Atypical optic neuritis: An overview

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Optic neuritis (ON) refers to conditions that involve inflammation of the optic nerve. Various autoantibodies have been found, which are associated with central nervous system inflammatory disorders and have provided much information about the immune targets and mechanisms that impact the prognosis, treatment, and recurrence of atypical ON. Therefore, neurologists and ophthalmologists together should work to find out clinical, laboratory, and imaging findings that may provide important clues to the etiology of atypical ON and its management. Various biomarkers have been identified to confirm and distinguish atypical optic neuritis from others. The purpose of this review is to present the current scenario of atypical ON and its clinical management.

Key words: Atypical optic neuritis, infectious optic neuritis, myelin oligodendrocyte glycoprotein antibody, neuromyelitis optica, optic neuritis

Optic neuritis (ON) refers to a group of conditions that involve inflammation of the optic nerve. The patients present with partial to complete vision loss within a few days of onset. They also have dyschromatopsia with pain on ocular movements at presentation.[1] A gamut of etiologies can be responsible for ON and are broadly classified as typical and atypical.

It has been seen earlier that acute inflammatory demyelinating ON (IDON) is very closely related to multiple sclerosis (MS). Initial presentation in approximately 20% of MS[2] patients will be with IDON, with 50% of MS patients developing IDON[3] during their disease. IDON is commonly observed in the early stages of MS, chiefly in Western countries, and this form of ON is usually referred to as “typical ON”.

ON with various etiologies, other than MS, is classified as “atypical ON.” Atypical ON is usually seen as an early example of neuromyelitis optica (NMO) or NMO spectrum disorder (NMOSD).[4] Such types of ON are generally seen in Asia and vary from traditional ON in terms of etiologies, management strategies, and ultimate neurological outcomes. It is, therefore, very important to distinguish between typical and atypical ON, especially in the early stages of presentation. Due to their clinically overlapping characteristics, a reliable biomarker is needed to distinguish between typical and atypical ON.

Methods

We searched PubMed for studies published in English between 1970 and February 2020, incorporating the general search term “atypical optic neuritis” with more precise search terms relevant to subheadings — e.g., “neuromyelitis optica,” “myelin oligodendrocyte glycoprotein antibody,” “infectious optic neuritis,” “optical coherence tomography,” “corticosteroid,” “visually evoked potential,” “magnetic resonance imaging,” etc. References from identified studies have been reviewed and included if deemed appropriate, valid, and scientifically important. If referenced in a selected English paper, we contemplated papers in other languages too. We also searched through our archives for the references. We preferentially selected papers that have been published in the last 10 years, but we have also included relevant older references.

India Vs West

Western data suggest that at least 50% of patients with ON will eventually develop MS,[5] but studies from Asia and Africa[6] present a contrasting scenario. An Indian study conducted before the commencement of the optic neuritis treatment trial (ONTT) had indicated that the clinical profile of ON in our country may be different from that presented in the Western literature.[6]

A research on optic neuritis from India revealed a clinical profile and outcome comparable to the majority of studies from the Asian continent and vastly different from the West.[7] The disparity in optic neuritis outcome between the West and the East was due to the increased prevalence of atypical optic neuritis and likely an ethnic variation in the course of the disease. In 99 eyes of 83 Indian patients, Saxena et al. studied...
the clinical profile and short-term visual effect of all types of optic neuritis.\[7\] The research found lower recurrence rates as compared to the western population.

Pandit et al. reports of 59 patients with optic neuritis from India and found comparable results to those recorded from the West.\[8\] The group stated that the correlation of visual improvement with the final diagnosis and outcome was positive in cases of optic neuritis with or without multiple sclerosis relative to the worse result in cases of optic neuromyelitis and chronic relapsing inflammatory optic neuritis.

**Atypical ON Variants**

**Neuroretinitis**
The disk is markedly swollen, and when the symptoms are most severe, the stellate figure of the hard exudate is seen in the macula. Inflammation often leaves behind marked damage, with cumulative damage after each recurrence. Several case reports have shown that the immune response is caused by various infectious organisms with Bartonella\[9\] as the most common pathogen.

**Infectious optic neuritis**
The involvement of the optic nerve with variable vision loss has been associated with a wide range of infectious disorders. This can occur as anterior optic neuritis, retrobulbar optic neuritis (normal optic disc), neuroretinitis (optic disc edema with the macular star), or anterior optic neuropathy. Direct involvement of the optic nerve via a pathogen and indirect involvement with inflammatory, degenerative, or vascular processes may lead to the involvement of the optic nerve. Below given are some commonly found infectious optic neuritis. Optic neuropathy has been reported in 11%–57% of acute retinal necrosis (ARN) cases.\[9\] Optic nerve involvement in ARN may occur before, after, or simultaneously with retinal necrosis and usually causes a rapid and severe vision loss. It may present as papillitis, neuroretinitis, retrobulbar optic neuropathy, or optic disc atrophy that may develop several weeks after ARN. The involvement of the optic nerve in herpes zoster can be caused by direct nerve inflammation or an ischemic mechanism leading to inflammatory thrombosis. The involvement of the optic nerve has been documented in 17 percent of eyes with progressive outer retinal necrosis (PORN),\[10\] including optic disc edema and optic disc atrophy. Papillitis of cytomegalovirus (CMV) was identified in 4%–14% of patients\[12\] with acquired immune deficiency syndrome (AIDS) and CMV retinitis.

HIV optic neuropathy can be unilateral or bilateral and may be present as retrobulbar optic neuropathy, papillitis, optic neuropathy, or optic disc pallor. Autoimmune, vascular, and degenerative pathways ischemic have been postulated to play a role in the pathogenesis of HIV-associated optic neuropathy. The findings indicate that HIV-infected macrophages can mediate optic nerve degeneration. The ocular involvement occurs in 5%–10% of individuals with cat scratch disease.\[13\] The main symptom of Bartonella is the abrupt unilateral loss of visual acuity although cases with bilateral affection have been described. The finding of disc swelling associated with macular star exudates is considered as a predictable sign of an ocular manifestation of cat scratch disease. The optic nerve involvement may be caused by optic nerve or intraocular infection by Bartonella, an immune response to bacterial infection, or a mixture of infectious and parainfectious mechanisms.

**Neuromyelitis optica**
It is the first antibody-mediated demyelinating disorder to be identified. It was first identified by Devic and Gault in 1894.\[14\] Patients with neuromyelitis optica (NMO) have severe optic neuritis with a slow recovery, which can be bilateral and chronic, often leading to blindness, and may also have extreme transverse myelitis.

In 2004, Dr. Lennon found that the antibody against aquaporin 4 (AQP4) is both a biomarker and pathological cause of NMO,\[15\] which cemented NMO as a distinct entity from MS. AQP4 is a water-channel protein expressed in the brain, spinal cord, and optic nerves that are affected by NMO. Binding of AQP4-IgG to AQP4 induces complement activation and astrocytic damage.

**Neuromyelitis optic spectrum disorder (NMOSD)**
This involves area postrema syndrome (APS) where patients present with intractable nausea and vomiting due to dorsal medullar lesions or symptomatic narcolepsy due to diencephalon lesions, acute cerebral syndrome, and symptomatic cerebral syndrome.

Patients experience acute vision loss and tend to have poor recovery. Optic neuritis will lead to legal blindness of 20/200 or worse in one eye in about 50 percent of patients with NMO optic neuritis.\[16\] Optic neuritis due to NMOSD tends to affect both the eyes and the chiasma. NMO usually follows a relapse without significant recovery between relapses and accumulation.

**Myelin oligodendrocyte glycoprotein-IgG associated disorder (MOG IgG)**
MOG is a transmembrane protein that is located on the surface of oligodendrocytes. MOG antibody is a biomarker of a specific demyelinating disease process — MOG-associated disorder — different from both MS and AQP4-IgG seropositive NMOSD. Patients with MOG optic neuritis have optic disk edema, which may be severe, bilateral, and recurrent optic neuritis. Recurrent optic neuritis occurs in approximately 50 percent of patients, with some cases being both steroid-responsive and steroid-dependent, causing chronic inflammatory optic neuropathy (CRION). Vision loss is typically significant, but recovery is usually better than seen with AQP4-IgG optic neuritis. JJ Chen et al. in their study found that just 6–10 percent of patients with MOG-IgG optic neuritis had a final visual result worse than 20/60 compared to 50 percent of patients with AQP4-IgG optic neuritis.\[16\]

**Chronic recurrent immune optic neuropathy (CRION)**
It begins like typical optic neuritis and improves quickly under steroid therapy, but recurs when the steroid dose is lowered. Recurrence is normal, and the disease sometimes affects one eye first and then the other. If untreated, it leaves marked damage behind.

The given Table 1 summarizes the various etiologies of ON.

**Inflammatory Injuries in Atypical Optic Neuritis**

1. AQP4-Ig mediated atypical ON
The discovery of NMO-IgG and AQP4 as its targeted
Table 1: Etiologies of atypical optic neuritis

| Assoc. with MS | Typical ON |
|---------------|------------|
| Demyelination of optic nerve |
| Atypical ON |
| Autoimmune disorders | Sarcoïdosis, Sjögren syndrome, rheumatoid arthritis, neuromyelitis optica, SLE |
| Infections | Bacterial (Tuberculosis, syphilis, meningitis, Lyme’s disease), Viral (Bartonella, measles, mumps, rubella, chicken pox, herpes) |

Antigen unequivocally confirmed neuromyelitis optica as a disease distinct from MS, and allowed its early laboratory recognition. Aquaporin-4 is widely expressed throughout the CNS. It is also highly expressed in the optic nerves and the spinal cord, explaining the disease’s preferential involvement. The AQP4-Ig antibody enters the CNS, binds the antigen to astrocyte processes, induces complement-mediated inflammation, granulocyte infiltration, and astrocyte death. Complement-mediated inflammation of secondary neutrophils and eosinophilic infiltration plays a key role in the pathophysiology of NMOSD attacks. Although AQP4-IgG may have direct access to AQP4 on astrocytes located in the circumventricular organs where the endothelial system lacks a tight junction, the mechanisms of its penetration into other CNS sites protected by blood-brain barrier (BBB) remains unclear.

Activation of the microvascular endothelial cells (BMECs) of the brain induces increased secretion of the vascular endothelial growth factor (VEGF) and metalloproteinase (MMP), resulting in disruption of the BBB. Leakage of the BBB enables the entry of AQP4-IgG into the CNS and its binding to AQP4 in the astrocytic end-feet. Evidence showing the causal role of AQP4-IgG in NMOSD includes its absolute disease specificity; its association with disease activity, the higher number of relapses and more extreme course compared to seronegative patients; some distinct demographic and clinical features; increased concentration of AQP4-positive plasma-blasts in NMOSD patients, particularly during disease relapses; and decreased serum AQP4-IgG concentration following successful treatments and during disease remission. Histopathological features such as a marked loss of astrocytes and accumulation of IgG and IgM around the blood vessels, the site of AQP4 expression; myelin and axons in some lesions suggest that astrocytes (which have a higher expression of AQP4) are the primary target of the disease; whereas in more recent lesions, glial fibrillary acidic protein (GFAP) may be retained, a marker of damage to astrocytes suggests that AQP4 is the primary target of the immune attack.

Optic neuritis in NMOSD can vary from isolated idiopathic optic neuritis and optic neuritis occurring in MS. In NMOSD, optic neuritis is characterized by more severe onset visual loss, bilateral optic nerve or optic chiasma involvement, relapse, poor response to IV corticosteroid pulses, poor recovery with permanent visual deficits, and association with normal brain MRI, or unpecific brain MRI lesions. Bitemporal hemianopsia points to the presence of chiasmal involvement, which is more common in AQP4-IgG NMOSD than in MS or anti-MOG syndromes.

Although the role of AQP4-IgG in NMOSD pathophysiology has been identified by a large number of clinical and experimental data, the innermost mechanisms underlying the variety of human demyelinating phenotypes in combination with anti-MOG antibodies remain to be better clarified.

2. Anti-MOG antibodies
They are developed peripherally and usually reach the CNS following a breakdown of the BBB secondary to infection. Almost 50 percent of patients report a history of previous infectious prodromes. The lack of restricted oligoclonal bands in patients with anti-MOG syndromes in the CSF supports the notion of peripheral origin. The circulation of lymphocytes may also move to the CNS with subsequent clonal expansion. Observation of complement-mediated cytotoxicity
from in vitro studies and the development of NMOSD-like disorder in animal models are strong evidence of MOG-IgG pathogenicity.\[21]\n
However, in some cases, reversible alterations to myelin occur without additional activation or inflammatory cell infiltration. This is consistent with better recovery of some patients with anti-MOG syndromes compared to NMOSD.

On anti-MOG syndromes, there are few clinical reports.\[22]\n
A brain biopsy of a patient with MOG-antibody-associated encephalomyelitis showed typical histopathological characteristics of MS-type II characterized by IgG deposition and activated complement at ongoing demyelination sites.

Nonetheless, the hunt for MOG-IgG and several other autoantibodies in a series of Type-II MS patients failed to demonstrate any direct relationship between Type II-MS and MOG-IgG.

Contrary to seropositive AQP4-IgG NMOSD, serum autoantibodies coexisting in anti-MOG syndromes are rare. Related autoimmune conditions are found in over one-third of AQP4-IgG seropositive NMOSD cases, but in only 9% of the anti-MOG syndromes.\[22]\n
**Evaluation of a Case Of Atypical ON**

**Blood investigations**

Thorough laboratory testing is required in case atypical ON is suspected [Table 2]. In the Optic Neuritis Treatment Trial, testing for antinuclear antibodies, syphilis serology, and chest X-rays was found to have no therapeutic consequence whatsoever in any of the 457 cases included in the trial.\[23]\n
**MRI**

It is one of the most important ancillary tests as it can directly reveal inflammation of the optic nerve, typically as contrast uptake in a contrast-enhanced T1 sequence [Table 3].

Brain MRI scans are abnormal in approximately 45% of patients at the onset,\[20]\n
with percentages increasing later in the course of the disease (i.e., up to 77% of patients). The majority has bilateral lesions at onset and around one-third have sub-tentorial lesions, predominantly in the brainstem. Typically, lesions are few (three or less) and appear as “fluffy,” i.e., poorly demarcated hyper-intensities on T2-weighted images. Dawson’s fingers, U-or S-shaped lesions, and ovoid lesions adjacent to the body of lateral ventricles are found less commonly.

When compared to MS-associated ON or AQP4-positive NMOSD-associated ON, the MRI appearance of the optic nerve in MOG (Myelin oligodendrocyte glycoprotein) associated ON is more edematous and shows extensive inflammatory lesions, usually sparing chiasma and optic tracts. Thalamic and pontine lesions are more common in MOG-AD compared to AQP4-positive disease. In children, bilateral thalamic lesions at onset are frequent and can be found in about 60% of patients.\[24]\n
Compared to AQP4-positive patients, cerebellar peduncle lesions are only found in MOG-positive children [Fig. 1].

The sensitivity to white tissue structure and association makes dissemination tensor imaging (DTI) and additionally dispersion tractography helpful as surrogate markers for axon and myelin damage. DTI values correspond well with visual impairment on VEP in optic neuritis with MS. Dissimilar to other clinical MRI groupings for the optic nerve, dissemination MRI gives a quantitative, target marker of optic nerve pathology and appears to be delicate to unobtrusive tiny tissue changes.

**VEP**

Early examinations demonstrated a predominance of expanded VEP inactivity in up to half 70% of patients with MS without visual objections. The sensitivity of VEP is approximately 20–50% in patients without a history of ON.\[25]\n
VEPs have been accounted as anomalous in 90% of patients who have been examined within a half year from the beginning of ON symptoms, and in about 70% when over 2 years have passed.\[24]\n
VEPs have been utilized to separate MS from inflammatory and demyelinating CNS diseases, for example, neuromyelitis optica spectrum disorder (NMOSD). It has been seen that P100 latency is more delayed in MS than in NMOSD, with a greater proportion of absent responses and less frequent subclinical alterations in the latter group.\[26]\n
From some studies of the 1980s and early 1990s, a significant association between

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**Table 2: Blood investigations for atypical optic neuritis**

| Laboratory tests | Other tests |
|------------------|-------------|
| Complete blood counts | ANCA |
| C-reactive protein | Mantoux test |
| Blood sugar | HIV serology |
| Vitamin B12 | HTLV1 |
| Rheumatoid factor | Mycoplasma serology |
| Antinuclear antibodies | |
| Anti-phospholipid antibodies | |
| Lupus anticoagulant | |
| Serum angiotensin-converting enzyme | |
| Urine analysis | |

**Table 3: MRI findings in optic neuritis**

| Etiology | MRI finding |
|----------|-------------|
| Isolated optic neuritis | MRI-swollen optic nerve with hyper intense signal on STIR images and intense post contrast enhancement. MRI brain to exclude MS, ADEM, and NMO |
| Multiple Sclerosis | Brain: Dawson’s finger due to flame-shaped plaques perpendicular to lateral ventricular margin. Callosal-septal interface involved. Spinal cord: Plaques involving short segment of cord and <2/3rd circumference |
| Neuromyelitis optica (NMO) | Spinal cord: Involvement of long segment of cord (>4 vertebral bodies) and extending more than 2/3 of cross section. Brain: peripendymal lesions surrounding third ventricle and cerebral aqueduct, thalamus, hypothalamus, and midbrain. |
| MOG | Long segments of optic nerve enhancement, enhancement with extension to the peribulbar fat may be seen |

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ff-VEP's alteration in patients with various initial neurological manifestations and MS development emerged, with risk increasing from 2.5-to 9-fold.\[37\]

A few investigations consolidated VEPs testing with retinal structure measures using OCT, to investigate the connection between demyelination and neuroaxonal degeneration. Association between VEP’s efficacy and RNFL thickness has been found for both ff-VEPs and mf-VEPs. mf-VEPs likewise indicated a high topographic correspondence with RNFL sectorial investigation.\[28\] A few specialists recognized a connection between RNFL and ganglion cell layer thickness and VEP latency, particularly in non-ON eyes, proposing constant subclinical demyelination may prompt dynamic axonal loss.\[29\]

The connection among demyelination and ensuing axonal loss appears rather to be less sure after ON.\[30\] Some studies have shown a higher sensitivity in detecting abnormalities with ff-VEPs over OCT in patients with ON, MS, and CIDS.\[31,32\]

VEPs have been correlated with MRI findings, of both brain and optic nerve. At the optic nerve level, great connections have been found between DTI and amplitudes for ff-VEPs and multifocal (mf)-VEPs. In patients with MS, mf-VEPs inactivity was found to associate with optic radiation injury load and DTI measures in eyes without past ON, demonstrating the presence of retrochiasmal and, specifically, retrogeniculate injuries.\[33\]

OCT RNFL

Axonal damage in the optic nerve manifests as retinal nerve fiber layer (RNFL) deficits, which can be readily quantified with optical coherence tomography (OCT) [Fig. 2]. Studies have shown that OCT exhibits *in vivo* thinning of the retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (GCIPL) thicknesses of the retina after optic neuritis, which emerge from retrograde axonal degeneration brought about by optic nerve injury.\[30\] Thinning of the RNFL and GCIPL has been seen as a biomarker of earlier optic neuritis. However, different investigations recommend that OCT has a generally low sensitivity (60%–68%) in distinguishing earlier optic neuritis.\[30\] Thus, the utility of OCT in diagnosing earlier optic neuritis has been dubious.

After initial swelling because of edema in the intense period of ON, RNFL thickness diminishes over the next 6 months. Intraretinal segmentation showed that GCIPL likewise diminishes fundamentally after ON. It was seen that initial swelling was limited to RNFL, proposing that the changes in the GCIPL are the more reliable parameter for longitudinal checking of ON-related retinal damage.\[36\]

RNFL decrease after ON is more articulated in NMO than in MS. Likewise, the GCIPL is all the more severely affected. The visual debilitation in NMO is thought to result from a specific threshold of neuroaxonal loss, from which retinal neurons and axons never again can adequately keep up visual capacity. Besides, macular microcysts occur at a higher recurrence in NMOSD-ON than MS-ON, demonstrating a stronger inflammatory process. This is in accordance with the increased inner nuclear layer (INL) thickness found in NMOSD after ON in contrast with MS. Interestingly, OCT results of NMOSD eyes not affected by a clinically reported\[30\] ON show no or only slight differences in comparison to healthy control subjects, which may be characteristic of either (or both) lesser diffuse direct optic nerve damage in NMOSD in comparison to MS, or less severe retrograde transsynaptic degeneration as an outcome of less serious affection of the posterior visual pathway in NMOSD.

In a study conducted by Naismith RT, Tutlam NT, Xu J, et al.,\[30\] it was seen that after a remote episode of optic neuritis, when comparing patients with comparable visual acuity and contrast sensitivity, NMO had a thinner RNFL thickness than MS. This suggests that there is greater axonal impairment following optic neuritis in NMO than in MS. In NMO, the upper and lower quadrants were affected to a greater degree than MS while the temporal quadrants were not demonstrably distinguished.

Severe optic neuritis (visual acuity <20/100) in NMO was consistent with vascular changes and more axonal losses compared to MS.\[37\] NMO optic neuritis cases had a diffuse pattern of thinning of RNFL, whereas MSON had mainly transient involvement in quadrants. Attenuation of the peripapillary vascular branch, arteriolar focal narrowing, was observed often with obstruction of the lumen.\[38\]

Other markers

Aquaporin-4-IgG (AQP4-IgG) and MOG-IgG

It is seen that ON onset in MOG-ON occurs at a younger age than AQP4-ON (range: 5–63 years vs. 8–72 years, respectively).\[39\] MOG-Abs can be detected in NMOSD with AQP4-Ab seronegative, recurrent optic neuritis, transverse myelitis, multi phasic acute disseminated encephalomyelitis, and combined central and peripheral demyelination (CCPD) syndromes; a proportion of these patients tend to develop a relapsing type of disease. The average peripapillary retinal nerve fiber layer (pRNFL) and macular ganglion cell–inner plexiform layer (mGCIPL) are preferentially damaged in

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**Figure 2:** OCT image of MS-ON (b) OCT image of NMO-ON. NMO-ON showing more severe damage compared to patients with MS. Citation: Tian G, Li Z, Zhao G, Feng C, Li M, Huang Y, Sun X. Evaluation of Retinal Nerve Fiber Layer and Ganglion Cell Complex in Patients with Optic Neuritis or Neuromyelitis Optica Spectrum Disorders Using Optical Coherence Tomography in a Chinese Cohort. J Ophthalmol. 2015;2015:832784
AQP4-ON eyes compared to the MOG-ON eyes. Vision loss is usually severe at nadir, but fortunately the recovery is typically better than seen with AQP4-IgG optic neuritis. Only 6%–10% of patients with MOG-IgG optic neuritis have a final visual outcome worse than 20/200 compared to 50% of patients with AQP4-IgG optic neuritis.\[45\]

Glia fibrillary acidic protein (GFAP)
GFAP, a marker of astrocytic damage, as well as N-acetyl aspartate may be elevated in NMO spectrum disease, compared with MS, and may help to distinguish between the two. Serum GFAP levels have also been shown to be elevated despite the absence of extra optic nerve disease.

Oligoclonal IgG bands
Oligoclonal IgG bands (OCGB) are useful to predict ON conversion to clinically definite MS (CDMS), although they do not inform about the quickness of the second relapse. Moreover, OCGB has not been calculated coupling with lipid-specific oligoclonal IgM bands (LS-OCMB) in ON patients. LS-OCMB is considered a marker of highly inflammatory MS with a shorter time to a second relapse and a worse disease prognosis.\[46\]

Neurofilament light protein
Neurofilament light protein (NFL) is considered as a biomarker of axonal damage and relates with conversion to MS in general clinically isolated syndrome (CIS) cohorts. High levels predict incomplete remission after an ON episode and higher disability in the long term. When evaluated in other series with longer follow-up, NFL levels predicted earlier conversion in univariate tests, but this could not be verified in multivariate analyses.\[47\]

Th17 and Treg/Th17
In both typical and atypical ON patients a significant up-regulation of Th17 cells, a down-regulation of Treg cells, and an imbalanced Treg/Th17 ratio is seen in various studies,\[48\] more in atypical ON. A balance between Th17 and Treg cells is crucial for immune homeostasis, as Th17 cells are a key player in the pathogenesis of many autoimmune diseases, and Treg cells function to restrain excessive effector T-cell responses. Treg cells are main for the maintenance of peripheral tolerance and findings are there showing that Treg cells can suppress ongoing immune reactions. Various mechanisms contributing to the loss of Treg subset in MS patients are (i) a lower release of Treg cells from the thymus; (ii) a change in Treg cell substrates or; (iii) a decrease in FoxP3 expression.

Interestingly, two recent studies\[49,50\] have reported that Th17 cells also increased and might play a “collaborative” role in NMO. It is possible that the increased frequency of Th17 in patients with atypical ON reflects the increased relapse frequency of atypical ON rather than the disease type itself, as repeated attacks may induce expansion in the auto-reactive Th17 cell pools. Table 4 summarises the various bio-markers in optic neuritis.

Treatment

ONTT
The main impact on the treatment and course of ON was studied in the Optic Neuritis Treatment Trial (ONTT), which was completed in 1991.\[51\] Patients with acute optic neuritis were randomized to IV steroids, oral steroids, or placebo in this study. The results showed that all cases of ON had recovered with or without treatment. An improvement of 6/12 or better was seen in 92% of patients. Nonetheless, not all situations have changed, with 3% continuing to be 6/60 or worse. Nevertheless, treatment with IV steroids led to a faster recovery, but did not change the final visual result. Low-dose oral prednisone resulted in an increased risk of relapse and is therefore not recommended for acute optic neuritis.

Corticosteroids
In 1961, Miller and colleagues\[52\] showed that multiple sclerosis (MS) patients treated with corticosteroids recovered faster and more fully from acute relapses than patients treated with saline.

In ONTT, patients were randomized to undergo placebo, oral (low-dose) prednisone (1 mg/kg/day for 14 days) or high-dose methylprednisolone intravenous (250 mg 4 times daily for 3 days), followed by oral treatment. It was observed that intravenous methylprednisolone increased the speed of visual recovery over the first 15 days.

IVMP (1,000 mg daily for 3 days) followed by oral prednisone (1 mg/kg/d for 11 days) has increased visual restoration and better functional short-term, but not long-term performance. However, no study has yet demonstrated any effect on long-term function or the subsequent development of optic nerve atrophy from high-dose IVMP or oral corticosteroids.

For the treatment of ON and MS-associated relapses, an intramuscular or subcutaneous adrenocorticotropic hormone is also licensed, providing an alternative route with stimulation of the hypothalamic–pituitary–adrenal axis. Because of the excellent bio-availability of oral corticosteroids, various drug regimens are now available for administration. Oral prednisone at lower doses, however, should be avoided because it increases the risk of ON relapse.

For acute attacks of NMO, Neuromyelitis Optica Study Group published the recent guidelines in 2014 recommend early treatment with 1-gram IV methylprednisolone daily for five days.\[53\] If symptoms worsen or do not improve, therapeutic plasma exchange is recommended by the Neuromyelitis Optica Study Group. The best clinical outcomes have been reported in patients who are treated with IV-MP and plasma exchange within 48 h of symptom onset, with similar outcomes in patients treated within the first 5 days.

ONTT is not informative on the impact of high-dose corticosteroids on visual recovery in NMOSD-ON and MOG-ON. However, it has been seen that visual outcomes after individual attacks of NMOSD-ON are significantly worse than MS-ON and MOG-ON with high dose steroid administration.

Intravenous immunoglobulin (IVIg)
IVIg acts as an alternative immunomodulatory therapy. Human IV Ig acts by decreasing lesion formation by inhibiting complement-dependent and cell-mediated cytotoxicity.

IVIg (0.4 g/kg) did not improve contrast sensitivity or visual function at 6 months after injury in a placebo-controlled trial of acute NMOSD-ON.\[54\] The same dosage did not improve refractory vision loss in patients with MS-ON.\[55\] Nonetheless, in both studies patient response may have been restricted by delayed IV Ig administration following corticosteroid therapy: 4 weeks in the acute ON trial and an average of 4 years in the refractory ON trial.
Plasma exchange (PLEX)
PLEX has been used successfully in the treatment of steroid-refractory ON and NMOSD-ON. PLEX is a nonselective extracorporeal blood purification process with the elimination of plasma and subsequent substitution. This also seems to be in accordance with the positive effects of PLEX in patients with other inflammatory demyelinating syndromes, including NMO who have been unresponsive to high-dose CS therapy. PLEX should be considered in resistant cases before optic atrophy develops.

However, the early, first-line use of PLEX in AON treatment has yet to be assessed. Moreover, because PLEX incurs significant cost and may result in serious side effects such as hypotension, infection, hypocalcemia, and coagulopathy, a randomized, prospective study of PLEX versus IVMP for the treatment of acute NMOSD-ON is warranted.

Immunomodulators
For individuals who do not respond to IVMP and PLEX, intravenous cyclophosphamide immunosuppression may represent a final resort avenue. In atypical progressive ON cases where treatment options have failed or remain to be limited, cyclophosphamide might be considered. Although no clinical studies on the response of severe ON to intravenous cyclophosphamide have been published, this approach has benefited a subset of patients with acute transverse myelitis.

Neuromyelitis Optica Study Group has considered using azathioprine and rituximab for long-term immunosuppression as first-line agents. A multicenter trial found that rituximab decreased relapse rate and improved disability scores after 2 years. Mycophenolate mofetil, methotrexate, and mitoxantrone can be used as second-line therapy. While there is currently no Food and Drug Administration approved NMOSD treatment, clinical trials are actively underway for tocilizumab (anti-IL6 monoclonal antibody), inebilizumab (anti-CD19 monoclonal antibody), and eculizumab (anti-C5 protein monoclonal antibody).

Immunoadsorption (IA)
Alternative form of therapeutic apheresis that allows plasma antibodies to be selectively removed using modified membranes. Supposed benefits of immunoadsorption over therapeutic plasma exchange (TPE) are the decreased chances of adverse events such as allergic reactions or infection. IA for the treatment of steroid-refractory relapse seems safe and effective. Immunoadsorption also benefits NMOSD-ON.

Recent developments
Erythropoietin
Systemic infusion of erythropoietin with and without methylprednisolone has shown beneficial effects on the role and survival of the retinal ganglion cell (RGC) in a rat model of experimental autoimmune encephalomyelitis. The administration of erythropoietin raised protein levels of phospho-Akt, phospho-MAPK 1 and 2, and Bcl-2, suggesting that activation of the Akt signaling pathway may be crucial. Recently, in a small cohort of participants, a phase 2 clinical trial compared systemic erythropoietin with a placebo in the treatment of AON. Treatment with erythropoietin resulted in significant improvements in mean visual acuity and in the mean thickness of peripapillary RNFL as calculated by optical coherence tomography (OCT) and increased VEP latencies in week.

Phenytoin
In Phase 2 randomized controlled trial, phenytoin was shown to ameliorate RNFL loss in acute ON. Treatment with phenytoin, however, had no effect on visual outcomes or visual evoked potentials (VEPs).

Opicinumab
It is a human monoclonal antibody against leu-cine-rich repeat and immunoglobulin domain-containing receptor-interacting protein-1 (anti-LINGO-1) neurite outgrowth antagonist was recently studied as a possible remyelinating treatment in acute ON. It is an antibody against LINGO1, a CNS protein that acts as a negative regulator of oligodendrocyte precursor differentiation, promoted CNS remyelination by creating a microenvironment conducive to oligodendrocyte differentiation. Treatment with opicinumab did not result in a significant change in the VEP latency in the intention-to-treat population at 24 weeks; however, there was a significant improvement in the VEP latency delay in the prescribed per-protocol patient at 24 and 32 weeks. There was no effect of anti-LINGO-1 treatment on RNFL or GC + IPL thickness in either the intention-to-treat or per-protocol patient population at 24 weeks.

ST266
It is a novel biological secretome of amnion-derived multipotent progenitor cells containing multiple growth factors and anti-inflammatory cytokines, attenuated visual dysfunction and prevented retinal ganglion cell (RGC) loss in experimental optic neuritis. ST266 (formerly Amnion-Derived Cellular Cytokine Solution) is the proprietary biologic secretome of amnion-derived multipotent progenitor (AMP) cells. ST266 modulates inflammatory responses by decreasing vascular permeability, immune cell infiltration, and edema; accelerates wound healing. Long-term effects and dose escalation studies have not been reported yet.

Other modalities
New treatments with novel pathways have been applied to therapies licensed in the 1990s, β-interferon and glatiramer acetate: reduction of leucocyte adhesion (natalizumab); interaction with S1P-mediated lymph node egress (fingolimod); interference with

Table 4: Summary of bio-markers in ON (Apart from imaging)

| Biomarker     | Concentration in NMO                                                                 | Concentration in MS                                                                 |
|---------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| AQP-4 Ab      | Positive in NMO                                                                     | Negative in MS                                                                      |
| MOG Ab        | Diagnosis of MOGAD                                                                   |                                      |
lymphocyte proliferation (teriflunomide), and activation of the pathway of oxidative stress reaction (dimethyl fumarate).

**ON post infection**

For cases of reported bacterial ON, such as Lyme disease, syphilis, and tuberculosis, effective antibiotics should be started as soon as possible. Unless otherwise contraindicated, if there is a strong likelihood of infection, antibiotic treatment should be started with symptomatic therapy. Based on subsequent imaging or diagnostic studies, antibiotic therapy may be suspended or tailored.

Table 5 summarizes the various clinical findings and treatment in the different etiologies of optic neuritis.

### Conclusion

Typical ON is most commonly associated with MS, and corticosteroid therapy may benefit selected patients on short term basis. The etiology of atypical ON varies widely and calls out for different treatment options. With the presence of old and new biomarkers, we are now in a better position to evaluate various etiologies of atypical ON and provide better outcomes in such, otherwise recalcitrant ON entities.

### Acknowledgements

Figure 1 (A, B, C): Lana-Peixoto, Marco A, and Natália Talim. “Neuromyelitis Optica Spectrum Disorder and Anti-MOG Syndromes.” Biomedicines vol. 7, 2 42. 12 Jun. 2019. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6631227/).

Figure 2: Tian G, Li Z, Zhao G, Feng C, Li M, Huang Y, Sun X. Evaluation of Retinal Nerve Fiber Layer and Ganglion Cell Complex in Patients with Optic Neuritis or Neuromyelitis Optica Spectrum Disorders Using Optical Coherence Tomography in a Chinese Cohort. J Ophthalmol. 2015;2015:832784.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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