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Optic Neuritis in the Era of MOGAD and NMOSD: Redefining the Atypical

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Optic neuritis (ON) is an acute inflammatory disorder of the optic nerve and is often the first manifestation of multiple sclerosis (MS). It occurs most frequently in young women. The key goal in the initial assessment is to distinguish typical ON from features suggesting an atypical presentation that warrants further investigation. This issue of *Ophthalmology Rounds* reviews the clinical presentation, pathophysiology, diagnostic criteria, and treatment of demyelinating ON in MS, neuromyelitis optica spectrum disorder, and myelin oligodendrocyte glycoprotein antibody-associated disease.

Optic neuritis (ON) is an inflammatory optic neuropathy involving one or both optic nerves. Typical ON, either idiopathic or associated with multiple sclerosis (MS), remains the most common form. Diagnosis is established by confirming optic neuropathy through reduced visual acuity (VA) or visual field (VF) loss, a relative afferent pupillary defect (RAPD), dyschromatopsia, and optic disc edema (in anterior ON). Once optic neuropathy is established, an inflammatory cause is suspected when symptoms such as eye pain or ocular pain with movement are present. Most patients recover VA and VF over several months. High-dose corticosteroids can accelerate this recovery, although long-term outcomes are usually favourable even without treatment.[1,2] The presence of demyelinating brain lesions on magnetic resonance imaging (MRI) significantly increases the risk of future MS.[3]

The definition of atypical ON has expanded to include a broad range of optic neuropathies, including autoimmune demyelinating conditions such as neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), inflammatory autoimmune diseases such as sarcoidosis, and infectious causes such as syphilis.[4,5] Clinical clues of atypical ON include male sex, onset before age 18 years or after 50 years, absent or minimal ocular pain, bilateral involvement, severe optic disc edema, and peripapillary hemorrhages. Additional atypical features include profound visual loss (no light perception), progression beyond 2 weeks, and poor spontaneous or steroid-related recovery.[6] Ocular findings such as uveitis or macular stars and systemic evidence of autoimmune disease, cancer, or infection further support alternative etiologies.[3,5] Radiographic findings, including extensive optic nerve enhancement, sheath-predominant enhancement, or involvement of the chiasm or optic tracts, also point toward NMOSD or MOGAD. These clinical and imaging features are summarized in **Table 1**.[6]

The discovery of novel autoantibodies has reshaped the diagnostic and therapeutic approach to ON, especially in NMOSD- and MOGAD-associated disease. Early recognition of characteristic clinical and radiologic patterns supports timely antibody testing and guides treatment to improve outcomes.

This review summarizes current clinical features, pathophysiology, diagnostic criteria, and treatment strategies for demyelinating ON in MS, NMOSD, and MOGAD. Other autoimmune, infectious, paraneoplastic, vaccine-related, and pediatric forms are beyond the scope of this article.

Cases

Case 1

A 41-year-old Caucasian woman presented with a 1-week history of blurry vision accompanied by pain with eye movements OD. She was 20/150 OD and 20/20 OS with a right RAPD on examination. Colour vision showed 0/14 Ishihara plates OD and normal OS. OD showed a normal fundus examination, peripapillary retinal nerve fiber layer (pRNFL) elevation on optical coherence tomography (OCT), and cecocentral scotoma VF. MRI orbit with contrast (T1 with fat suppression post-gadolinium) showed enhancement of a short segment of the right intraorbital optic nerve. The brain and spinal MRI were normal. She was treated with intravenous methylprednisolone (IVMP; 1 g for 5 days). At the 6-month follow-up, her VA, colour vision, and VF were back to baseline with no RAPD.

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Table 1. Clinical and radiographic features of MOGAD- and NMOSD-associated atypical ON

Features	MOGAD- and NMOSD-associated atypical ON
Clinical	• Bilateral • Painless • Severe optic disc edema or disc hemorrhage • Male predominance • Onset <18 years or >50 years • Progressive vision loss over >2 weeks • VA ≤20/200 • No visual recovery after 3 months • VA decline after corticosteroid withdrawal
Radiographic	• Longitudinal extensive optic nerve, chiasmal, or optic nerve sheath enhancement

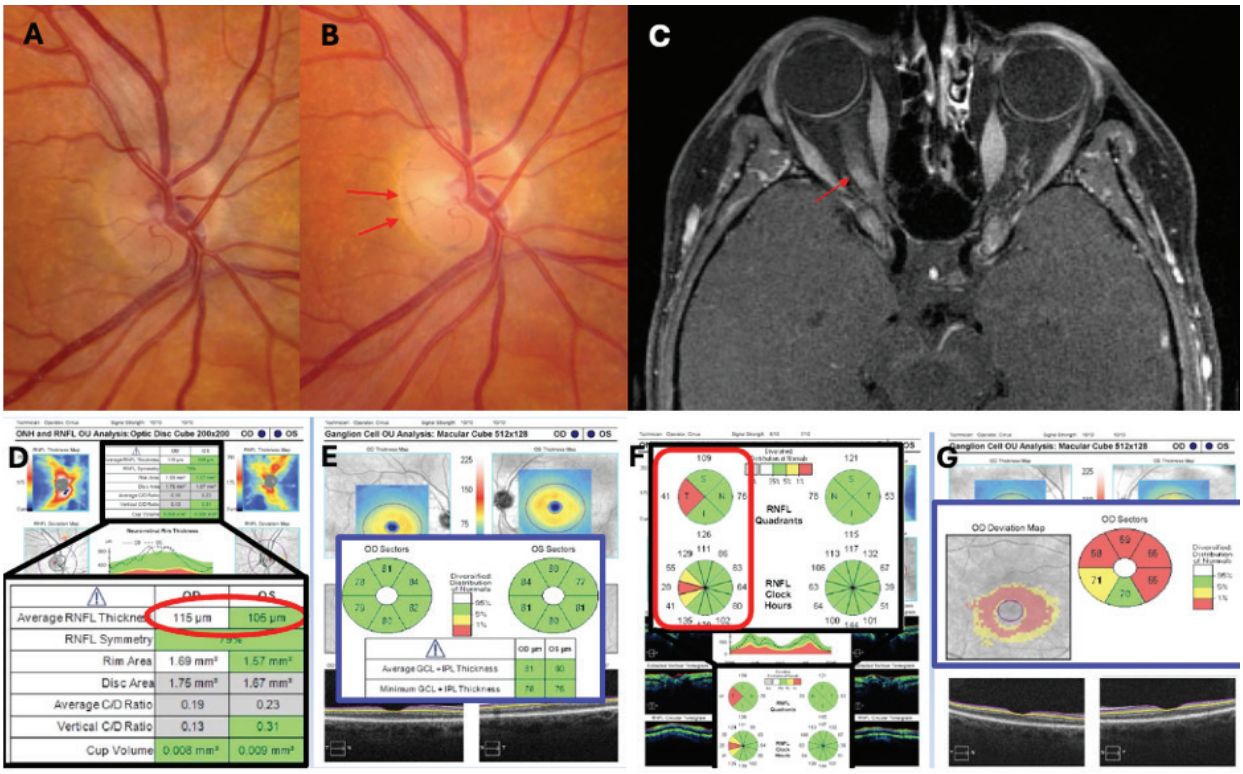
MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; VA, visual acuity

There was right temporal pallor of the optic disc and corresponding temporal thinning of pRNFL and macular ganglion cell–inner plexiform layer (mGCIPL; **Figure 1**).

Case 2

A 44-year-old woman had a 2-month history of progressive limb weakness, numbness, intractable hiccups with nausea, and right blurry vision associated with pain on eye movement. She was 20/400 OD and 20/20 OS with a right RAPD on examination. Colour vision showed 0/14 Ishihara plates OD and normal OS. OD also showed optic disc edema, diffuse restriction on VF, and pRNFL elevation on OCT. MRI orbit with contrast (T1 with fat suppression post-gadolinium) showed longitudinal extensive enhancement of the optic nerve bilaterally, with extension to the right intraorbital segment and left optic chiasm. Brain MRI was normal. She received IVMP 1 g for 5 days, followed by an oral prednisone taper and declined plasma exchange (PLEX). At the 4-week follow-up, her serum testing was positive for aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies, and her VA improved to 20/25 OD with no RAPD and normal colour vision. There was a significant reduction of the optic disc edema on fundus examination and OCT (**Figure 2**).

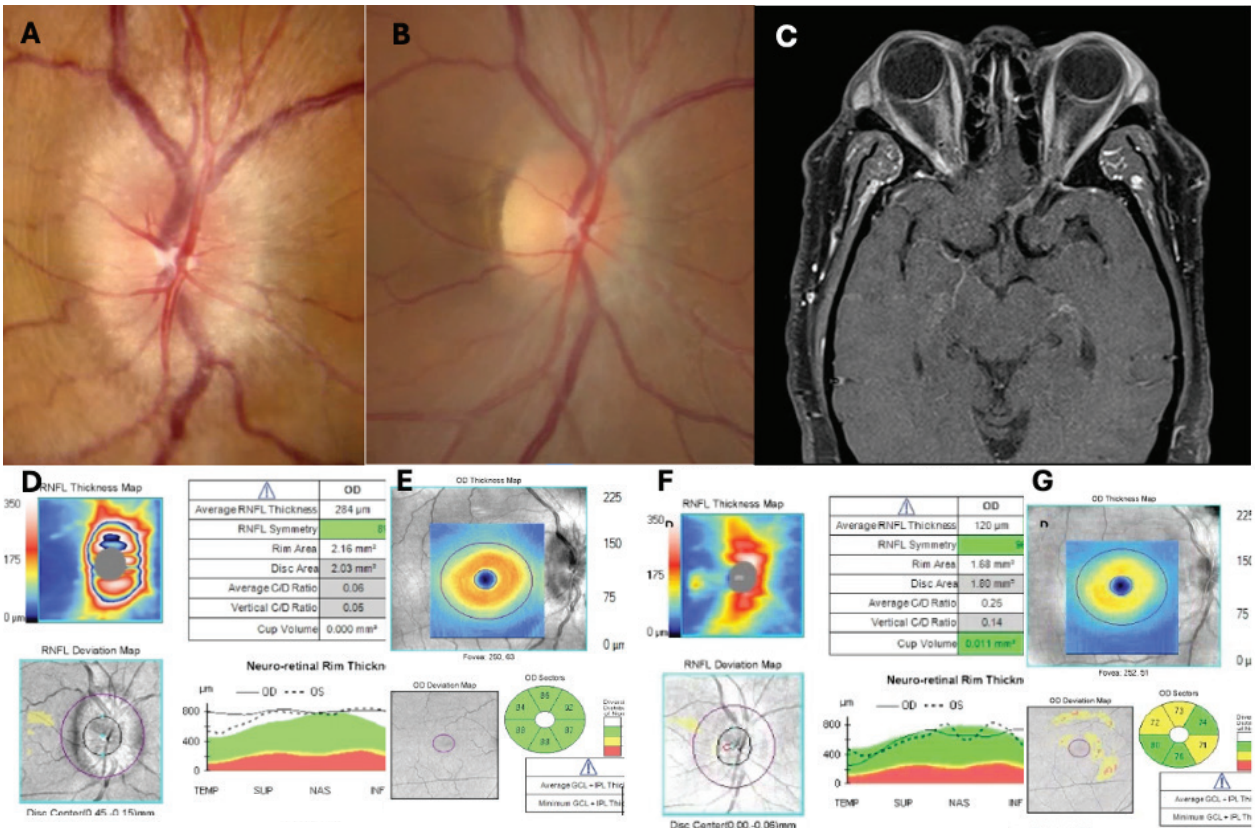
Figure 1. Fundus image, MRI, and OCT in idiopathic ON.



A Fundus photograph of the right eye at initial presentation showed a normal optic disc. **B** Fundus photograph of the right eye at 6-month follow-up demonstrated temporal disc pallor (red arrows). **C** Axial MRI of the orbits with contrast (T1 with fat suppression) showed enhancement of a short segment of the right intraorbital optic nerve (red arrow). **D–E** OCT of the pRNFL showed increased thickness in the right eye (115 µm) and normal thickness of the mGCIPL. **F–G** OCT of the pRNFL showed temporal thinning in the right eye and reduction of the mGCIPL thickness at follow-up.

MGCIPL, macular ganglion cell-inner plexiform layer; MRI, magnetic resonance imaging; OCT, optical coherence tomography; pRNFL, peripapillary retinal nerve fibre layer

Figure 2. Fundus image, MRI, and OCT in AQP4-positive NMOSD-associated ON.



A Fundus photograph of the right eye at presentation showed marked optic disc edema. **B** Fundus photograph of the right eye at 4-week follow-up demonstrated reduction of edema with temporal pallor. **C** Axial MRI of the orbits with contrast (T1 with fat suppression) showed longitudinal extensive enhancement of the right optic nerve extending to intraorbital segment and longitudinal extensive enhancement of the left optic nerve extending to optic chiasm. **D–E** OCT at presentation showed significant elevation of the pRNFL and normal mGCIPL thickness. **F–G** Follow-up OCT demonstrated reduction of pRNFL swelling and early thinning of the mGCIPL.

AQP4, aquaporin-4

Case 3

A 17-year-old boy presented with a 4-week history of blurry vision OD, followed by 3 days of blurry vision OS, accompanied by pain with eye movements. He was LP OD and 20/80 OS with a right RAPD. Colour vision testing showed an inability to identify the control plate OU. There was significant optic disc edema with peripapillary wrinkles and large central scotomas on VF OU. MRI of the orbits with contrast (T1 with fat suppression) showed bilateral longitudinal extensive enhancement of the optic nerves but a normal MRI brain scan. He received IVMP 1 g daily for 5 days, followed by an oral prednisone taper and 7 sessions of PLEX. At the 6-week follow-up, myelin oligodendrocyte glycoprotein (MOG)-IgG testing was positive, and his vision had returned to baseline OU with no RAPD. He also had normal colour vision and nonspecific scattered depressed points OU (**Figure 3**).

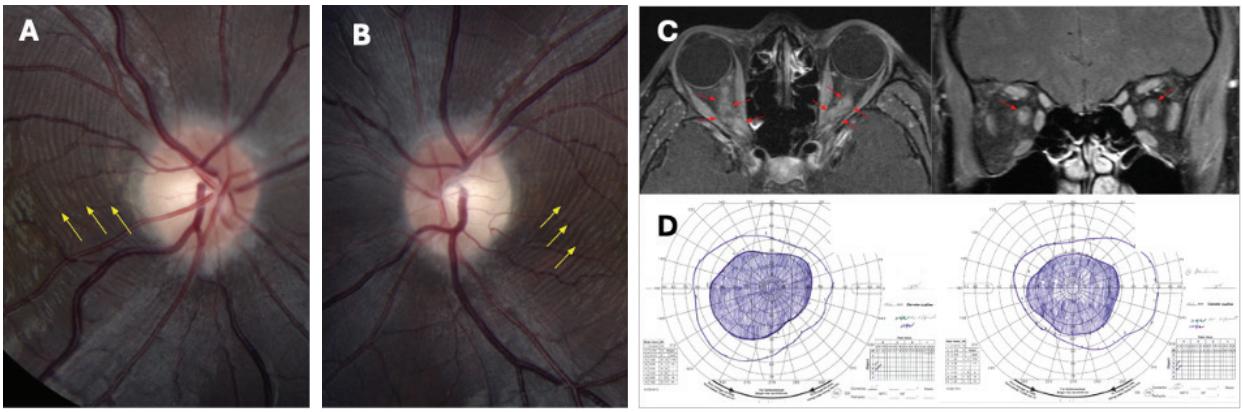
Clinical Presentation

MS-associated and idiopathic ON

MS-associated and idiopathic ON are classified as "typical" ON and account for up to 90% of cases.[7] The usual presentation is acute, unilateral visual loss with a RAPD, pain on eye movements, and impaired colour vision. It occurs mainly in women (female-to-male ratio ~3:1) of Caucasian ancestry, with a mean age of 32 years.[2] Vision typically reaches nadir within days; deterioration beyond 2 weeks is atypical and warrants investigation for other causes. Most patients begin recovering within the first month, even without treatment.[8] A unilateral RAPD is expected but may be absent in bilateral ON or in patients with prior ON in the fellow eye, and this should be considered during evaluation.

Much of the current understanding of typical ON comes from the Optic Neuritis Treatment Trial (ONTT), a prospective, multicenter, randomized controlled study of 457 adults (ages 18–46 years) presenting within 8 days of unilateral ON between 1988 and 1991.[2] The cohort, composed of 77% women and 85% Caucasian, was followed for 15 years to assess the effects of corticosteroids. About 50% were ultimately classified as MS-associated ON, and the remainder as idiopathic.[2] The ONTT likely overestimated idiopathic ON due to the exclusion of bilateral disease and marked disc swelling, as well as its predominantly Caucasian sample. This may explain why only 1.7% were later found to be MOG-IgG-positive, and none were AQP4-IgG-positive.[2]

Figure 3. Fundus image, MRI, and VF in anti-MOG antibody-associated bilateral ON.



A–B Fundus photographs at presentation showed significant optic disc edema with peripapillary wrinkles (yellow arrows). **C** Axial and coronal MRI of the orbits with contrast (T1 with fat suppression) demonstrated bilateral longitudinal extensive enhancement of the optic nerves (red arrows). **D** Goldmann VF at presentation showed large central scotomas.

MOG, myelin oligodendrocyte glycoprotein

A contemporary study showed approximately 57% were MS-associated, 29% idiopathic, 5% MOG, and 3% AQP4 ON.[7]

In ONTT, most patients had mild-to-moderate visual loss at nadir: 67% between 20/20 and 20/200 and 33% between 20/200 and hand motions; no light perception was rare. More than 90% recovered to ≥20/40 by 1 year. High-dose corticosteroids accelerated improvement by 1–2 Snellen lines in the first 2 weeks, but final VA at 1 year was similar between the treatment and observation groups.[2] Pain occurred in 92%, often worsened with eye movements (87%), and preceded vision loss in about 40%. Dyschromatopsia (93.8%) and RAPD were typical findings. VF defects were present in 97.5% but lacked a pattern to distinguish typical from atypical ON. Fundus examination was usually normal because most cases were retrobulbar; only ~35% showed papillitis, and disc edema was generally mild without hemorrhages or exudates.[2]

AQP4-associated ON

NMOSD (Devic disease) is a severe inflammatory demyelinating disorder of the central nervous system (CNS) with a predilection for the optic nerves and spinal cord.[9] It represents ~3% of all ON cases[7] and predominantly affects females (9:1) of Asian or African descent, with a mean onset of ~41 years, older than in MS-associated ON.[9] Once viewed as an MS variant, NMOSD is now recognized as a distinct disease strongly linked to antibodies against AQP4-IgG.[10,11] Although "NMOSD-associated ON" and "AQP4-associated ON" are often used synonymously, only 70%–90% of patients with NMOSD are AQP4-IgG positive,[12] and up to 42% of patients with AQP4-IgG–negative NMOSD may test positive for MOG-IgG.[13,14] Thus, this review uses antibody-based terminology when appropriate.

AQP4-associated ON typically causes severe visual loss: >80% have VA of ≤20/200 at nadir, and outcomes depend heavily on treatment timing, with delays worsening prognosis. Even with prompt therapy, long-term vision is generally poorer than in typical ON; ~60% of episodes end with final VA of ≤20/200,[5,15] and most patients relapse despite immunosuppressive or immunomodulatory treatment.[16] Although presentations vary, red flags include severe bilateral simultaneous ON, longitudinally extensive transverse myelitis, and area postrema syndrome (intractable hiccups or nausea/vomiting). Pain occurs in about 50% of cases and is less frequent than in MS-associated ON. Despite early reports emphasizing bilateral disease, most patients present unilaterally, with bilateral onset in ~20%–30%.[10,11,17] Fundus examination shows disc edema in <30% of cases, reflecting predominant posterior nerve involvement and frequent chiasmal extension.[11]

MOG-associated ON

MOGAD presents with ON and other demyelinating syndromes, including transverse myelitis, acute disseminated encephalomyelitis, brainstem syndromes, encephalitis, and seizures.[18] Serum MOG-IgG detected by live cell-based assays is the diagnostic biomarker.[11] MOG-associated ON accounts for ~5% of adult ON and up to 50% of pediatric cases.[7,19] Unlike MS and AQP4 disease, MOGAD shows no sex or racial predilection, with an approximate 1:1 male-to-female ratio.[18]

Nadir vision is often severe (>80% worse than 20/200), similar to AQP4-associated ON, but long-term outcomes are more favourable, with mean final VA near 20/30.[20] Bilateral simultaneous involvement is ~50% with frequent pain (~90%), resembling MS-associated ON and exceeding AQP4-associated cases.[11] Fundus examination shows disc edema in 70%–80%, often with hemorrhages and retinal streaks, which may mimic nonarteritic anterior ischemic optic neuropathy and help distinguish MOG-associated ON from the typically retrobulbar AQP4- and MS-associated ON.[11] About 50% of patients relapse, more often with positive MOG-IgG, although relapses can still occur with seronegativity; antibody status alone does not reliably predict disease course.[5]

Of 177 stored sera in ONTT, 3 were MOG-IgG-positive (none AQP4-IgG-positive), which was expected due to MOGAD/NMOSD rarity and ONTT's exclusion of bilateral

disease and marked disc edema. None developed MS over 15 years, and all had disc edema and recovered to 20/20 vision, including 1 placebo-treated patient who presented with hand motions. Two experienced a single recurrence.[21]

Key demographic and clinical distinctions among MS-, AQP4-, and MOG-associated ON appear in **Table 2**.[5]

Pathophysiology

ON is an immune-mediated disorder involving inflammation and demyelination. In MS-associated ON, no single target antigen has been identified, but both B- and T-cell–mediated mechanisms are involved. Active MS lesions show humoral immunopathology with complement deposition and infiltration by B cells and CD8+ T cells, which damage myelin and release inflammatory mediators that drive demyelination, axonal loss, and neuronal death.[5,11]

AQP4 is a water channel on astrocytes throughout the CNS, including optic nerve astrocytes, retinal astrocytes, and Müller cells, providing multiple sites for visual dysfunction. AQP4-IgG binding activates complement, generating anaphylatoxins and causing bystander injury to nearby oligodendroglia. Recruited microglia and polymorphonuclear/mononuclear leukocytes amplify injury via antibody-dependent cytotoxicity, complement-mediated degranulation, cytokine release, and antibody-dependent phagocytosis. Optic nerve astrocytes are the primary target, while involvement of retinal astrocytes and Müller cells shows mixed evidence.[11]

MOG is located on the outer myelin sheath. Histopathology in MOG-associated ON shows antibody-dependent and independent injury, including complement deposition, CD4+ T-cell infiltrates, astrogliosis, and microglial activation. Unlike AQP4-IgG, MOG-IgG alone produces minimal demyelination, suggesting that complement is not the initiating event. Tissue damage is likely driven by antibody-dependent cell-mediated phagocytosis involving MOG-IgG, CD4+ T cells, and MOG-laden macrophages.[11]

Diagnosis

Typical ON remains a clinical diagnosis, classically presenting with unilateral, subacute vision loss, pain on eye movements, RAPD, and characteristic optic nerve findings. Extensive testing is unnecessary in typical cases, but atypical features require further evaluation. When AQP4- or MOG-associated disease is suspected, serum AQP4-IgG and MOG-IgG should be obtained. MRI, OCT, and automated perimetry provide complementary diagnostic information.

AQP4 is concentrated on astrocytes and ependymal cells, especially at perivascular foot processes along the blood-brain barrier. AQP4-IgG testing is best performed using a fluorescence-activated cell sorting live cell-based assay (~75% sensitivity, ~99% specificity).[22] MOG is a myelin surface glycoprotein in the optic nerves, brain, and spinal cord. MOG-IgG establishes MOGAD in compatible clinical/MRI contexts. Titer interpretation is essential: titers of 1:20–1:40 have ~50% positive predictive value (PPV; vs 100% at 1:1000); in atypical phenotypes, titers

Table 2. Detailed demographics and clinical features in MS-associated ON, AQP4-associated ON, and MOG-associated ON

Feature	MS or idiopathic	AQP4	MOG
Prevalence	Up to 90%	3%	5%
Age	~30 years	~40 years	Affects adults and children equally
Female: male ratio	3:1	9:1	1:1
Pain	90%	50%	90%
Bilaterality	5%	20%–30%	50%
Optic disc edema	35%	30%	70%–80%
Acute VA <20/200	30%	80%	80%
Chronic VA <20/200	4%	60%	5%

MS, multiple sclerosis

<1:100 have ~10% PPV.[23] MOG-IgG often becomes undetectable after the initial attack (~33%), and associated MRI lesions frequently resolve, more so than in MS or AQP4 disease, making retrospective diagnosis difficult without acute-phase studies.[24]

Orbital MRI helps differentiate ON subtypes. Acute ON generally shows T2 hyperintensity and/or T1 gadolinium enhancement. Typical ON is retrobulbar in ~67% and demonstrates short-segment enhancement without chiasmal, tract, perineuritic, or orbital fat involvement.[5] AQP4-associated ON usually shows longitudinally extensive lesions (>50% of nerve length) with posterior predilection (~70%) and minimal perineuritic/orbital fat enhancement.[11] Isolated chiasmal or optic tract lesions are more frequent in AQP4 ON.[25] It is important to distinguish between AQP4 and MS ON, as several MS therapies (e.g., β-interferons, fingolimod, natalizumab) can worsen NMOSD.[26] MOG-associated ON is also longitudinally extensive but favours the anterior segment of the optic nerve (70%–80%).[11] Chiasmal involvement usually occurs as a continuum of a long-segment nerve lesion rather than isolated chiasmal disease, as in AQP4 ON.[25] Perineuritic/orbital fat enhancement is common in MOG (~50%) but uncommon in AQP4 or typical ON.[25]

Brain MRI is the gold standard for MS risk stratification. About 20% of MS patients initially present with ON.[27] In ONTT and the longitudinal ON Study, ~50% of monosymptomatic ON patients had MRI changes suggestive of MS.[28] A normal baseline MRI confers ~15% MS risk at 5 years and ~25% at 15 years, whereas ≥3 lesions confer ~50% and ~75% risk, respectively.[3] MRI also helps distinguish among different ON: MS shows periventricular "Dawson fingers," juxtacortical and infratentorial lesions, and short (<3 segments) partial spinal cord lesions.[29] NMOSD involves regions with

high AQP4 expression and longitudinally extensive transverse myelitis (≥3 segments) with central, often complete, cord involvement.[17] MOGAD shows fluffy cortical-subcortical lesions and gray-matter–predominant "H-sign" spinal lesions, with better recovery than NMOSD.[30] The 2024 McDonald,[29] 2015 NMOSD,[17] and 2023 MOGAD[30] criteria are not discussed in detail due to character limits.

VF defects are variable and nonspecific. Diffuse or central depression predominates in typical ON and MOGAD, whereas altitudinal defects are relatively more frequent in AQP4-associated ON.[11] Serial perimetry helps track recovery and correlates with OCT structural loss.

OCT provides reproducible quantification of retinal axonal and ganglion cell loss. pRNFL and mGCIPL are the key metrics.[6] Acute pRNFL swelling is greater and more frequent in MOG-associated ON than in AQP4 or typical ON.[5] The magnitude of pRNFL/mGCIPL loss predicts long-term vision.[11] pRNFL thinning may not appear for ~3 months, whereas mGCIPL loss can occur within 1 month.[5,6] Chronic atrophy is most pronounced in AQP4 disease, paralleling its poorer visual prognosis.

Visual-evoked potential (VEP) assesses afferent pathway integrity. Demyelination prolongs P100 latency with preserved amplitude; ischemic, compressive, and toxic neuropathies more often reduce amplitude without significant latency change. Thus, prolonged latency with preserved amplitude supports ON.[6] VEP has limited diagnostic utility but can help in subtle or bilateral cases.[5] OCT generally outperforms VEP for detecting structural sequelae, and its ubiquity has reduced VEP use outside academic centres.[31]

Management

Acute treatment

For acute MS-associated ON, high-dose corticosteroids or observation are both appropriate. ONTT showed that steroids accelerate visual recovery by ~1–2 Snellen lines in the first 2 weeks but do not change the final outcome.[2] Standard therapy mirrors ONTT: IVMP 1 g/day for 3–5 days, with or without an oral prednisone taper.[2] High-dose oral prednisone (1250 mg/day for 5 days) or oral MP provides noninferior outcomes and may be more cost-effective.[32,33] Low-dose oral prednisone (1 mg/kg) increases early relapse risk and is not recommended.[2]

In suspected atypical ON, early treatment is preferred because earlier therapy correlates with better pRNFL preservation and vision,[11] and antibody testing may take weeks. In NMOSD, IVMP is typically given for ≥5 days, followed by a slow prednisone taper (1 mg/kg/day for 6–8 weeks).[5] Adding PLEX improves outcomes: final VA averages ~20/50 with IVMP+PLEX vs ~20/400 with IVMP alone, and randomized data show ~50% complete recovery when PLEX is started within 2 days vs ~5% when begun after 20 days.[34,35] Retrospective data consistently support early PLEX for severe attacks.

MOGAD ON generally responds to IVMP (3–5 days), followed by an oral prednisone taper (1 mg/kg/day for 6–8 weeks); high-dose oral regimens may be effective.[5] Early PLEX is advised for severe attacks or lack of improvement by 2 weeks.[5,36] IV immunoglobulin (IVIG) is a reasonable option for refractory disease.[37] Randomized trials of non-steroid agents – including simvastatin, erythropoietin, phenytoin, opicinumab, amiloride, lipoic acid, fingolimod, and interferon-β – have not shown benefit.[38]

Long-term management

Long-term therapy aims to prevent relapses and preserve vision and must be tailored to the specific disease. In MS, disease-modifying therapies (DMTs) reduce relapse risk through lymphocyte sequestration, cytokine modulation, and immune depletion. Early DMT initiation after a first demyelinating event delays conversion to definite MS and lowers future relapse rates. Interferon-β and glatiramer acetate remain first-line options, while higher-efficacy monoclonal antibodies (e.g., natalizumab, ocrelizumab) offer greater protection in high-risk patients. Accurate distinction between MS and NMOSD is essential because several MS therapies, including β-interferons, fingolimod, and natalizumab, can trigger severe NMOSD attacks.[5] For details on MS DMTs, see McGinley et al.[39]

Four agents are approved for NMOSD.[38] Eculizumab (C5 inhibition) is approved for both AQP4-IgG–positive and –negative disease. Inebilizumab (anti-CD19) and satralizumab (interleukin-6 receptor inhibition) are approved for AQP4-IgG–positive NMOSD, and ravulizumab-cwvz is a long-acting C5 inhibitor for AQP4-IgG–positive adults. Azathioprine, mycophenolate mofetil, and rituximab remain widely used off-label based on long-standing experience.[38] Additional detail can be found in Gospe et al.[40]

In MOGAD, ~50% of patients experience only one attack with good recovery, so long-term therapy is often deferred. Treatment is considered for poor recovery or relapsing disease.[38] No Health Canada-approved therapies exist. Observational data associate mycophenolate mofetil, azathioprine, IVIG, and rituximab with reduced relapse rates; the lowest rate is frequently associated with IVIG.[38] A meta-analysis of 41 primarily retrospective studies supports azathioprine, mycophenolate, rituximab, IVIG, and tocilizumab in lowering relapse risk in both pediatric and adult MOGAD.[41] Prospective controlled trials remain urgently needed.

Future directions in ON treatment

Despite advances in acute treatment, current therapies are primarily anti-inflammatory and do not reverse structural damage, driving interest in neuroprotection and remyelination. Neuroprotective strategies aim to limit axonal injury during acute inflammation, while remyelinating therapies seek to restore conduction and tissue integrity. Agents such as memantine, erythropoietin, interferon-β, phenytoin, and clemastine have been studied; however, recent reviews have shown no consistent clinical benefit, and further investigation is warranted.[42] Candidate remyelinating approaches, including opicinumab, ibudilast, and mesenchymal stem cell (MSC)-based therapies, have not demonstrated reliable visual recovery in ON. Opicinumab showed preclinical promise but failed multiple Phase II endpoints and was discontinued. Ibudilast has neuroprotective properties in MS, and MSC-derived therapies have shown potential for myelin repair, but both remain investigational.[42] Gene therapy

targeting neuroprotection or retinal ganglion cell regeneration is at an early preclinical stage and remains far from clinical translation in ON.[42]

Cases Continued

Case 1

This is a typical demyelinating ON case. The acute, unilateral, painful visual loss in a young Caucasian woman is consistent with idiopathic or MS-associated ON. MRI of the orbits confirmed focal enhancement of the intraorbital optic nerve. The absence of demyelinating lesions in the brain or spine was correlated with an estimated 15-year conversion risk of 25%. Excellent recovery was observed across all modalities, underscoring the generally favourable prognosis of typical ON with corticosteroid therapy.

Case 2

This is a case of AQP4-associated ON. The patient presented with classic features of subacute neurological symptoms from spine and area postrema involvement, as well as painful, unilateral vision loss with marked optic disc edema, diffuse VF restriction, and profound colour vision loss. The serum AQP4-IgG established the diagnosis. It should be noted that NMOSD is highly relapsing with less favourable outcomes. In case of relapse, consider escalation to PLEX or long-term therapy.

Case 3

This case illustrates the clinical features of MOG-associated ON, characterized by bilateral, sequential vision loss, simultaneous bilateral optic nerve edema, and longitudinal extensive enhancement of the optic nerves on MRI, without clear age or sex predilection. MOG-associated ON is generally more steroid-responsive and has a better visual prognosis than AQP4-associated ON. Prophylactic long-term immunotherapy is typically not initiated until further relapses.

Conclusion

Recognition of MOGAD and NMOSD as distinct immunopathologic entities has reframed “atypical” ON from a diagnosis of exclusion to a set of disorders with specific biomarkers, imaging patterns, prognoses, and treatments. Early differentiation among MS-, AQP4-, and MOG-associated ON is crucial because therapeutic urgency and long-term immunotherapy choices directly impact visual outcomes and may prevent irreversible loss. Advances in serology and MRI pattern recognition now allow a move beyond the ONTT-era paradigm toward a precision, antibody-guided approach. While high-dose corticosteroids, PLEX, and targeted biologics have improved acute outcomes and reduced relapse rates, current treatments primarily suppress inflammation rather than address axonal or neuronal damage. Emerging neuroprotective, remyelinating, and gene-based strategies are promising but remain investigational. Continued research and collaboration will be essential to develop therapies that not only preserve but also restore vision in ON in the era of MOGAD and NMOSD.

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