

Demyelinating and inflammatory optic neuropathies: an update

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Abstract

Optic neuritis is one of the leading causes of vision loss in young to middle-age populations worldwide. Although it has been documented to account for the initial presentation in up to one-fifth of multiple sclerosis patients among Caucasian populations, the clinical course and etiologies of the condition are less well-defined in Asians. Chinese patients have lower conversion rates to multiple sclerosis as well as a higher incidence of neuromyelitis optica-associated optic neuritis and optic perineuritis, demonstrating considerable ethnic differences. The need to better characterize the differentiating features between three clinically similar entities: multiple sclerosis-associated optic neuritis, neuromyelitis optica-associated optic neuritis and optic perineuritis, is warranted to facilitate proper management.

Key words: Multiple sclerosis; Neuromyelitis optica; Optic neuritis

Introduction

Optic neuritis (ON) is a disorder of the optic nerve that classically presents with the triad of vision loss, periocular pain and dyschromatopsia.^{1,2} It is conventionally classified into typical and atypical forms, whereby typical ON is taken to be demyelinating cases associated with multiple sclerosis (MS) and atypical ON with non-MS immune-mediated etiologies including neuromyelitis optica (NMO-

ON) and systemic disorders such as connective tissue and granulomatous conditions.³ For the purpose of this review, we will focus on MS-ON and NMO-ON because of their clinical importance and demand for early differentiation given their dissimilar management modalities and prognoses. Meanwhile, optic perineuritis (OPN), a form of idiopathic orbital inflammatory disease (IOID) that targets the optic nerve sheath, has in recent years been found to share deceptively similar presentations to ON, with both conditions bringing about acute monocular vision loss, pain on eye movement and a normal or swollen optic disc. OPN therefore represents a key differential diagnosis in cases of suspected ON, and will for this reason also be included in our discussion.⁴ This article will review our current understanding of the three disease entities, MS-ON, NMO-ON and OPN; delineate features crucial for their differentiation in terms of presentation, investigative findings,^{5,6} treatment and prognosis; and propose recommendations for the most appropriate clinical approach.

Idiopathic demyelinating optic neuritis / multiple sclerosis-associated optic neuritis

A patient who develops typical idiopathic demyelinating optic neuritis (IDON) is usually an otherwise healthy young adult, commonly 20 to 45 years of age and 3 times more likely to be a woman than a man. It is also more reliably associated with MS when found at higher latitudes and in Caucasians.

IDON usually presents with acute painful monocular vision loss accompanied by field loss, dyschromatopsia and periocular pain.⁷ The classic pattern is loss of vision progressing over a span of hours to 10 days, with a spectrum

of severity ranging from mild to no light perception and normally reaching its nadir within 2 weeks. Any form of visual field defect is possible in IDON, although the 15-year follow-up report from the Optic Neuritis Treatment Trial (ONTT) reported diffuse and central field losses to be more commonly detected at the initial visit, and partial arcuate, paracentral and arcuate type losses at subsequent follow-ups.⁸ Complete or near-complete recovery of visual acuity and field loss is common, and in fact any progressive worsening of vision lasting over 2 weeks, or a lack of recovery beyond 8 weeks after symptom onset should prompt investigations for an alternative diagnosis.⁹ Dyschromatopsia, or impaired color vision, occurs early on in the course of IDON and is often out of proportion to the degree of visual acuity deficit. The type of color defect, however, does not appear to correlate with severity of visual impairment. The ONTT described mostly mixed color defects, with blue-yellow defects prevailing in the acute phase and red-green defects more common at 6 months,¹⁰ while other studies largely reported red-green and blue-yellow defects with no particular predominance.¹¹ Up to 30%



Figure 1. A 25-year-old female with first episode of left idiopathic demyelinating optic neuritis: the magnetic resonance imaging scan shows T2 homogeneous hyperintensity over the whole course of optic nerve (arrow).

of IDON patients experience phosphenes¹² that are bright, fleeting flashes of light with eye movement. Periocular pain and retro-orbital pain occur in more than 90% of cases¹³; it can precede or coincide with the onset of vision impairment and is aggravated by eye movement but is usually non-severe and often resolves within days. Additional clinical findings may include the MS-specific but semi-sensitive Uhthoff's phenomenon¹⁴ and Pulfrich phenomenon, being rather non-specific for MS-ON.¹⁵

The diagnosis of MS-ON is a clinical one. The ONTT supports that for a patient who presents with typical ON, laboratory studies and radiological imaging of diagnostic intent are unnecessary.¹⁶ That said, findings from investigations, if performed, can aid the differentiation between MS-ON, NMO-ON and OPN, as well as prognosticate the future risk of developing clinically definite multiple sclerosis (CDMS). In MS-ON, magnetic resonance imaging (MRI) of the optic nerve with gadolinium pinpoints the culprit optic nerve lesion in 95% of patients (**Figure 1**)¹⁷; contrast enhancement of the optic nerve is a sensitive (94%) finding in acute ON,¹⁸ but no published data have yet elucidated its role in MS-ON/NMO-ON distinction. Brain MRI with gadolinium may reveal the characteristic spatial and temporal dissemination of lesions required for a diagnosis of MS set forth by the 2010 McDonald MRI criteria (**Table 1**).¹⁹ The presence of demyelinating white matter lesions in brain MRI scans, 3 mm or larger in diameter, ovoid in shape, located in periventricular areas of the white matter and radiating toward the ventricular spaces, has been identified as the single most predictive factor for conversion to CDMS.²⁰ In the ONTT, 25% of patients with no MRI lesions at presentation still went on to develop MS; 50% of those with one or more MRI lesions developed MS within 5 years²¹ and 72% within 15 years.²² Optical coherence tomography may be employed to visualize the retinal nerve fiber layer (RNFL); the thickness of which increases in the initial period of optic nerve swelling but subsequently decreases secondary to axonal loss. Such thinning, albeit present, should be to a lesser extent than that in NMO-ON eyes; results of one study propounded that any RNFL thickness loss greater than 15 μ m in patients without established symptoms or signs of MS should impel investigations for underlying NMO-ON.²³ Finally, a lumbar puncture performed in MS-ON will demonstrate raised cerebrospinal fluid (CSF) oligoclonal bands alongside mild pleocytosis. A high CSF pleocytosis is, however, a very rare occurrence in MS-ON and heightens the likelihood of an alternative, atypical etiology.²⁴

Table 1. 2010 McDonald magnetic resonance imaging (MRI) criteria for multiple sclerosis.¹⁹

Diagnosis of multiple sclerosis requires elimination of other diagnoses and demonstration of dissemination of lesions in space and time	
Dissemination in space	At least one lesion visible on T2-weighted scan in at least 2 of 4 locations: juxtacortical, periventricular, infratentorial and spinal cord
Dissemination in time	(1) A new T2 lesion or gadolinium-enhancing lesion visible on a follow-up MRI scan when compared with a previous scan (which is taken as the baseline scan) obtained at any time following the onset of symptoms; or (2) An MRI scan showing simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time

The clinical course of IDON follows a reasonably predictable trajectory. Spontaneous improvement in visual function is observed in more than 80% patients within 2 to 3 weeks even in the absence of treatment,²⁵ followed by stabilization or sustained improvement over a period of up to 1 year. Nonetheless, despite the relatively rapid and apparently complete recovery (median visual acuity at 6 months of 20/16,²⁶ and >85% patients scoring 20/25 or better at 5 years²⁷), significant persistent complaints are not rare. Treatment options for MS-ON are manifold; acute treatment can take the form of corticosteroids, plasmapheresis or intravenous immunoglobulins, and long-term treatment can take the form of the disease-modifying drugs beta-interferon and glatiramer acetate. To date, only corticosteroid therapy has consistently produced beneficial therapeutic effects in the acute management of MS-ON, whereby high-dose intravenous corticosteroids followed by an oral taper accelerates initial visual recovery. Multiple studies, however, have concurred that corticosteroids have no bearing on the eventual vision outcome when compared with placebo, among which the ONTT offers the most reliable information regarding the long-term outcome.²⁸ Intravenous methylprednisolone delayed the onset of CDMS at 2 years, but this difference dwindled over time and no statistically significant difference in visual function was discernable between the groups in the long run.²² Based on the findings of the ONTT, treatment with oral corticosteroids in conventional doses alone is contraindicated due to the proven increased risk of a second episode.²⁹ Intravenous corticosteroid therapy, meanwhile, is recommended for typical ON patients in the presence of 3 or more MRI signal abnormalities, as well as for patients in whom there exists a need for prompt resolution of visual deficits, including monocular patients, bilateral disease involvement, patients with employment demands and according to individual patient preference, with the rationale of reducing 2-year risk of MS development.³⁰

Regarding long-term management, a number of placebo-controlled trials have demonstrated the efficacy of disease-modifying agents in delaying subsequent relapse and conversion to CDMS in MS-ON patients positive for MRI demyelinating lesions^{31–33} persisting for 5 years in one particular follow-up study.³⁴ The latest guidelines from the Association of British Neurologists recommend that disease-modifying drugs be considered for patients who present with clinically isolated syndrome and demyelination on MRI, but precise clinical protocols remain locality specific.³⁵ The CHAMPS (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study)³⁶ was a randomized, double-blind trial involving 383 patients with an initial, acute monosymptomatic demyelinating event—either unilateral ON, incomplete transverse myelitis or brainstem/cerebellar lesion, and at least 2 silent T2 lesions on MRI brain—who were given either weekly intramuscular interferon- β 1a or placebo. Acutely the treatment group exhibited statistically significant improvements in all MRI parameters, and 10-year follow-up demonstrated that patients treated as soon after their first episode as possible had a significantly lower chance

of having a second episode than those who received delayed (beyond 30 months) treatment, corroborating the benefits of prompt initiation of interferon- β 1a. This was confirmed by the PRISMS (Prevention of Relapses and Disability by Interferon β -1a Subcutaneously in Multiple Sclerosis) Trial,³⁷ which established that interferon treatment in dosages of 22 μ g and 44 μ g yielded lower relapse rates than control, as well as the BENEFIT (Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment) study³⁸ that described a 50% reduction in risk of MS at 2 years in patients treated with interferon β -1a. Nevertheless, immunomodulatory treatment is not routinely recommended for all patients with MS-ON for the following reasons: (1) low prevalence of MS in Asian countries; (2) lack of consensus on ideal treatment endpoint; (3) efficacy of disease-modifying drugs in preventing long-term disability is yet unproven and (4) MS, as opposed to NMO, tends to follow a favorable disease course. On this basis, the current recommendation is for patients with a normal initial MRI brain to be followed up with surveillance MRI at least annually, to look for the development of any new white matter lesions. Patients with one or more MRI lesions, on the other hand, should be given the option of immunomodulatory treatment and closely followed up with serial MRI scans.³⁹

Inflammatory optic neuropathy

Neuromyelitis optica-associated optic neuritis

NMO is an autoimmune inflammatory disorder of the central nervous system characterized by recurrent bouts of ON and transverse myelitis, features also found in MS. NMO has therefore for decades been considered a variant of MS rather than an independent disease entity. This notion, however, evolved upon the discovery in 2005 of serum antibodies against the water channel protein aquaporin-4 (AQP4) in NMO patients,⁴⁰ and demonstrated fundamentally distinct immunopathogenesis between NMO and MS. Traditionally, NMO was thought to be a monophasic disorder characterized by simultaneous onset of bilateral ON and transverse myelitis, but in 2006 the incorporation of AQP4-immunoglobulin G (IgG) serology into the diagnostic criteria permitted more liberal clinical requirements, allowing unilateral ON or asymptomatic MRI brain lesions to be counted. Nevertheless there exist patients with overlapping features of both NMO and MS, who test negative for serum AQP4 antibodies, and in whom a definitive diagnosis may not be confidently made. In some instances the diagnosis of NMO is made after deterioration following disease-modifying treatments set out to target MS. A year later in 2007, the term neuromyelitis optica spectrum disorder (NMOSD) was coined, having established that the diagnosis of NMOSD should not be based solely upon the presence or absence of AQP4-Ab. The International Panel for NMO Diagnosis published a set of diagnostic guidelines for NMOSD in 2015, stratified according to AQP4-IgG status (**Table 2**).⁴¹ Due to the dissimilar first-line management options and prognoses of NMO-ON and MS-ON, it is critical that guidelines be developed to better differentiate between the two.

Table 2. International Panel for NMO Diagnosis—2015 diagnostic criteria for NMOSD.⁴¹

Disorder	Diagnostic criteria
NMOSD with AQP4-IgG	(1) At least 1 core clinical characteristic* (2) Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended) (3) Exclusion of alternative diagnoses
NMOSD without AQP4-IgG or AQP4-IgG status unknown	(1) At least 2 core clinical characteristics* occurring as a result of ≥ 1 clinical attacks and meeting all of the following requirements: (a) At least 1 must be optic neuritis, active myelitis with LETM, or area postrema syndrome (b) Dissemination in space (2 or more core clinical characteristics) (c) Fulfillment of additional MRI requirements [†] , as applicable (2) Negative test for AQP4-IgG using best available detection method, or testing unavailable (3) Exclusion of alternative diagnoses

Abbreviations: AQP4 = aquaporin-4; IgG = immunoglobulin G; LETM = longitudinally extensive transverse myelitis; MRI = magnetic resonance imaging; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder.

* Core clinical characteristics include:

- (1) Optic neuritis
- (2) Acute myelitis
- (3) Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
- (4) Acute brainstem syndrome
- (5) Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
- (6) Symptomatic cerebral syndrome with NMOSD-typical brain lesions

[†] Additional MRI requirements for NMOSD without AQP4-IgG or AQP4-IgG status unknown:

- (1) Acute optic neuritis: requires brain MRI showing (a) normal findings or only non-specific white matter lesions, or (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over 1/2 optic nerve length or involving optic chiasm
- (2) Acute myelitis: requires associated intramedullary MRI lesion extending ≥ 3 contiguous segments (LETM) or ≥ 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
- (3) Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
- (4) Acute brainstem syndrome: requires associated peripendymal brainstem lesions

The epidemiologic and demographic differences between NMO and MS may prove helpful in the initial prioritization of the two conditions. While MS displays a prominent geographic distribution and prevails in the white population, NMO in comparison appears to have a more worldwide occurrence, with 20% to 50% of NMO patients quoted to be of non-white ethnicity in the UK and US studies.⁴² The age of onset of symptoms is also different. NMO patients are on average 10 years older than MS patients at initial presentation, with a mean age of onset at 40 years and 30 years for NMO and MS, respectively. Worthy of note is the fact that while late-onset MS after the age of 50 years is not unseen, a very late onset beyond the age of 70 years is exceptionally uncommon.⁴³ This is in stark contrast to NMO, for which the UK studies have reported over one-fifth of Caucasian patients have an age of onset of over 60 years.⁴⁴ A very late age of onset may thus favor a diagnosis of NMO.

Approximately 50% of NMO patients initially present with isolated ON, among whom 20% have bilateral involvement.⁴⁵ Isolated simultaneous bilateral ON in particular is a syndrome classically associated with NMO-ON and only rarely encountered in MS-ON. Moreover, as opposed to MS-ON, which tends to yield a good prognosis, NMO-ON usually causes more profound and persistent vision loss. During an acute attack, 80% of NMO-ON patients experience a visual acuity of less than 20/200, with a corresponding 36% in MS-ON. Approximately 60% of NMO-ON patients experience unilateral or bilateral blindness at a median of 7.7 years following disease onset,

in contrast to only 4% of MS-ON patients at 15-year follow-up.^{46,47} The pattern of visual field defects also provides valuable diagnostic information; altitudinal field deficits, if present, corroborate a diagnosis of NMO-ON as it is encountered only in NMO-ON (in >10% patients), not MS-ON (**Figure 2**).⁴⁸

Apart from clinical features, NMO-ON may be distinguished from MS-ON by imaging and investigative findings. In pediatric NMO-ON patients, the MRI findings are quintessentially long-segment, occasionally bilateral, optic nerve enhancement with extension into the optic chiasm,⁴⁹ whereas in adults the lesions are usually more extensive with posterior portions of the optic nerve more commonly involved in NMO-ON than in MS-ON.⁵⁰ Optical coherence tomography of eyes affected by NMO-ON exhibits more marked peripapillary RNFL loss than in MS-ON²³; in the first reported Chinese case of NMOSD associated with ocular myasthenia gravis, the patient had an average RNFL thickness of only 33 μ m and 39 μ m over the right and left eye, respectively, much thinner than the mean thickness of those with idiopathic ON at 3 months post attack (103.9 ± 6.0 μ m)⁵¹; and while RNFL thinning in MS-ON shows a definite predilection for the temporal quadrant, more widespread atrophy involving the superior and inferior quadrants is often seen in NMO-ON.⁵² In terms of CSF findings, patients with NMO often have more prominent pleocytosis⁵³ and possibly neutrophils and eosinophils, in contrast to the presence of lymphocytes and macrophages in MS patients.⁴⁶ Oligoclonal bands, present in up to 95% of patients with MS, are

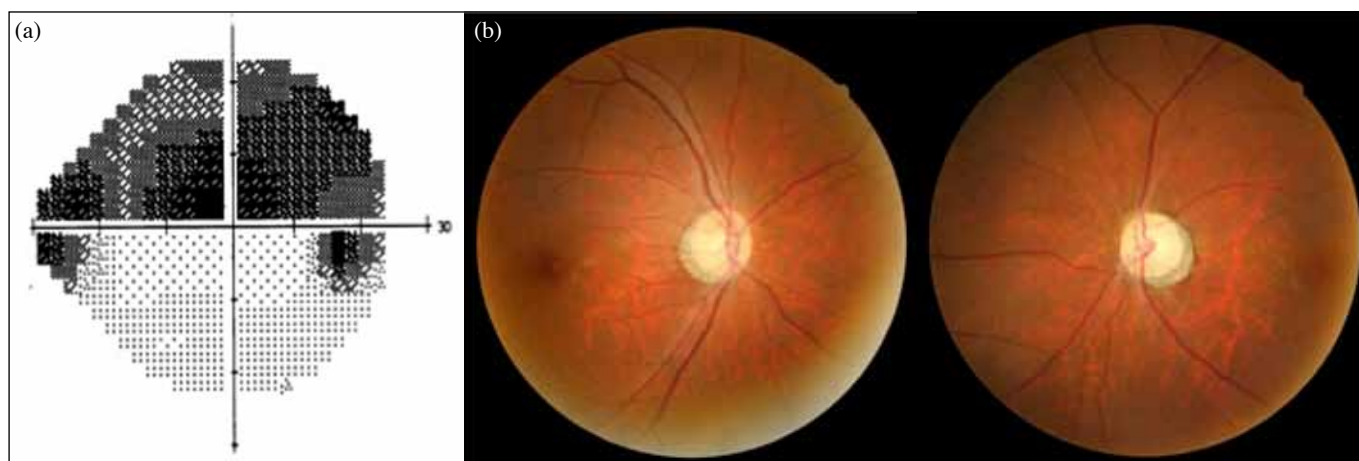


Figure 2. A 33-year-old female initially presented with reduced visual acuity (VA) of 6/12 in the right eye.

(a) Superior altitudinal visual field loss and pain on eye movement. Her VA returned to 1.0 but had an incomplete visual field recovery after Optic Neuritis Treatment Trial (ONTT) regimen. Later on she had two further episodes of left severe visual loss, with nadir VA down to 0.4 and finger count of 1 m. Unfortunately she only received further ONTT regimen without long-term maintenance. Finally, she ended up with VA of 1.0 in the right eye and no light perception in the left eye. (b) There is bilateral optic disc pallor and severe nerve fiber layer loss, worse in the left eye. A subsequent aquaporin-4 antibody testing turned out to be positive.

detected in 10% to 25% of patients with NMO.⁵⁴

Finally, knowledge of the pathogenesis of NMO has prompted the measurement of astrocyte-specific biomarkers, including AQP4 antibodies and glial fibrillary acidic protein (GFAP). A 2010 study demonstrated much higher levels of GFAP during an acute relapse of NMO than would be present in a case of MS, with a mean of 2477 ng/mL and 0.8 ng/mL, respectively.⁵⁵ Furthermore, pro-inflammatory cytokines such as interleukin 6, involved downstream of astrocyte destruction in the pathogenesis of NMO, may also be employed as potential biomarkers. In several preliminary studies increased interleukin 6 levels were detected in NMO but not in MS patients.⁵⁶ Antibodies to AQP4 in particular are a sensitive and highly specific serum marker of NMO that can aid the differential diagnosis of NMO-ON and MS-ON. To date, a multitude of assays exist for the detection of AQP4 antibodies and, depending on the substrate used, these may be classified into cell-based assays, tissue-based assays or protein-based assays. A comparison of their respective working mechanisms, advantages and limitations is made in **Table 3**.⁵⁷ The International Panel for NMO Diagnosis recommends the use of cell-based serum assays because of their superior accuracy, but these are not yet widely available.

The management of NMO-ON is two-tiered. First, during initial and subsequent acute attacks, patients should be treated with high-dose intravenous methylprednisolone (1 g daily for 3-5 consecutive days) because of the implications for prognosis if treatment is delayed. For patients in whom symptoms are severe or refractory to glucocorticoids, plasmapheresis is the recommended

adjunct. Second, as soon as the diagnosis of NMO-ON is established, attack prevention should be viewed as an essential component of patient management, taking the form of long-term systemic immunosuppression via agents such as azathioprine, mycophenolate mofetil, rituximab and oral glucocorticoids. To date there is no consensus on the optimal duration of immunosuppressive treatment, but the prevailing practice is for AQP4-seropositive patients to receive immunosuppression for a minimum of 5 years.⁵⁸ The Expanded Disability Status Scale, annualized relapse rate and visual outcome scores may be employed where necessary to determine treatment efficacy with immunosuppressants. According to one study, efficacy of azathioprine was associated with an increased mean corpuscular volume by at least 5 points from baseline, but further studies are needed to delineate the correlation between rise in mean corpuscular volume and efficacy of azathioprine.⁵⁹ As previously put forth, NMO-ON and MS-ON have heterogeneous pathogeneses and treatment responses. This is particularly relevant in the context where exacerbation of underlying, misdiagnosed NMO-ON occurs as a result of treatment with MS-modifying drugs such as interferon beta,⁶⁰ with consequent catastrophic outcomes with the development of extensive brain lesions. The differential diagnosis between the two is therefore paramount. The above-mentioned NMO/MS discriminators — in terms of demographics, clinical features, laboratory and imaging findings — may prove useful in the assessment of the patient who presents with equivocal symptoms.

Optic perineuritis

OPN also known as peri optic neuritis, is a rare form of an IOID that affects dural sheath of optic nerve and is distinct from demyelinating ON. Although most cases are isolated

Table 3. Comparison of assay methods for detection of AQP4 antibodies.⁵⁷

	Cell-based assays	Tissue-based assays	Protein-based assays
Mechanism	Cell lines such as human embryonic kidney cells transfected with the target antigen are allowed to react with patient serum. Mock-transfected or non-transfected cells from the same cell line are employed as control. Binding of patient serum to the test but not control set indicates presence of antibodies of interest	Tissue sections are prepared from tissues known to express the target antigen and incubated with patient serum. A secondary antibody to human IgG, either labeled with a fluorescent (IHC-F) or non-fluorescent (IHC-C) dye, is applied and a diagnosis made based on antibody- and tissue-specific binding patterns	Recombinant AQP4 protein is incubated with patient serum
Subtype	(a) IHC-F (b) Flow cytometry (FACS) (c) Cell-ELISA	(a) IHC-F (b) IHC-C	(a) RIPA (b) FIPA (c) WB (d) ELISA
Advantage	Higher sensitivity and specificity than tissue-based assays	(a) Widely available (b) Only method that allows the detection of coexisting paraneoplastic or connective tissue-disease associated antibodies, especially relevant in NMO-IgG/AQP4-Ab-negative patients	(a) ELISA provides quantitative data, useful for long-term monitoring of antibody levels (b) Good for large sample sizes (c) WB allows detection of some paraneoplastic antibodies (d) Higher sensitivity in ELISA than tissue-based assays
Limitation	(a) The use of non-stably transfected cell lines implies a need for them to be maintained over time and transfected just prior to testing, hence limited reproducibility and availability (b) Semi-quantitative and observer-dependent (c) Rheumatic, paraneoplastic and new autoantibody reactivities cannot be detected	(a) Results are observer-dependent and subjective, and at best semi-quantitative (b) Lower sensitivity than protein-based assays (c) IHC-F is labor-intensive and time-consuming	(a) Lower sensitivity than cell-based assays (b) High false-positive rate due to patient antibodies binding to fluorophores (in FIPA) (c) FIPA is labor-intensive and time-consuming (d) Limited availability

Abbreviations: AQP4 = aquaporin-4; ELISA = enzyme-linked immunosorbent assay; FACS = fluorescence-activated cell sorting; FIPA = fluoroimmunoprecipitation assay; IgG = immunoglobulin G; IHC-C = conventional immunohistochemistry; IHC-F = fluoroimmunohistochemistry; ; NMO = neuromyelitis optica; RIPA = radioimmunoprecipitation assay; WB = western blotting.

and idiopathic, OPN occasionally occurs as a manifestation of a specific infectious or inflammatory disorder, such as Wegener's granulomatosis, giant cell arteritis,⁶¹ Crohn's disease,⁶² acute phase of secondary syphilis⁶³ as well as a manifestation of neurosyphilis⁶⁴ and with pre-B-cell lymphocytic leukemia.⁶⁵

OPN has been known to present in 2 forms, first as an exudative form with a focal non-suppurative pachymeningitis and second as a purulent form with leptomeningitis and involvement of the subarachnoid space around the optic nerve. These occur as a result of varied processes such as granulomatous inflammation of the sheath,⁶⁶ and necrobiotic degeneration of collagen in the dura or perivascular lymphocytic infiltration of small optic nerve vessels (vasculitis). Regardless of the initiating mechanism, non-specific fibrotic thickening of the dural nerve sheath ensues⁶⁴ and leads to secondary demyelination and/or infarction of the optic nerve as a result of compression by the thickened nerve sheath. This has led to the belief that OPN represents a response to a spectrum of disorders.⁶⁷ ON, on the other hand, consists of myelin degeneration and axonal death secondary to type IV hypersensitivity reaction.

OPN is difficult to differentiate from ON clinically as both conditions present with similar symptoms and signs. In ON,

vision loss usually occurs in younger females and is central and often self-limiting. In OPN, vision loss tends to occur in older patients (age >50 years) and is peripheral or arcuate. It is therefore important to consider the possibility of OPN in all patients diagnosed with ON and to distinguish the 2 by clinical course, radiologic appearance and treatment response.⁶⁷

Inflammation of the optic nerve (ON) and its sheath (OPN) can have similar initial clinical presentations.⁶⁸ Both disorders present with symptoms of inflammatory optic neuropathies characterized by visual disturbances with signs of optic nerve dysfunction that include acute to subacute monocular vision loss (including color vision), pain with eye movement and a swollen or more often a normal-appearing optic disc.⁶⁷

Regarding the demographics, OPN occurs in a broad age distribution with a majority of patients being over 50 years of age while ON tends to affect young adults with a female predominance.⁶⁷ Considering the tempo and pattern of vision loss, in OPN, the vision loss is usually peripheral or arcuate and progresses for several weeks. In ON, vision loss is usually central and/or altitudinal, occurs over several days, and is often self-limiting. For the associated symptoms, in OPN, there may be IOID-associated orbital

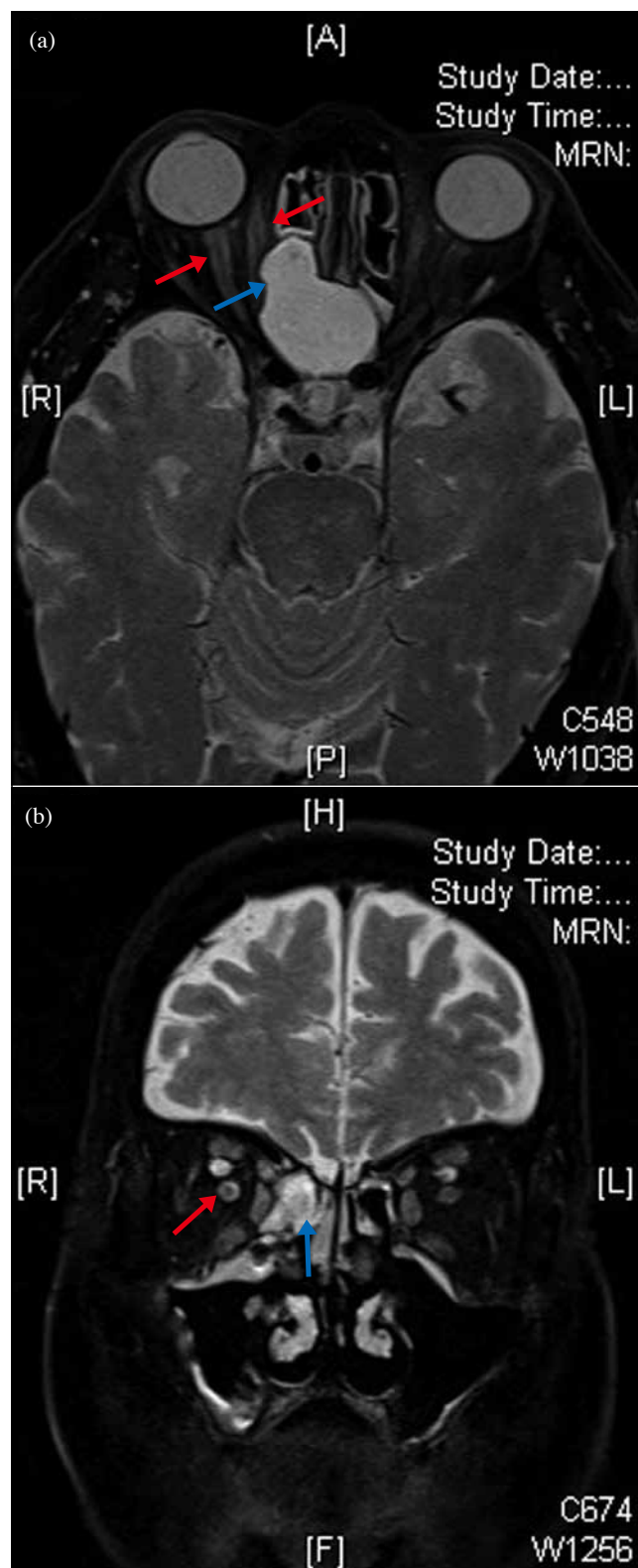


Figure 3. An 80-year-old male having right optic perineuritis after an episode of upper respiratory tract infection, with visual acuity down to light perception: T2 magnetic resonance imaging of the optic nerve demonstrates the (a) tram track sign (red arrows) and (b) donut sign (red arrow). There is a coincidental finding of mucocoele in the ethmoid sinus (blue arrows).



Figure 4. A 36-year-old female had recurrent episodes of optic neuritis and transverse myelitis, with positive aquaporin-4 antibody testing. She was wheelchair bound having visual acuity of hand movement in both eyes. The magnetic resonance imaging of her spine shows longitudinally extensive transverse myelitis (arrow). There is central gray matter involvement in the majority of the cervical spinal cord, and to a lesser extent in the thoracic spinal cord.

signs⁶⁹ in addition to the optic neuropathy, for example, mild motility disturbance secondary to extraocular muscle inflammation. These are not typical features of ON unless there is associated brainstem involvement due to multifocal demyelinating disease.⁶⁸ In ON, there may be other neurologic symptoms such as progressive limb weakness or ataxia that may indicate a more generalized pathology like MS.

Along with the clinical picture, a contrast MRI brain and orbit⁶⁸ should be performed as it can facilitate the differentiation of OPN from ON and help detect subtle orbital features and MS-related brain changes.⁶⁹ This is particularly important in patients with features such as those older than 45 years, sparing of central vision, vision loss that progresses for longer than 2 weeks, recurrence of pain and vision loss after discontinuation of corticosteroid therapy, pain out of proportion to vision loss, persistence of disc edema and evidence of orbital involvement (diplopia, subtle ptosis and chemosis).⁶⁸ It is worth noting that there should generally be a low threshold for neuro-imaging in Chinese patients to exclude OPN that is relatively more common.⁶⁹

MRI findings can be grouped anatomically into perineural, intraneural and orbital. There is a characteristic pattern of enhancement around the optic nerve (i.e. in the optic nerve

Table 4. Comparison of MS-ON, NMO-ON and OPN.

	MS-ON	NMO-ON	OPN
Etiology	T-cell linkage problem causing demyelination	B-cell linkage problem, autoantibody-mediated inflammatory disorder	Idiopathic inflammation of dural sheath of the optic nerve
Demographics	(a) More common in Caucasians (b) Female predominance (3 times than male) (c) Association with higher latitudes	(a) More common in Chinese population (b) Female predominance	(a) More common in Chinese population (b) No sexual predominance
Median age (years) of presentation	30	40	Older (35% >50 years)
Clinical features	(a) Self-limiting mild vision loss with prominent dyschromatopsia and phosphenes over days, affecting central field (b) Periocular and retrobulbar pain on movement (c) Swollen optic disc (papillitis) in 1/3	(a) Profound and persistent vision loss (b) Isolated ON, with 20% having bilateral involvement (c) Painful tonic spasm—specific for NMO-ON (d) Altitudinal field deficits—specific for NMO-ON (e) Optic disc usually normal	(a) Progressive vision loss over weeks, affecting paracentral or arcuate field (b) IOID-associated orbital sign—diplopia, subtle ptosis and chemosis
Investigations	Contrast MRI brain and orbit (a) optic nerve—short-length contrast-enhancing lesion (b) brain—ovoid enhancing lesion and Dawson finger perpendicular to ventricles, with possible cortical and perivenous involvement (c) spinal cord—peripheral posterior involvement, T1 hypo-intensity is rare (d) OCT (RNFL)—atrophy especially in temporal quadrant (e) LP—raised CSF oligoclonal bands and mild CSF pleocytosis (lymphocytes)	Contrast MRI brain and orbit (a) optic nerve—long-length/posterior-chiasma contrast-enhancing lesions (b) brain—cloud-like enhancing lesion in periependymal area, with possible hemispheric and corticospinal tracts involvement (c) spinal cord—LETM ≥ 3 contiguous segment, with central/gray matter involvement, T1 hypo-intense acute lesion (Figure 4) (d) OCT (RNFL) (e) more marked loss than in MS-ON ($>15 \mu\text{m}$) (f) widespread RNFL atrophy in superior and inferior quadrants (g) LP—more prominent pleocytosis (neutrophils and eosinophils) (h) Serology—anti-AQP4-IgG sensitive and highly specific	Contrast MRI / CT brain and orbit (a) Perineural—‘donut’ and ‘tram track’ sign (b) Intraneural—inflammation of intraneural pial septa (c) Orbital—streaky enhancement of extraocular muscles and/or orbital fat
Treatment	Expectant or corticosteroid +/- immunomodulatory agents	Early high-dose (1 g/day) intravenous methylprednisolone +/- immunomodulatory agents for 3-5 years	Early prolonged high-dose oral corticosteroid, slow taper
Prognosis	Variable response to steroid; overall good prognosis and relapse uncommon	Delayed treatment associated with poor outcome; worse prognosis and recurrence common	Excellent response and visual outcome upon early withdrawal of corticosteroid; relapse common upon brief treatment

Abbreviations: AQP4 = aquaporin-4; CSF = cerebrospinal fluid; CT = computed tomography; IgG = immunoglobulin G; IOID = idiopathic orbital inflammatory disease; LETM = longitudinally extensive transverse myelitis; LP = lumbar puncture; MRI = magnetic resonance imaging; MS-ON = multiple sclerosis-associated optic neuritis; NMO-ON = neuromyelitis optica-associated optic neuritis; OCT = optical coherence tomography; ON = optic neuritis; OPN = optic perineuritis; RNFL = retinal nerve fiber layer.

sheath)—‘tram track sign’ and ‘donut sign’ on axial and coronal cuts (**Figure 3**); along with streaky enhancement of the extraocular muscles, sclera or orbital fat. In occasional cases there is intraneural enhancement due to inflammation of pial septa.^{68,70} In contrast, ON tends to show enhancement of the optic nerve itself along with other features of demyelinating disease such as spinal lesions (in MS and NMO), and white matter changes in the brain (as in MS).⁶⁸

Alternatively, contrast computed tomographic orbit may also give a hint to the diagnosis of OPN, by showing prominence and enhancement of the affected optic nerve and/or perineural tissues and streaky enhancement of the

surrounding orbital fat.⁶⁹

Distinguishing OPN from ON has important management and prognostic implications. Intravenous methylprednisolone (1 g/day) can be considered an initial treatment to cover both ON and OPN, especially if neuro-imaging is not readily available.⁶⁹ The speed of response to steroids can help distinguish the 2 conditions and hence guide future management. Early initiation of high-dose oral prednisone (e.g. 80 mg/day) and prolonged steroid treatment for OPN are essential to prevent irreversible vision loss and recurrent attacks.⁶⁸ Delay in initiating therapy with oral corticosteroids can result in vision loss, while a dramatic response upon

steroid initiation and a recurrence of pain and/or vision loss upon steroid tapering suggest a diagnosis of OPN. The prognosis for vision outcome in these patients is generally excellent if prompt diagnosis and treatment are given.

Regarding secondary causes, specific inflammatory and neoplastic entities such as sarcoidosis, lymphoma, leptomeningeal carcinomatosis and fungal infiltrations, may demonstrate a similar response to treatment. These disorders, however, soon declare themselves by demonstrating recurrence and progression without managing the underlying cause.⁶⁸

Conclusion

MS-ON, NMO-ON and OPN have disparate pathogeneses and treatment responses. An accurate diagnosis is vital as misdiagnosis and maltreatment may result in poor ophthalmological and neurological outcome. Discriminators, in terms of demographics, clinical features, laboratory and imaging findings, are summarized in **Table 4**.

Declaration

All authors have disclosed no conflicts of interest.

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