Optic neuritis

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Introduction

Optic neuritis, taken literally, means inflammation of the optic nerve. However, clinically the definition implies demyelination as the pathology[1]. In many areas of the world, optic neuritis is the most common cause of unilateral painful vision loss in a young adult[2]. Closely associated with multiple sclerosis, optic neuritis is one of the clinically isolated syndromes (CIS), defined as an acute or subacute episode of neurological dysfunction in the absence of fever, infection or encephalopathy[3]. In the United States the rate of multiple sclerosis (MS) is closely correlated with the incidence of optic neuritis. Optic neuritis remains a clinical diagnosis, although imaging with MRI and other modalities can be helpful, especially in atypical cases[2]. The 15 year follow up data from the Optic Neuritis Treatment Trial (ONTT) showed a 25% chance of developing MS when no lesions were present on MRI and a 72% chance when lesions were present[4]. The cases of optic neuritis associated with MS would be classified as "typical" cases and all other cases of inflammatory optic neuropathy would be categorized as "atypical" cases.

Pathogenesis

The precise pathogenesis is uncertain, but is believed to involve a delayed type IV hypersensitivity reaction involving activation of peripheral T-lymphocytes by an inflammatory process. Lymphocytes cross the blood-brain barrier, resulting in axonal loss by destruction of the myelin sheath[2]. In the acute activation phase there is a

predominance of T-cell activation with associated release of cytokines. Additionally, there may be some involvement of B-cells as well as microglial activation. As vision recovers there is reduced inflammation and remyelination begins to occur; although it is often incomplete[5].

Clinical features

The typical patient affected by optic neuritis is 20-45 years old with the median age of 30 years. Women are three times more likely than men to develop this disease. Caucasians are also more likely to be affected (85%), with whites from a Northern European descent eight times more likely to develop optic neuritis than African Americans or Asians[3, 6-8]. The incidence is greater at higher latitudes in comparison to areas closer to the equator.

The presenting symptoms include visual loss, dyschromatopsia, and peri-ocular pain, especially with eye movement. The vision loss is commonly unilateral and can vary from very mild to severe, including no light perception. Over 90% of patients who develop optic neuritis report peri-ocular pain[6, 8]. Visual symptoms may vary and any defect of the retinal nerve fiber layer can be seen[3, 6-7]. Color vision and contrast sensitivity are often disproportionately affected. A relative afferent pupillary defect (RAPD) develops in unilateral or asymmetric disease.

Some distinguishing features of "typical" optic neuritis include: unilateral vision loss of any severity that recovers over time, peri-ocular pain that does not persist or is not severe, and a lack of other systemic symptoms. The patient may also have an edematous disc but this is not absolutely necessary for the diagnosis. Additionally, the patient may describe additional symptoms like the Uhthoff phenomenon (worsening in vision affected by a rise in body temperature) or the Pulfrich effect (different stereoscopic view of objects due to conduction delay in the affected optic nerve). Other features that can distinguish optic neuritis from other optic neuropathies include findings on brain MRI and other laboratory testing suggesting MS as a possibility[5-6].

Testing and management

One of the most clinically useful tests for optic neuritis is an orbital MRI with contrast, which shows enhancement in 95% of patients eventually diagnosed with acute optic neuritis (fig. 1)[5]. The 2010 McDonald Criteria for CIS permits the diagnosis of MS from an episode of optic neuritis with a simplified criteria for dissemination in space and time. The "dissemination in space" criteria includes over one T2 lesion in at least 2 of 4 of the following areas: 1) periventricular, 2) juxtacortical, 3) infratentorial, and 4) spinal cord (fig. 2). However, symptomatic lesions in brainstem or spinal cord syndromes were excluded from the criteria count. "Dissemination in time" is either: 1) A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan; no matter the timing of the baseline scan or 2) Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time[3, 9]. MRI of the brain, orbit, and neck can also help stratify the risk of developing MS. The Optic Neuritis Treatment Trial 15 year follow up study showed that patients with no lesions on baseline MRI had a 25% risk of developing MS in the following 15 years compared to 78% risk associated with patients with >3 lesions on baseline MRI[4]. Other tests such as visual evoked potentials, electroretinography, and optical coherence tomography can help distinguish between optic nerve and macular abnormalities[5]. Additionally, some clinicians think there is utility of cerebrospinal fluid looking for oligoclonal bands whereas others think that oligoclonal band positive findings are only likely in patients with lesions on MRI[6].

Optic Neuritis Treatment Trial

This large, multi-center trial had 15 years of follow up and included 389 patients; Mean age of 32 years old, 77% female, and 85% white. The treatment groups were randomly divided into either oral prednisone (1 mg/kg/d) for 14 days, intravenous (IV) methylprednisolone (250 mg every 6 hours for 3 days) followed by oral prednisone (1 mg/kg/d) for 11 days, or oral placebo

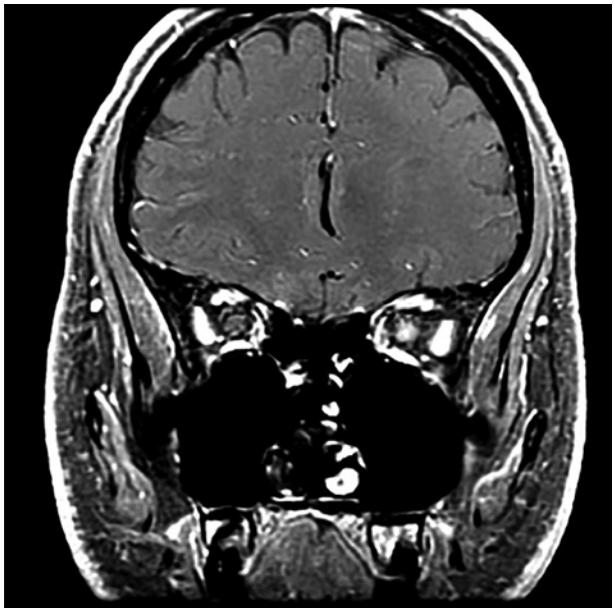

Figure1. Coronal T1-weighted MRI of the orbits with fat suppression shows enhancement of the left intraorbital optic nerve in a patient with optic neuritis.

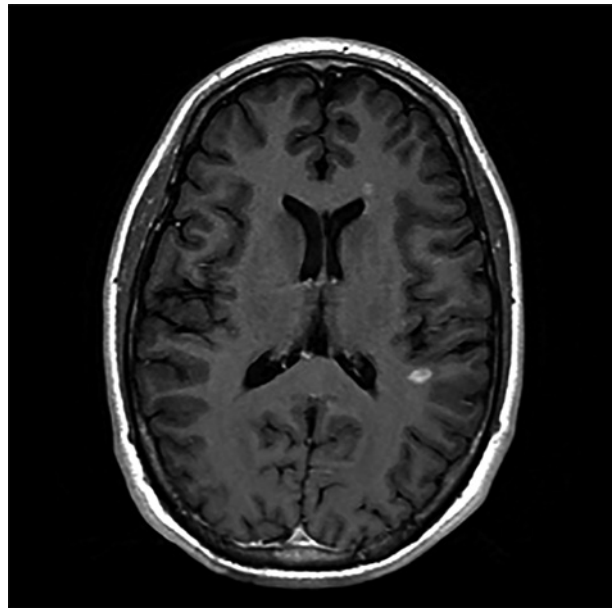

Figure 2. Axial T1-weighted MRI showing contrast enhancement of a characteristic white matter lesion in a patient with multiple sclerosis.

for 14 days. The patients were then evaluated frequently for the first 6 months (7 visits), then at 1 year, then yearly for several years, and at a final visit for 15 year follow up.

Most patients in all 3 treatment groups experienced rapid visual recovery within the first 2 weeks. Many others would improve within 4-6 weeks, but some patients had visual recovery up to 1 year after the onset of symptoms. The only predictor of visual recovery at 6 months was the severity of vision loss at the first recorded visit. The study found that the IV methylprednisolone group had a faster visual recovery but did not have improved visual acuity compared to the other groups. However, the IV methylpredisolone group reported the perception of better vision on a patient questionnaire than the other two groups and had improved contrast sensitivity, visual field, and color vision at 6 months follow-up. Additionally, the oral prednisone group also had a similar final visual acuity, but it was associated with a higher recurrence rate of optic neuritis. An important and unexpected finding of the study was that the IV methylprednisolone group had a reduced risk of a secondary demyelinating event of any kind for the first 2 years after treatment compared to the other two treatment groups; however, this protective effect was lost by year 3 and at all subsequent time points. The study concluded that patients with acute optic neuritis could be given the options of no treatment or IV methylprednisolone followed by oral prednisone. Also, the study concluded that oral prednisone in the standard dosage used in the study was not a viable treatment option[4, 10].

Long-term management

As described previously, patients with optic neuritis generally recover good visual function.

Long-term management to prevent recurrence in these patients has been studied and suggests that immunomodulatory agents like beta-interferon delay the diagnosis of clinically definite MS in patients with optic neuritis and white matter lesions on MRI. The studies also show improvement in brain MRI in treated patients compared to placebo. These studies might move clinicians to treat all patients with optic neuritis with immunomodulatory agents, but there is expected hesitation to initiate treatment given that over 40% of these patients will not progress to clinically definite MS at 10 years. The decision to treat is carefully weighed against the risks given that initiating treatment takes about 6 years to prevent one case of recurrence[8, 11-13].

"Other" optic neuropathies

Neuromyelitis optica (NMO)

This variant of optic neuritis, also known as Devic disease, is a demyelinatinng autoimmune disease felt to be different than "typical" optic neuritis associated with MS in that it primarily affects the optic nerve and spinal cord. These patients typically experience bilateral vision loss that is more severe, recurrent, and less likely to recover compared to typical optic neuritis. Up to 50% of patients are blind in one or both eyes or require a walking aid in the first 5 years. Additionally, these patients will have CSF negative for oligoclonal bands. The definition of the disease includes the criteria: 1) Longitudinally extensive spinal cord lesions over 3 or more spinal cord separate segments; 2) Absence of brain lesions at disease onset that fulfill MS criteria; and 3) positive serum antibodies for aquaporin-4 (AQP-4). All of these criteria are not essential for the diagnosis as they are not present in all cases. Antibodies to AQP-4 are only positive in 80% of patients, which leaves 10-20% of cases as seronegative. This accounts for about 40% of cases initially mistaken for MS in at least one large study. Also, it is important to note that not all patients present with bilateral viusal loss[7, 14-15]. Differentiating between NMO and MS can be important because the treatments differ. NMO requires immunosuppressive therapy such as corticosteroids and second-line treatments such azathioprine and mycophenolate. The typical immunomodulatory therapy used in MS has been associated with worse outcomes in the NMO variant[8, 14].

Ischemic optic neuropathy (ION)

Ischemic optic neuropathy (ION) could be mistaken for the MS variant because it commonly presents with unilateral vision loss and disc swelling. However, in ION the typical age of onset is older (>50 years old), there is no peri-ocular pain with eye movement, and the disc edema is more severe and associated with disc hemorrhages[6, 16].

Hereditary optic neuropathy

This broad category includes many different inherited disorders. Leber hereditary optic neuropathy (LHON) is the most common which may mimic demyelinating optic neuritis. In LHON there is often a family history of men with the disease and vision loss that is progressive and involves both eyes within weeks to months. There is typically no enhancement of the affected optic nerve on MRI[6, 16].

Autoimmune optic neuropathy

Isolated autoimmune optic neuropathy is different than the typical MS variant in that is less likely to have pain as a distinguishing feature, more often to have bilateral vision loss, and more likely to cause progressively worsening vision loss. Around 80% of cases are associated with positive antinuclear antibodies and anticardiolipin titers. Skin biopsies will show IgG antibodies in the collagenous matrix and around blood vessels[7, 14].

Recurrent demyelinating optic neuropathies

These can be broken up into Chronic Relapsing Inflammatory Optic Neuritis (CRION) and

Relapsing Idiopathic Optic Neuritis (RION). CRION is a painful and progressive condition that appears to relapse during steroid tapering. RION has been linked to other central nervous system (CNS) diseases and falls into the category as "steroid-responsive optic neuropathy". Some of these over time have been associated with neuroretinitis, NMO, SLE, sarcoidosis, and Wegener granulomatosis[7, 14].

Atypical features

There are some features that should raise awareness of the possibility of an atypical case for demeylinating optic neuritis, and may suggest the need for additional evaluation[5, 7]:

- Age over 50 years old or under 12 years old
- African, Asian, or Polynesian ethnicity
- Severe pain
- Severe visual loss with no recovery of vision
- Rapid progression of visual loss
- Familial history
- History of neoplasm (especially CNS)
- Severe optic disc edema with disc hemorrhage
- Bilateral vision loss
- Presence of intraocular inflammation

Conclusion

Optic neuritis is a broad term that is usually associated with the "typical" MS variant. Although this variant is very important because it can lead to early recognition of a debilitating disease, it is important to be aware of the "atypical" features that should suggest an alternative diagnosis for the inflammatory optic neuropathy.

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