Content available at: https://www.ipinnovative.com/open-access-journals

IP International Journal of Ocular Oncology and Oculoplasty

Journal homepage: https://ijooo.org/

Review Article

Approach towards typical and atypical optic neuritis

Shrinkhal[1]*, Pragati Garg[1], Swarastra Prakash Singh[1], Ruchi Shukla[1]

[1]*Dept. of Ophthalmology, All India Institute of Medical Sciences, Raebareli, Uttar Pradesh, India*

ARTICLE INFO

Article history:
Received 05-03-2024
Accepted 30-03-2024
Available online 03-05-2024

Keywords:
Optic neuritis
Atypical optic neuritis
Multiple sclerosis
MOGAD
NMOSD

ABSTRACT

Optic neuritis (ON) is a visually disabiliting disease, characterized by acute or sub-acute loss of vision due to inflammation of the optic nerve. When it is associated with a swollen optic disc, it is called papillitis. When the optic disc appears normal due to involvement of the retro-bulbar portion, the term retro-bulbar optic neuritis is used. ON can be broadly classified as typical and atypical. The diagnosis and management of these two types are very different and needs aggressive approach. This article focuses mainly on the approach towards a case of ON.

This is an Open Access (OA) journal, and articles are distributed under the terms of the Creative Commons AttribFution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

1. Introduction

Optic neuritis (ON) is an inflammatory disease of optic nerve, leading to decreased visual acuity. ON can be grouped under typical and atypical ON. A typical optic neuritis is a disease of young age (usually 20-40 years), unilateral, acute or sub-acute loss of vision, usually associated with pain on extra-ocular movements, retro-bulbar optic nerve involvement with no evident disc edema and associated with demyelinating disease, the most common being multiple sclerosis (MS). Retro-bulbar ON is classically described as the disease of the optic nerve where "neither the patient nor the physician sees anything". Nettleship was the first who described a syndrome characterized by "failure of sight limited to one eye, often accompanied by neuralgic pain about the temple and orbit andby pain in moving the eye; many recover but permanent damage and even total blindness may ensue; there is at first little, sometimes no, ophthalmoscopic change, but the disc often becomes more or less atrophic in a few weeks".[1]

MS is a demyelinating disease of the central nervous system characterized by relapses or progression of demyelinating episodes depending on the clinical subtype. Around 20% of MS patients have ON as their first presentation and about 70% of MS patients will develop ON somewhere during the course of their disease. Typical optic neuritis commonly affects Caucassian female population. Optic neuritis treatment trial (ONTT),[2–10] was the first landmark multi-centric clinical trial funded by the National Eye Institute of the National Institutes of Health in the United States to establish the relationship between MS and ON, treatment options and prognosis.

Any deviation from this pattern will fall in the category of atypical optic neuritis. The deviations can be any combination of age either less than 20 years or older patients, bilateral involvement, no pain on extra-ocular movements, presence of disc edema and association with diseases other than multiple sclerosis. The etiology of atypical ON can include infections, autoimmune causes etc.

Any case of optic neuritis will present with sudden diminution of the vision in the affected eye with relative afferent pupillary defect (RAPD) if unilateral or bilaterally asymmetrical. The most common autoimmune mediated

* *Corresponding author*.
E-mail address: shrinkhalbhu@gmail.com (Shrinkhal).

https://doi.org/10.18231/j.ijooo.2024.003
2581-5024/© 2024 Author(s), Published by Innovative Publication.

atypical optic neuritis and its associated disease are neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD). NMOSD is also known as Devic's disease. Both of these entities are antibody mediated, however the target antigens are different. Previously, NMOSD was considered as a variant of MS, but now it comes as a separate demyelinating entity. NMO antibody is against aquaporin-4 water channels, present at the foot process of the astrocytes and MOG antibody is against the oligodendrocyte and myelin sheath glycoprotein. NMOSD and MOGAD are more commonly seen in the Asian population as compared to MS associated ON, which is more prevalent among Caucassians.

NMO antibodies attack the water channel aquaporin-P4 (AQ P4 IgG) rich regions i.e. hypothalamus, optic chiasm, area postrema and brainstem.[11] The diagnosis of these entities is sometimes difficult because of their atypical presentation. So, in NMO, the clinical features along with optic neuritis can be symptomatic narcolepsy (due to hypothalamus involvement), which is characterized by excessive daytime sleepiness, nausea and vomiting due to area postrema involvement, bilateral vision loss due to chiasmal involvement and intractable hiccups, nystagmus, internuclear ophthalmoplegia etc. due to brainstem involvement. Associated transverse myelitis leads to limb weakness and numbness, decreased motor skills, decreased sensation etc. The cerebrospinal fluid (CSF) analysis shows pleocytosis with >50 cells/ microliter with polymorphonuclear cells dominance, presence of eosinophils and rarely presence of aquaporin P4 IgG antibody.[12]

The clinical picture of MOG associated disease is similar to NMO disease; however it can be differentiated on several other clinical and radiological features.

Various infections can also cause optic neuritis. The infectious causes should be excluded by proper history taking (will be associated with fever), other prodromal and systemic findings, history of the travel to an endemic zone, blood examination etc. The most common cause of infectious ON are tuberculosis, syphilis, Lyme disease, herpes, HIV. It is not necessary to order a long list of the investigations to rule out the infectious etiology. A proper history and examination will help to taper the differential diagnosis. Various auto-immune diseases can also cause ON like Sjogren's syndrome, sarcoidosis, systemic lupus erythematosus, and antiphospholipid syndrome.

There is one more important entity known as chronic inflammatory optic neuritis (CRION). It is an ON which is highly steroid sensitive but also highly steroid dependent. Thus, it is also known as steroid-dependent ON. It may involve any age group and shows female preponderance.[13] The disease presents similarly to atypical ON with either simultaneous or sequential involvement of both the optic nerve. The visual loss is severe and painful.

2. Diagnosis

2.1. Clinical

The diagnosis of Optic neuritis is mainly clinical. The patient will present with acute vision loss, which may or may not be associated with pain on the extra-ocular movement. The visual acuity however, may range from normal to severe vision loss. The color vision in the affected eye will be markedly decreased, out of proportion to the visual acuity. Ishihara pseudoisochromatic color plates are easily available colour vision test, very useful for retrobulbar optic neuritis with normal-appearing optic discs. A typical case of optic neuritis is also associated with Pulfrich phenomenon and Uhthoff's phenomenon. In Pulfrich phenomenon, a two dimensional (2-D) object is perceived as three-dimensional (3-D) due to unequal visual signal transmission time between the two eyes to the visual cortex. It is typically seen in demyelinating optic neuritis. The delay in the transmission in the affected eye is due to the loss of myelin sheath of the optic nerve leading to loss of faster salutatory transmission of the nerve. Uhthoff's phenomenon is characterized by a temporary worsening of vision when the body temperature is raised by either fever or exercise etc. This phenomenon is not completely understood till now, however it is proposed to be some defect induced in the electrical channels during the depolarisation of the impulse transmission.

When there is bilateral optic disc involvement, the most important differential diagnosis is papilloedema. In papilloedema, there is no vision loss in the early stages. Also, it will be associated with other clinical signs and symptoms of raised intracranial pressure as transient obscuration of vision, headache present before awaking or on bending forward. There may be associated nausea and vomiting (projectile type). Magnetic resonance imaging (MRI) with Magnetic resonance venography (MRV) is the radiological investigation of choice. MRI will demonstrate combination of fluid in the sheath, flattening of the globe, empty sella turcica, stenosis at the junction of the transverse and sigmoid cerebral venous sinus. However, in optic neuritis, these signs will be missing. In optic neuritis, there will be enhancement of the optic nerve. MRV is done to rule out any thrombosis of cerebral venous sinus.

MOGAD is diagnosed on the basis of the latest proposed criterion published in January 2023 in the journal LANCET Neurology.[14] In summary, the proposed MOGAD diagnostic criteria require all three of the following: A) a core clinical demyelinating event, B) positivity for MOG antibody, and C) exclusion of a better explanation, including MS. The core clinical demyelinating event includes optic neuritis, myelitis, ADEM, brain lesions. Positivity for MOG antibody in serum based on cell-based

assay includes either a clear positivity requiring no further additional features, or low positive, positive but titre not mentioned, negative in serum but positive in CSF; these require an additional supporting one or more clinical or MRI evidence.

NMOSD is diagnosed on the basis of International consensus diagnostic criteria for NMOSD published in July, 2015 in the journal, American Academy of Neurology.

CRION is a diagnosis of exclusion, meaning all other causes of ON including, demyelination, autoimmune disease, and infection should be ruled out before making the diagnosis. The diagnostic criteria for CRION include recurrent ON with seronegative for AQP-4 and MOG, response to steroids, and relapse on withdrawal of steroids. Maybe, the cases previously labelled as CRION is actually MOG-ON.

2.2. Radiological

In all the case of optic neuritis, Magnetic resonance imaging (MRI) brain and orbit with gadolinium contrast with fat suppression is the investigation of choice. In case MRI is not available, contrast enhance computed tomography (CECT) can be done. In a case of typical case of optic neuritis, radiological evidence will show optic nerve enhancement with a short segment involvement, most commonly intra-orbital area. The diagnosis of MS is based on the modified Mc Donald's criterion given in 2017. Cerebral picture of multiple sclerosis (MS) shows T2-hyperintense, multifocal, peri-ventricular, ovoid, white matter lesions, mainly around lateral ventricles. The lesions are separated from each other in both time and space and are present both infra and supra tentorial. These lesions in the sagittal section seen over the corpus callosum are typically named as Dawson's fingers. In NMO, there will be bilateral of optic nerve enhancement with involvement of the long segment including optic chiasm, optic tract. There will be associated involvement of brainstem, area postrema and spinal cord. There will be three or more segment of the vertebral column involvement of the spinal cord i.e. longitudinally extensive transverse myelitis (LETM).The MOG antibody associated optic neuritis will show bilateral optic nerve sheath enhancement (peri-neuritis) with shaggy margin and involvement of the surrounding intra-orbital fat. It means that, coronal section will demonstrate target-like lesion and axial section will show tram-track like appearance. These radiological pictures help to differentiate between the different entities of optic neuritis. MS is not associated with peri-neuritis.

2.3. Serological

Serological examination for the detection of various antibodies plays a key role for confirmation of the diagnosis. Serum testing is more sensitive than CSF for both AQP4 and MOG antibodies. The sensitivity and specificity of the test for the detection of AQP4 and MOG antibodies depend on the type of assay used for the detection. The assay based on cell line of HEK293 is the most sensitive (77%) while cell-binding assays with fixed cells have a sensitivity of 73%. Serological tests should also be done to rule out the infective causes and auto-immune causes of ON. Serological work-up commonly include autoantibodies like ANA, ds-DNA, ss-DNA, La-and Sm antibodies, Rho antibodies should be done to confirm the diagnosis.

2.4. Cerebrospinal fluid (CSF) analysis

CSF analysis plays a key role in the diagnosis of MS. In MS, the CSF may show oligoclonal bands in 90 percent of the cases, elevated immunoglobulin G (IgG) levels and increased Ig G by albumin index. It is important to note here that, these findings are not specific for MS, but only suggestive. NMOSD patients may also show oligoclonal bands in around 20 percent cases, pleocytosis >50 cells/microliter, increased protein levels, eosinophils and rarely AQP 4 antibodies.

3. Management

Demyelinating ON has a typical feature of spontaneous recovery within 2-3 weeks in more than 80% of patients without treatment [15–18]. Inspite of visual recovery, persistence of the long-term defects in visual functions is possible. In any case of the optic neuritis, whether typical or atypical, the acute management is intravenous (i.v.) methylprednisolone.

Management of a typical optic neuritis is based on the Optic neuritis treatment Trail (ONTT).[2] The ONTT had three treatment arms: intravenous steroids group, oral steroids group and placebo group. The results favoured intravenous steroids in the terms of faster visual recovery; however, the final visual recovery at 1-year follow-up was similar irrespective of treatment. The recommended treatment as per the trial is giving intravenous methylprednisolone 250 mg four times a day for three days, followed by oral prednisolone 1 mg/kg body weight for 11 days and then sudden taper in 3 days. Atypical optic neuritis cases require a longer intravenous methylprednisolone, may be 3-5 days. Once the patient has shown good visual recovery, they can be shifted to oral prednisolone 1 mg/kg body weight for a longer duration and with very gradual taper. There is no specific duration of the oral steroids. The dose and the duration of the oral steroids will depend on the response of the patient. Fortunately the visual response in MOGAD is very good, but in NMOSD the response may not be very good. However, if in atypical optic neuritis, we did not achieve a good response by i.v. methylprednisolone (given for up to 5 days), the patient can be immediately be given plasma exchange therapy (PLEX) or intravenous

immunoglobulin (IVIG). PLEX is considered also in the recurrent disease or aggressive NMOSD. If the response to it is good, then we can shift the patient to immunomodulators (IMT) slowly for long term therapy. In 2020, FDA has approved eculizumab, inebilizumab, satralizumab for the treatment of NMOSD.

3.1. Prognosis

The visual prognosis in MS associated typical optic neuritis is usually good and steroid responsive. NMOSD patients have presenting visual acuity usually worse than MS associated ON, and the prognosis is usually poor. MOGAD associated ON usually has a very good steroid response with good visual prognosis. However MOGAD ON shows frequent relapses and is sometimes steroid dependent also. These steroid dependent cases are ideal case of IMT.

4. Conclusion

We suggest a thorough examination in all the cases of ON. A stepwise approach is required for the diagnosis and management of an acute episode of ON. ON cases require an urgent diagnosis and management, because the vision loss is acute and even permanent if not managed early. The role of clinical acumen followed by radiological and serological support is paramount in the diagnosis. A long-term management protocol is a need to prevent further attacks.

5. Author Contributions

All authors participated in the conception of the article, interpretation of the data, and revision of the manuscript, and they approved the final version. The authors had full editorial control of the paper and provided their final approval of all content.

6. Source of Funding

None.

7. Conflicts of Interest

None

References

1. Nettleship E. On cases of retro-ocular neuritis. *Trans Ophthalmol Soc UK*. 1884;4:186–226.
2. Beck RW. Optic Neuritis Study Group. The Optic Neuritis Treatment Trial. *Arch Ophthalmol*. 1988;106:1051–3.
3. Optic Neuritis Study Group. The clinical profile of acute optic neuritis: experience of the Optic Neuritis Treatment Trial. *Arch Ophthalmol*. 1991;109(12):1673–8.
4. Beck RW, Cleary PA, Anderson M, Keltne JL, Cleary PA, Shults WT, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. *N Engl J Med*. 1992;326(9):581–8.
5. Beck RW. Optic Neuritis Study Group. The Optic Neuritis Treatment Trial: implications for clinical practice. *Arch Ophthalmol*. 1992;110(3):331–2.
6. Beck RW. Corticosteroid treatment of optic neuritis: a need to change treatment practices. The Optic Neuritis Study Group. *Neurology*. 1992;42(6):1133–5.
7. Beck RW, Kupersmith MJ, Cleary PA, Katz B. Fellow eye abnormalities in acute unilateral optic neuritis: experience of the Optic Neuritis Treatment Trial. *Arch Ophthalmo*. 1993;100(5):691–7.
8. Beck RW, Arrington J, Murtagh FR. Brain MRI in acute optic neuritis: experience of the Optic Neuritis Study Group. *Arch Neurol*. 1993;8:841–6.
9. Beck RW, Cleary PA, Trobe JD, Kaufman DI, Kupersmith MJ, Paty DW, et al. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *N Engl J*. 1993;329(24):1764–9.
10. Beck RW, Cleary PA. Optic Neuritis Treatment Trial: one-year follow-up results. *Arch Ophthalmol*. 1993;111(6):773–5.
11. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. 2004;364(9451):2106–12.
12. Takano R, Misu T, Takahashi T, Sato S, Fujihara K, Itoyama Y, et al. Astrocytic damage is far more severe than demyelination in NMO: a clinical CSF biomarker study. *Neurology*. 2010;75(3):208–16.
13. Petzold A, Plant GT. Chronic relapsing inflammatory optic neuropathy:A systematic review of 122 cases reported. *J Neurol*. 2014;261(1):17–26.
14. Banwell PPB, Jeffrey L, Bennett. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. *The Lancet neurology*. 2023;22(3):268–82.
15. Dooley MC, Foroozan R. Optic neuritis. *J Ophthalmic Vis Res*. 2010;5(3):182–7.
16. Voss E, Raab P, Trebst C, Stangel M. Clinical approach to optic neuritis: pitfalls, red flags and differential diagnosis. *Ther Adv Neurol Disord*. 2011;4(2):123–34.
17. Mehrotra A, Jaffery N, Saxena R, Menon V. Comparative evaluation of megadose methylprednisolone with dexamethasone for treatment of primary typical optic neuritis. *Indian J Ophthalmol*. 2007;55(5):355–9.
18. Sethi H, Sharma P, Tandon R, Khokhar S, Menon V. Visual outcome after intravenous dexamethasone therapy for idiopathic optic neuritis in an Indian population: A clinical case series. *Indian J Ophthalmol*. 2006;54(3):177–83.

Author biography

Shrinkhal, Assistant Professor

Pragati Garg, Professor

Swarastra Prakash Singh, Associate Professor

Ruchi Shukla, Assistant Professor

Cite this article: Shrinkhal, Garg P, Singh SP, Shukla R. Approach towards typical and atypical optic neuritis. *IP Int J Ocul Oncol Oculoplasty* 2024;10(1):15-18.