plasma exchange has also been used in the treatment of NMO, where circulating NMO antibodies are targeted for removal from the blood. It has been suggested that plasma exchange only changes the outcome of severe ON when given early.^[7] Controlled clinical trials have not been conducted on this disease.

Autoimmune Optic Neuropathy

Isolated autoimmune optic neuropathy can be distinguished from typical ON by clinical presentation, laboratory findings and response to treatment.^[8] It is more often bilateral than unilateral, and the onset of vision loss is progressive and often painless, unlike typical ON. The distinguishing laboratory abnormalities are the presence of antinuclear antibodies and

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anticardiolipin antibodies. Biopsy of nonsun exposed skin should be done to confirm the diagnosis; immunoflourescent staining shows IgG deposits in the collagenous matrix and around blood vessels in the epidermis.^[8] In the largest study, 10 patients were treated with pulse dose intravenous methylprednisolone, 1-2 g/d for 5-7 days followed by oral prednisone and other immunosuppressants. Ten patients had visual improvement, nine of whom had previously failed to improve on oral prednisone. As prednisone was tapered after pulse treatment, adjuvant immunosuppression was needed including azathioprine, chlorambucil, or cyclophosphamide to maintain vision.^[8]

Chronic Relapsing Inflammatory Optic Neuropathy

Chronic relapsing inflammatory optic neuropathy is a recently described entity characterized by painful, subacute visual loss in patients without evidence of additional neurologic deficits, sarcoidosis, or other systemic autoimmune disease.^[9] This entity should be considered when demyelinating and autoimmune diseases have been excluded. No specific lab or clinical criteria have been described in CRION. In contrast with typical ON, this condition is steroid dependent and relapsing, with an interval between episodes of days to 14 years. Kidd *et al.* described a series of 15 patients with ON, who met these criteria. These patients suffered a more severe degree of vision loss and worse pain than in typical ON. The pain also persisted longer than with typical ON. Involvement of both optic nerves was common, usually sequentially.

Table 1: Signs differentiating typical from atypical optic neuritis

Typical optic neuritis	Atypical optic neuritis
Normal disc or mild disc edema without hemorrhage or exudate	Normal disc to severe optic disc edema with or without hemorrhage and exudate
Spontaneous improvement after 1-3 months	No recovery and possible continued worsening over weeks or months
No relapse after steroid withdrawal	Relapse after steroid withdrawal

Treatment with steroids induced abrupt and prompt relief of pain and restoration of vision. However, after steroid withdrawal, these patients relapsed, necessitating long-term immunosuppression with medium-dose corticosteroids. In certain cases, immunosuppressants like azathioprine were required in addition to prolonged corticosteroids. In instances where azathioprine was not tolerated, methotrexate was used. In contrast to patients with typical MS, no patients in this series had oligoclonal bands in their CSF, all patients had normal brain MRI, and 19 of the 30 optic nerves imaged had MRI abnormalities (thickened, high signal intensity, or enhancement). It is important to consider and diagnose this condition when appropriate because visual preservation requires prolonged steroids with a gradual reduction in dose.^[9]

Idiopathic Recurrent Neuroretinitis

Neuroretinitis is an inflammatory disorder of the optic nerve head, characterized by acute vision loss, optic disc edema, and macular star of exudate.^[10] The inflammatory process is associated with leaky optic disc vasculature, causing a peripapillary serous detachment followed about 10 days later by formation of hard exudates that track toward macula in characteristic star pattern [Fig. 1].^[11] NR has been associated with a variety of infectious etiologies, most commonly *Bartonella henselae*. However, 25-50% of cases remain idiopathic.^[12,13] Most patients with NR have excellent visual prognosis with spontaneous recovery and low rate of recurrence. However, a subset of patients has been described who have only partial visual recovery and experience subsequent attacks, and fall under the category of idiopathic recurrent NR. This entity affects young adults with an average age of 28 years (10-54 years), has no gender predilection, is rarely associated with eye pain or a viral prodrome, and has no seasonal predilection.^[10] The visual loss is usually unilateral initially, but becomes bilateral in the majority of cases (83%). The interval between attacks ranges from 1 month to 16 years. Incremental visual loss occurs as attacks recur. Corticosteroids seem to eliminate the disc swelling but not reverse the visual loss. Once two or more episodes have been documented a diagnosis can be made. Suggested treatment is corticosteroids acutely, but chronic low dose corticosteroids and azathioprine may prevent further episodes and visual loss.^[10]

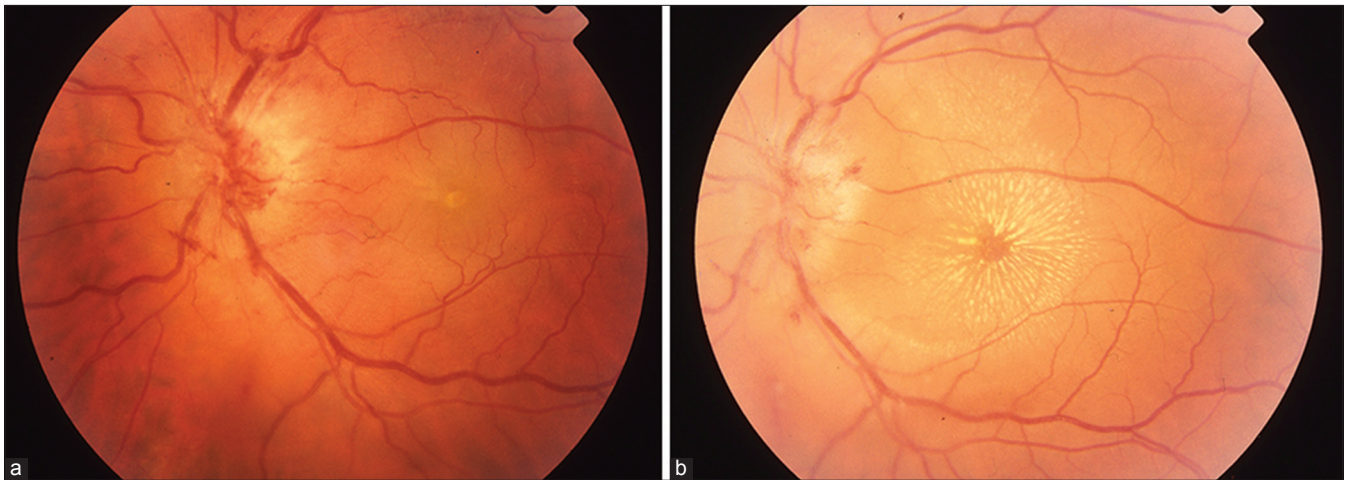


Figure 1: Neuroretinitis. A 26-year-old man presented with decreased vision in the left eye of 3 days duration (a). The optic disc was moderately swollen and there was fluid in the macula. Seven days later, a macular star of exudate had formed (b)

Optic Neuropathy Associated with Systemic Diseases

Connective tissue disorders such as systemic lupus erythematosus, Sjogren's syndrome, Behcet's disease, rheumatoid arthritis, or other systemic vasculitides can all be associated with optic neuropathy, but a detailed discussion of these entities is beyond the scope of this review. In vasculitides, inflammation damages blood vessels, causing secondary ischemic damage to the optic nerve parenchyma. In most patients with these diseases, there is a history of a multisystem disorder. However, the inflammatory activity can be initially restricted to the optic nerve. Typically, these optic neuropathies are characterized by severe eye pain and progressive visual loss. Treatment is by immunosuppressive drugs specific to each entity.^[14]

Granulomatous vasculitides including Wegener's granulomatosis and sarcoidosis can also cause an atypical optic neuropathy. Wegener's granulomatosis can be identified based on the presence of cytoplasmic staining antineutrophil cytoplasmic antibodies that react with the enzyme proteinase 3. Patients typically present with proptosis and upper or lower respiratory disease or glomerulonephritis. In one series of patients with Wegner's granulomatosis, ocular abnormalities were found in 15% of patients at presentation and >50% developed ocular complications over time.^[15] Many of these patients have pain, simulating idiopathic orbital inflammation. Half of the patients with pain and proptosis lost vision from optic nerve ischemia (8% of the entire series of 158 patients) and several had diplopia from muscle involvement. Optic nerve disease usually occurs in the setting of orbital disease but isolated optic nerve granulomatous inflammation and/or vasculitis with optic nerve ischemia have been described.^[16] Treatment with high dose steroids along with immunosuppressants like cyclophosphamide should be initiated early to achieve favorable outcomes.^[17]

Sarcoidosis is a multisystem disease that involves the central nervous system in about 5-10% of patients and neuro-ophthalmic involvement occurs in about half of these.^[18] African Americans and Japanese have an increased rate of sarcoidosis. The diagnosis is suggested by positive angiotensin converting enzyme (60-70% of patients) and chest X-ray with hilar adenopathy (90% of patients), but definitive diagnosis is based on biopsy showing noncaseating granulomas.^[18] Optic nerve involvement may present as retrobulbar optic neuropathy, mild to severe disc swelling, NR and when discovered late' optic atrophy. The optic neuropathy of sarcoidosis typically is painless or presents with mild pain, and visual loss is subacute. Involvement can be unilateral or bilateral. Sarcoid optic neuropathy is often very responsive to moderate oral corticosteroids which must be tapered over months to years even if there is a dramatic initial visual response. Occasionally, high dose intravenous pulse corticosteroids are required. Recurrences are frequent, and low dose corticosteroids are often required chronically. Steroid-sparing agents such as methotrexate, azathioprine, mycophenolate may be required. If these agents are unsuccessful, infliximab, adalimumab, or pulse cyclophosphamide can be considered.^[18]

Summary

Atypical ON encompasses a variety of inflammatory optic nerve conditions that typically require treatment to improve and/or stabilize vision. Therefore, it is crucial to consider these conditions,

make the correct diagnosis and treat appropriately. Furthermore, several of these conditions have systemic ramifications, and the patient may initially present to the ophthalmologist with optic neuropathy as their initial manifestation.

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