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The changing landscape of optic neuritis: a narrative review

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Abstract

Optic neuritis (ON) is an inflammatory optic neuropathy that is often a harbinger of central nervous system (CNS) demyelinating disorders. ON is frequently misdiagnosed in the clinical arena, leading to either inappropriate management or diagnostic delays. As a result, patients may fail to achieve optimal recovery. The treatment response to corticosteroids and long term risk of multiple sclerosis was established in the first clinical trials conducted roughly 30 years ago. Spontaneous resolution was observed in the vast majority of patients and intravenous high-dose corticosteroids hastened recovery; half of the patients eventually developed multiple sclerosis. Over the ensuing decades, the number of inflammatory conditions associated with ON has significantly expanded exposing substantial variability in the prognosis, treatment, and management of ON patients. ON subtypes can frequently be distinguished by distinct clinical, serological, and radiological profiles allowing expedited and specialized treatment. Guided by an increased understanding of the immunopathology underlying optic nerve and associated CNS injuries, novel disease management strategies are emerging to minimize vision loss, improve long-term surveillance strategies, and minimize CNS injury and disability. Knowledge regarding the clinical signs and symptoms of different ON subtypes is essential to guide acute therapy, prognosticate recovery, accurately identify underlying CNS inflammatory disorders, and facilitate study design for the next generation of clinical and translational trials.

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Declarations

INTRODUCTION

Optic neuritis (ON) is a term used to describe any inflammatory condition affecting the optic nerve. Because ON is caused by a variety of central nervous system (CNS) and systemic disorders, incidence rates vary from 1.4 to 33 per 100,000 people, depending on diagnostic accuracy, efficient case capture, and population demographics.[1–5] ON, however, is frequently misdiagnosed because of errors in eliciting or interpreting the history and physical examination.[6]

Distinguishing between subtypes of ON is both challenging and important in the current era, as serological and radiographic biomarkers can help refine diagnoses and tailor treatments. Clinical and radiologic features, such as older age, bilateral optic nerve involvement, and location of optic nerve inflammation may signal a specific etiology. Furthermore, treatment algorithms established by the Optic Neuritis Treatment Trial (ONTT)[7], conducted roughly 30 years ago, are not universally applicable.

This narrative review will focus on the salient features that distinguish ON from other common causes of optic neuropathy in adults. Moreover, we will highlight clinical phenotypes of that characterize specific subtypes of autoimmune ON associated with CNS disease—multiple sclerosis and idiopathic (MS-ON; considered together as the phenotypes overlap), myelin oligodendrocyte glycoprotein (MOG-ON), and neuromyelitis optica spectrum disorder (NMOSD-ON). Although it does not seem to cause a retrobulbar ON, we have also included glial fibrillary acidic protein (GFAP-ON) because it is an autoimmune meningoencephalitis with inflammatory optic disc edema (papillitis) that should be considered when evaluating patients with possible ON. Within this context, we will discuss evolving diagnostic algorithms, acute treatment options, long-term surveillance strategies, and prognostic indicators for recovery.

METHODS

We searched Pubmed/Medline and the Cochrane Database of Systematic Reviews for English-language studies using the following terms: optic neuritis, neuromyelitis optica spectrum disorder, aquaporin-4 antibodies, myelin oligodendrocyte glycoprotein antibodies, glial fibrillary acidic protein antibodies. All relevant articles were reviewed. Articles that were not captured in the initial search, but known to the authors were also reviewed. ClinicalTrials.gov was searched to obtain all relevant phase 2 and 3 clinical trials not returned in the search.

CLINICAL PRESENTATION

History and Examination

As the diagnosis of ON remains largely clinical, knowledge regarding the cardinal symptoms and signs of optic nerve dysfunction is key to avoiding diagnostic errors. Table 1 provides clinical characteristics of ON subtypes compared to other important optic neuropathies. With the exception of GFAP, which presents with concurrent meningoencephalitis, ON may be isolated and the initial presentation of MS, NMO, or

MOG.[8] It can be challenging to distinguish ON subtypes acutely, because vision loss may be variable at onset, and clinical phenotypes may overlap. Patient demographics may provide initial clues to the underlying etiology. MS-ON predominantly presents in young women (mean age of 32 years; female:male-3:1)[7] while NMOSD-ON presents in slightly older individuals and shows a prominent female bias (mean age of 40 years; female:male-9:1).[9, 10] MOG-ON may present at multiple ages and shows no sex bias. Similarly, GFAP-ON shows no sex bias; the median age is approximately 40 years.[11]

While eye pain that worsens with eye movement is a common symptom in most cases of ON, over-emphasizing the significance of pain may be a diagnostic pitfall. Stunkel and colleagues reported that over-reliance on the presence of eye pain or pain with eye movements represented a critical diagnostic error in 12% of patients referred for evaluation of ON.[6] Indeed, pain that is recurrent with stereotyped features, and accompanied by aura would be highly unusual for ON, and more likely representative of a headache disorder. Moreover, pain persisting over many days or longer in the presence of a normal visual examination would not be consistent with ON and should raise clinical suspicion for an alternative process. However, it is important to recognize that pain preceded visual signs and symptoms in 39.5% of ONTT participants.[12] In NMOSD- and GFAP-ON, eye pain may be less prominent due to the mechanisms and location of optic nerve injury. Phosphenes are another common symptom of ON, particularly MS-ON, but are not specific and can occur in other optic neuropathies and retinopathies.[12]

Examination of a patient with acute ON reveals visual acuity loss, visual field deficits, color vision impairment, and a relative afferent pupillary defect (RAPD) in the affected eye. The absence of an RAPD should raise diagnostic concern unless the patient has bilateral involvement or a history of optic neuropathy in the fellow eye.[13] The extent of visual acuity loss may vary across ON subtypes during the acute phase. In MS-ON, high-contrast visual acuity loss is moderate, with the majority of patients having acuity better than 20/200.[7] In contrast, NMOSD-ON and MOG-ON often present with more significant vision loss, worse than 20/400.[11, 14] Visual acuity is largely preserved in GFAP.[8] Bilateral involvement is also more common with MOG-ON than with MS-ON or NMOSD-ON.[15] As with any optic neuropathy, color vision loss is often disproportionately affected relative to high contrast acuity, and therefore, not specific for ON. It may, however, be useful in distinguishing retinal diseases that can mimic ON. Although infrequently utilized in the neurology clinic, perimetry testing may reveal diffuse or discrete patterns of visual field loss. In most adult MS-ON cases, the funduscopic examination is normal, with less than 30% of patients presenting with clinically apparent optic disc edema.[7, 13] Severe optic disc edema and optic disc hemorrhages should raise concern for MOG-ON or GFAP-ON. Although ocular inflammation (e.g. uveitis, perivascular sheathing, retinal vasculitis) can accompany MS-ON, possibly MOG-ON, and GFAP (vitritis), these findings should prompt also consideration of infectious or systemic inflammatory causes of optic nerve and/or retinal dysfunction.[13, 16–18]

The value of optical coherence tomography (OCT) is in distinguishing ON from other causes of vision loss, rather than distinguishing between ON subtypes. Acute optic neuropathies, such as ON, can cause thickening of the peripapillary retinal nerve fiber

layer (RNFL), a measure of axonal integrity. If the ganglion cells are permanently injured, the macular ganglion cell inner plexiform layer (GCIPL) will begin to thin followed by thinning of the RNFL. The timing and severity of this progression can provide some clues as to the cause of the optic nerve injury. For example, in patients with monocular vision loss from Leber's Hereditary Optic Neuropathy, the RNFL will thicken acutely, just as in ON, but thinning of GCIPL occurs earlier than in patients with ON. Likewise, both non-arteritic ischemic optic neuropathy and ON will cause thickening of the RNFL acutely, but the subsequent GCIPL and RNFL thinning tends to conform to the visual field loss in ischemic optic neuropathy and it is more diffuse in ON. OCT can also be quite valuable in distinguishing retinal masqueraders of vision loss by identifying subtle retinal changes that are difficult to appreciate on the dilated funduscopic examination. However, OCT provides little additional diagnostic information about ON subtypes than is available from the fundus examination alone, particularly during the acute phase. Within the context of longitudinal OCT studies, patterns of peripapillary RNFL thickening acutely, thinning of the macular GCIPL, followed by thinning of the RNFL emerge among ON subtypes, but the clinical utility of these patterns is uncertain when caring for individual patients.[19]

PATHOPHYSIOLOGY

The distinct clinical presentations and outcomes of autoimmune ON subtypes are the direct result of diverse inflammatory pathophysiology.[20] Antigenic targets have been identified in two subtypes of ON, NMOSD and MOG, yet the focus of the immune response remains unknown in the majority of ON cases. While acute histopathology is lacking in human ON, autopsy tissue and animal models have provided insight into the impact of various components of the innate and adaptive immune systems.[21, 22] In NMOSD, aquaporin-4 autoantibodies (AQP4-IgG) [23, 24] targeting CNS astrocytes are sufficient to drive optic nerve, spinal cord, and brain lesions through complement and cell-mediated mechanisms (Figure 1, NMOSD).[25, 26] While bystander injury from AQP4-IgG-mediated complement activation is a source of oligodendrocyte injury in experimental models,[27] acute disruption of glial-neuronal coupling from astrocytopathy may also play an important role[28–33]. In MOG-ON, MOG autoantibodies (MOG-IgG) are likely to directly and indirectly augment optic nerve injury through complement-mediated cytotoxicity, antibody-dependent cell-mediated phagocytosis (ADCP) and cytotoxicity (ADCC), and antigen presentation[33, 34] (Figure 1, MOG). In animal models induced with MOG peptide immunization, optic nerve injury occurs in the absence of MOG-IgG and results from sequential microglial activation, astrogliosis, immune cell infiltration, and neuronal degeneration.[35–37]. This may indicate that there are antibody-dependent and -independent immunopathologies in MOG-ON. Indeed, histopathology of MOG-IgG lesions obtained at biopsy and autopsy reveal mixed features of cellular and humoral immunopathology. Recently, GFAP-IgG antibodies have been identified in patients with optic disc edema and associated visual changes consistent with isolated optic nerve head inflammation (papillitis).[8] Whether GFAP-IgG, directed against an intracellular astrocytic intermediate filament, is truly pathogenic remains to be determined; however, GFAP-specific CD8 T cells have been shown to induce relapsing CNS autoimmune disease in animal models (Figure 1, GFAP).[38] A target antigen has remained elusive in MS, yet myelin autoantibodies derived from MS patients have

been shown to induce complement-mediated lysis of target oligodendrocytes.[39] These antibodies may contribute to MS-ON in active MS lesions a similar manner to MOG-IgG in MOG-ON (Figure 1, MS). For infectious (e.g., syphilis, Lyme, Bartonella, tuberculosis) and non-infectious systemic causes of optic nerve inflammation (sarcoidosis, granulomatous polyangiits, systemic lupus erythematosus, Sjogrens syndrome) the mechanisms underlying optic nerve tissue injury are likely complex[13, 20] Novel experimental models are needed to identify the optimal regimens of antimicrobial, antiviral, and immunosuppressive therapies for these conditions.

ACUTE MANAGEMENT

Diagnostic testing

The history and clinical examination are typically sufficient to distinguish ON from other common causes of vision loss. Ideally, patients with ON should be evaluated with orbital and cranial MRI scans to assist with diagnosis, treatment, and long-term management. Orbital imaging can be helpful to distinguish ON from other common optic neuropathies (e.g. compressive optic neuropathy) and help to differentiate ON subtypes within the correct clinical context. The sensitivity of MRI for acute ON is approximately 80–94% when imaging occurs within 30 days of symptom onset.[4, 40–42] Although patterns of optic nerve enhancement can help distinguish different ON subtypes, these features are not exclusive (Table 2). For example, longitudinal involvement of the intraorbital and intracranial optic nerve segments are highly suggestive of MOG-ON, and NMOSD-ON, respectively, but can also occur in MS-ON[43] (Table 2). The variability in MRI sensitivity underscores the importance of using history and clinical examination features to enhance pre-test diagnostic probability. When MRI is performed, the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-up of Early MS recommend that orbital imaging include coronal short tau inversion recovery or fat suppressed T2 images and post-gadolinium fat-suppressed T1 images with section thickness of ≤2 mm with coverage through the chiasm.[44] Concurrent brain MRI may demonstrate lesions diagnostic (or strongly suspicious) for MS, or suggest alternative inflammatory disorders. Additional radiographic testing (Table 2) may be warranted based on the demographics, presentation, and clinical examination.

Recommendations regarding serologic and specific autoantibody testing are evolving (Table 2) and should target the potential underlying condition. Patients with radiographic features suggestive of NMOSD or MOG, should undergo serologic testing for AQP4-IgG and MOG-IgG with a serum cell-based assay. Specific clinical features that suggest NMOSD or MOG and should prompt testing for these conditions include, severe optic disc edema, severe vision loss (worse than 20/200), progressive or bilateral vision loss, relapsing or recurrent ON. Notably, testing for AQP4-IgG in the CSF is not sensitive or cost-effective and, therefore, it is not routinely recommended.[45] Like AQP4-IgG, MOG-IgG is primarily produced in the periphery and therefore, the utility of testing the CSF is likely to be low. In the largest study to date of GFAP, Chen *et al* recommend CSF GFAP autoantibodies in patients with bilateral optic disc edema with unexplained meningoencephalitis or radial perivascular enhancement on MRI.[8]

Acute Treatment

High-dose corticosteroids, both oral and intravenous (IV), are the most commonly used treatment for acute ON. A meta-analysis of three randomized controlled trials found no benefit in visual acuity recovery at 1 month, 6 months, and 1 year based on the dose or duration of oral treatment.[46] A meta-analysis of two trials comparing placebo to IV corticosteroids of over 3000 mg total also found no significant improvement in visual acuity, contrast sensitivity, or visual field at 6 months.[46] These meta-analyses were strongly influenced by the results of the ONTT, the largest therapeutic trial conducted for acute ON. The ONTT found that the only benefit of corticosteroids was hastened visual recovery within the first 2 weeks, which is the primary indication for treatment. Secondary analyses of the trial data suggest that this early benefit is only about 1–2 lines of Snellen acuity.[47]

An unexpected finding from the ONTT was that subjects receiving lower dose oral prednisone (1mg/kg) were at an increased risk of ON relapse within the first 2 years.[7] Therefore, low-dose oral prednisone is not recommended for treating acute ON. Oral prednisone in doses that are bioequivalent to 1000 mg per day IV doses of methylprednisolone used in the ONTT, may be an option, but the benefit of faster recovery has not been assessed.[48] The risk of ON relapse with high dose oral corticosteroids has also not been studied. Other therapies investigated in phase 2 and 3 randomized, controlled trials are summarized in Table 3. Most recent studies have focused on the potential neuroprotective role of various agents using structural and electrophysiological primary endpoints. None have demonstrated clinical value and should therefore not be used within the context of routine clinical care.

Due to disparate levels of visual recovery observed with ON associated with NMOSD, MOG, GFAP and other inflammatory diseases (see “Prognosis”), acute treatment algorithms are being proposed based on expert opinion and retrospective studies (Table 4). It is important to appreciate that the results of the ONTT may not apply to all ON subtypes since only three trial participants were MOG-IgG positive and none were positive for AQP4-IgG (177 out of 457 participants total had serum available for analysis).[49] Furthermore, IV corticosteroids (e.g. methylprednisolone 1g daily IV for 3 to 5 days) alone may be suboptimal for visual recovery in non-MS-ON variants, particularly NMOSD-ON.[50] Retrospective studies on the acute treatment of NMOSD-ON support the early use of plasma exchange as add-on therapy.[14, 51, 52].

LONGTERM SURVEILLANCE AND MANAGEMENT

Multiple Sclerosis

As noted previously, all patients diagnosed with ON should undergo MRI to evaluate for MS or risk of developing MS. The ONTT found that half of all patients with ON will develop clinically definite MS after 15 years, the highest risk occurring in those patients with at least one white matter lesion of 3 mm or more. As the diagnostic criteria for MS have increased in sensitivity since the completion of the ONTT, the risk of MS following an episode of ON is now likely higher, and the 2017 McDonald Criteria allow for the diagnosis of MS to be made after a single, isolated attack of ON based on MRI criteria for dissemination in space,

and MRI or CSF criteria for dissemination in time.[53] Importantly, the radiological lesion in the optic nerve itself, cannot be counted toward meeting MRI criteria for dissemination in space or time. Injectable, infusion, and oral-based disease modifying therapies for the treatment of MS exist to slow disease progression. For patients with isolated ON with normal MR imaging, or for ON patients with MRI lesions that do not meet criteria for MS, screening neurologic examinations and yearly surveillance brain MRI for 5 years may be considered.[54, 55] Impromptu imaging should occur if any new neurologic signs or symptoms arise.

Other CNS autoimmune disorders with optic neuritis

Standard recommendations for long term surveillance or treatment of other disorders that may manifest with ON are currently evolving. The primary goal is to detect the earliest evidence of ongoing CNS inflammation and select therapies that will minimize new attacks and mitigate long term disability.

If diagnostic criteria for NMOSD are met[56], immunosuppression should commence immediately to prevent further neurologic disability. The optimal first line agent and duration of treatment in this context are uncertain,[57] but have historically included rituximab,[58] azathioprine,[59, 60] mycophenolate mofetil,[61] and chronic corticosteroids.[62, 63] Recent Phase 3 clinical trials have resulted in the emergence of 3 new therapeutics that significantly reduce the risk of future NMOSD attacks (drug mechanism; proportion with attacks in the treatment group versus controls): eculizumab (complement C5 inhibition; 3% [3 of 96] vs. 43% [20 of 47], hazard ratio 0.06 [95% CI, 0.02 to 0.20]; p<.001)[64], satralizumab (IL-6 receptor inhibition; 20% [8 of 41] vs. 43% [18 of 42] 0.38, hazard ratio 0.38 [95% CI: 0.16 to 0.88], p=0.02)[65], and inebilizumab (CD-19-targeted B cell depletion; 12% [21 of 174] vs. 39% 22 of 56], 0. 27 [95% CI 0.15 to 0.50]; p<.001)[66].

MOG-ON may be monophasic, but up to 85% may have relapsing disease.[11, 67–71] Therefore, expert opinion currently suggests that long term immunosuppression should be considered after the first attack if visual recovery is poor or in patients who have experienced multiple attacks.[72] In one recent retrospective multicenter study of 70 MOG-ON patients, the annualized relapse rate was 1.6 prior to initiating immunosuppressive therapy and 0.3 following immunosuppression suggesting that immunosuppression is effective in suppressing relapses.[73] The optimal therapy and duration of treatment remain unclear, but the most commonly used treatments include intravenous immunoglobulin, rituximab, mycophenolate mofetil, and azathioprine.[11, 72, 73]

GFAP may also have monophasic, relapsing, or progressive course.[8, 74] Long term immunosuppressive therapy may be needed for some patients. For relapsing ON and inflammatory optic neuropathies, such as those secondary to rheumatologic conditions, similar steroid sparing agents are often necessary to allow corticosteroid weaning.

PROGNOSIS

For patients with idiopathic or MS-ON, recovery of visual acuity is good.[7, 75] At one year, regardless of treatment, 75% have a visual acuity of 20/20 or better and 95% have 20/40 or

better acuity.[47, 75] Only 2.4% of idiopathic or MS-ON patients have a recovered visual acuity of 20/200 or worse.[75] Despite visual improvement, patients are often left with reductions in visual quality of life likely attributable to incomplete recovery of contrast sensitivity or higher order visual function.[76] Racial and gender disparities in visual recovery after idiopathic and MS-ON also exist, with worse outcomes noted among men and non-white patients.[77, 78]

For patients with MOG-ON, the final visual outcomes tend to be favorable. In the largest series to date, 5.7% (5 of 87) of patients were left with a visual acuity of 20/200 or worse, which is slightly worse than the prognosis for idiopathic or MS-ON.[11] Of note, the five patients in the study with poor recovery were treated with IV corticosteroids and one also underwent plasma exchange. For patients with NMOSD-ON, visual recovery is not as robust and worsens with subsequent episodes. Approximately 20–30% of NMOSD patients will remain functionally blind in the affected eye (20/200 or worse) after their initial ON episode whereas approximately 70% of those with a relapsing course will have a visual acuity of 20/200 or worse in the affected eye(s).[79, 80] Vision is typically preserved in patients with GFAP throughout their course. Visual prognosis is uncertain for other inflammatory optic neuropathies.

CONCLUSION

ON is a common cause of vision loss, but the causes, and treatments vary. Knowledge of the clinical signs and symptoms of ON subtypes is essential to guide diagnostic investigations, accurately prognosticate recovery, delineate treatment, and identify CNS inflammatory disorders. Previously, the ONTT experience highlighted the favorable natural history of ON, and informed our understanding regarding the association between ON and future MS risk. In the current era, however, treatment recommendations from the ONTT are not extendable to other ON subtypes, particularly NMOSD-ON and MOG-ON. Understanding the diverse pathophysiology of optic nerve inflammatory injury is likely to yield novel acute and prophylactic therapies for established and emerging ON subtypes in the future.

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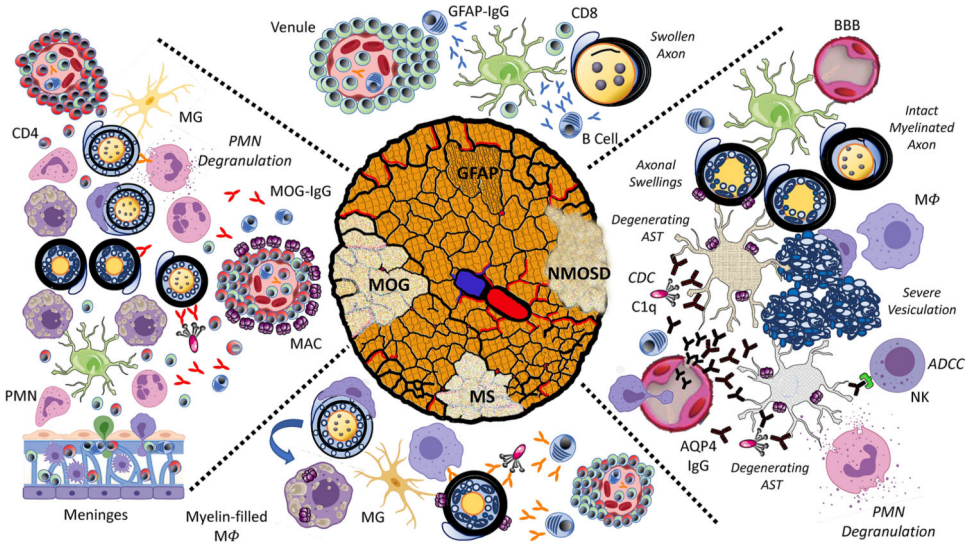

Figure 1.

Schematic of the immune pathophysiology of neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte glycoprotein (MOG), glial fibrillary acidic protein (GFAP), and multiple sclerosis (MS) optic neuritis. **NMOSD**: AQP4-IgG enters through defects in the blood-brain barrier (BBB), bind to astrocytes (AST), and initiate complement dependent cytotoxicity (CDC) by assembling complexes for complement C1q (C1q) binding. AQP4-IgG also activates antibody-dependent cell-mediated cytotoxicity (ADCC) by natural killer (NK) cells and complement products stimulate degranulation of polymorphonuclear cells (PMNs). Membrane attack complex (MAC) may transit to adjacent oligodendrocytes resulting damage represented histopathologically by myelin vesiculation. Degenerating ASTs alter oligodendrocyte physiology resulting in axonal swelling. Myelin debris is removed by infiltrating macrophages (Mϕ). **MOG**: Perivenous and confluent demyelination are mediated by combined humoral and cellular mechanisms. CD4-lymphocyte and granulocytic infiltrates emerging from venous and meningeal sources result in focal and confluent regions of demyelination highlighted by nascently demyelinated axons with split myelin sheaths and vesiculation, myelin-laden macrophages within active demyelinating regions, and activated microglia (MG) in the periplaque area. Peripherally generated MOG-IgG may contribute to myelin destruction through CDC and ADCC, as well as activated T cell infiltration by facilitating phagocytosis and antigen presentation. Perivenous MAC deposition and diffuse myelin protein loss are histologic features supporting diffuse antibody-mediated myelin destruction. **GFAP**: GFAP papillitis results from secondary axonal swelling. GFAP-IgG is predominantly generated intrathecally; however, its role in driving disease pathology is unclear. Animal models demonstrate a predominantly perivascular, meningeal, and vascular CD8 T cell infiltrates. **MS**: Active MS lesions are characterized by the deposition of complement and immunoglobulin. The perivenous inflammatory infiltrates are mainly composed of CD8+ T cells and B cells producing intrathecal IgG in association with activated microglia and macrophages. MAC complexes are observed along myelin sheaths and within myelin-laden Mϕ, suggestive of active CDC.

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Table 1.

Clinical characteristics of optic neuritis subtypes and other common optic neuropathies.

	Optic neuritis subtypes				Other common optic neuropathies[a]			
	MS ON[7, 12][b]	**MOG ON[11]**	**NMOSD ON[10, 79]**	**GFAP ON[8]**	**NA-AION**	**LHON**	**Compressive optic neuropathy**	**Toxic/Metabolic optic neuropathy**
Age	20–30s	30s	40s	40s	Over 50	Younger	Variable	Variable
Sex	75% Women	Women = Men	90% Women	60% Men	Men > Women	Men > Women	Variable	Variable
Onset	Subacute	Subacute	Subacute	Subacute	Acute	Acute to sub-acute	Often chronic and progressive, with subacute awareness of vision loss when central vision in affected	Sub-acute to chronic
Pain	Common (92%)	Common (86%)	Variable	Uncommon	Rare	Uncommon	Uncommon (unless orbital involvement)	Uncommon
Laterality	Unilateral, rarely bilateral	Unilateral, ~30–40% bilateral	Unilateral, 20–30% bilateral	Bilateral	Unilateral	Bilateral	Unilateral or bilateral	Bilateral
Positive Visual Phenomena	Phosphenes in 30%	Unknown	Unknown	Unknown	Uncommon	Uncommon	Uncommon	Uncommon
Recurrence	Can occur	Common	Common	Uncertain	Uncommon	Uncommon	Variable with lesion type	Possible partial reversal upon elimination of toxic factors or treatment of metabolic factors
Visual acuity at onset	Variable, but approximately 35% 20/200 or worse	Variable, often worse than 20/200	Severe vision loss worse than 20/200 in ~80%	Vision usually preserved	Variable	Often poor	Variable	Variable
RAPD [c]	Present	Present	Present	Absent	Present	May be absent in early phase	Present	Absent
Color Vision	Abnormal	Abnormal	Abnormal	Normal	Abnormal	Abnormal	Abnormal	Abnormal
Visual Fields	Diffuse, central scotoma	Variable	Total, quadrant, central, Altitudinal defects	Big blind sports, and variable visual field defects reporter	Arcuate, altitudinal, cecocentral scotoma	Central and cecocentral	Temporal, central, altitudinal	Central, cecocentral scotomas, temporal defects
Fundus	Normal to mild optic disc edema in ~35%	Moderate to severe optic disc edema in ~85%	Variable optic disc edema	Moderate to severe optic disc edema	Optic disc edema	Normal or “pseudo”optic disc edema	Normal, swollen or pale optic disc with possible increased cupping	Normal, swollen or pale optic disc

	Optic neuritis subtypes				Other common optic neuropathies[a]			
	MS ON[7, 12][b]	**MOG ON[11]**	**NMOSD ON[10, 79]**	**GFAP ON[8]**	**NA-AION**	**LHON**	**Compressive optic neuropathy**	**Toxic/Metabolic optic neuropathy**
OCT [d]	Mild RNFL increase acutely, GCIPL thinning in early weeks	Significant RNFL thickening acutely, early GCIPL loss	Variable RNFL thickening acutely, with profound GCIPL loss	RNFL thickening acutely with or without GCIPL loss	RNFL thickening (resolves in two months) acutely with early GCIPL loss	RNFL thickening acutely, early GCIPL loss	Variable RNFL loss, hemiretinal GCIPL thinning (pituitary tumors)	Variable RNFL thickening acutely, early GCIPL loss
Visual Recovery	Good, 95% 20/40 or better	Good (~20/30)	20–30% with poor recovery	Good	Variable but some vision loss generally persists	Variable, but generally poor	Variable	Variable

Legend: MS ON = multiple sclerosis optic neuritis, MOG ON = myelin oligodendrocyte oligoprotein optic neuritis, NMOSD ON = neuromyelitis optica spectrum disorder optic neuritis, GFAP ON = glial fibrillary acidic protein optic neuritis, NA- AION = non-arteritic anterior ischemic optic neuropathy, LHON = Leber hereditary optic neuropathy, RAPD = relative afferent pupillary defect, OCT=optical coherence tomography, RNFL= retinal nerve fiber layer (peripapillary), GCIPL=ganglion cell inner plexiform layer (macular), RPE=retinal pigmented epithelium, INL=inner nuclear layer

a. Other optic neuropathies that should be considered include infectious (e.g. Lyme, syphilis, tuberculosis, viral), systemic immune (e.g. Lupus), infiltrative (e.g. neoplastic), seronegative (autoimmune, chronic relapsing inflammatory optic neuropathy), and paraneoplastic (e.g. collapsing response-mediator protein-5).[13] Neuroretinitis, either idiopathic or infectious (Bartonella henselae, toxoplasmosis, etc), may also present like ON.

b. Idiopathic ON has the same features as MS-associated ON.

c. Relative afferent pupillary defect may be absent in patients with bilateral optic neuropathies or prior optic neuropathy in the fellow eye.

d. General OCT patterns within the early weeks of vision loss.

Table 2.

Serologic testing and MRI features of optic neuritis subtypes

	Multiple sclerosis	Neuromyelitis optica spectrum disorder	Myelin oligogendrocyte glycoprotein	Glial fibrillary acidic protein
Specific laboratory tests	None	Aquaporin 4 antibody, cell based assay[a,c]	MOG antibody, cell based assay[b,c]	GFAP antibody[b]
Acute orbital imaging features[d]	Short segment of optic nerve T1 gadolinium enhancement. Optic nerve enlargement may also be present.	T1 gadolinium – enhancing lesion extending over more than one half of the optic nerve length or involving the optic chiasm or juxtachiasmal[43, 56]	Short or long segment of T1 gadolinium enhancement, perineural and peribulbar T1 gadolinium enhancement[11]	Optic nerve enhancement is often not present, but other imaging features may suggest the diagnosis[e] [81]

Legend: MRI= magnetic resonance imaging, MOG=myelin oligodendrocyte glycoprotein, GFAP=glial fibrillary acidic protein

[a.] Sensitivity of the cell based assay in serum: 0.76 (95% CI: 0.67–0.82); specificity of cell based assay in serum: 0.99 (95% CI: 0.97–0.99).[82]

[b.] Seropositivity currently defines the presence of the disease (100% sensitive). Specificity unknown.

[c.] May be falsely negative in the setting of immunosuppressive therapy or plasma exchange.

[d.] These features are not exclusive to any specific ON subtype.

[e.] Radial, perivascular T1 gadolinium enhancement in the cerebral hemispheres

Table 3.

Completed Phase 2 and 3 randomized trials of treatments for acute optic neuritis[a]

Citation	Pertinent enrollment criteria	Country, single or multi-center	Design	Analysis plan	Number enrolled	Intervention	Primary outcome	Results (Treated vs Placebo)
Trials with primary visual outcomes								
Roed, et al (2005) [83]	Inclusion: Clinical diagnosis of ON, age 18–59, symptoms <4 weeks Exclusion: prior ON in same eye, corticosteroid with I month, immunosuppression within 12 months 2000–2003	Denmark, single center	Double-blind, parallel arms	Intention-to-treat	34 treatment 34 placebo	IVIg 0.4 g/kg (infusions at 0,1,2,30,60 days)	Contrast sensitivity (Arden gratings) at 6 months	Median score of 93 (IQR 77, 94) vs 89 (IQR 77, 107); P=0.16
Tsakiri, et al (2012)[84]	Inclusion: Clinical diagnosis of ON, age 18–59, symptoms <4 weeks Exclusion: prior ON in same eye, corticosteroid with I month, immunosuppression within 6 months 2006–2008	Denmark, single center	Double-blind, parallel arms	Intention-to-treat	32 treatment 32 placebo	Simvastatin 80 mg	Contrast sensitivity (Arden grating) at 6 months	93 {95%CI 82, 103) vs 84 (95%CI 76, 92); P=0.06
(unpublished) Results reported on clinicaltrials.gov January 2020	Inclusion: at least 1 episode of optic neuritis in the last 12 months, clinically definite MS, age 18–70, VA of 20/30 or worse Exclusion: use of 4 aminopyridine in the past 4 weeks, seizure, ocular disease 2011–2013	USA, single center	Crossover assignment, blinding uncertain	Intention-to-treat and per-protocol	23, dalfampridine followed by placebo 23, placebo followed by dalfampridine	Placebo or dalfampridine 10mg twice daily for 3 weeks each with 2 week wash out between treatment assignments	8 primary outcomes listed: VA (logMAR score and raw letters) at visits 2 and 3 compared to visit 1 using intention to treat and per protocol analyses	No differences in multiple analyses
Trials with structural/physiologic primary outcomes								
Suhs, et al (2012)[b][85]	Inclusion: first episode of ON with VA ≤0.5 (decimal system) diagnosed by an ophthalmologist, onset within 10 days, age 18–50 years Exclusion: ocular disease in either eye, treatment with corticosteroids, erythropoietin, or immunosuppression within 30 days 2006–2011	Germany; multicenter (3)	Double-blind, parallel arms	Intention-to-treat with replacement of missing values using the last observation	21, treatment 19, placebo	Erythropoietin 33,000 units as add on to methylprednisolone	Reduction in RNFL thickness from baseline at 16 weeks	Median change: 7.5 μm (IQR 1.5, 14.5) vs 16.0 μm (IQR 8.0, 20.0); P=0.04

Citation	Pertinent enrollment criteria	Country, single or multi-center	Design	Analysis plan	Number enrolled	Intervention	Primary outcome	Results (Treated vs Placebo)
Raftopoulos, et al (2016)[86]	Inclusion: first episode of ON confirmed by a neuro-ophthalmologist, 18–60 years, within 14 days of onset with VA 6/9 or worse Exclusion: sodium or calcium channel inhibitors in the past 2 weeks, ocular disease, immune therapies within 2 months 2011–2015	UK, multicenter (2)	Double-blind, parallel arms	"Modified" intention-to-treat in all patients in which there was baseline and 6 month data	42 treatment 44, placebo	Phenytoin 15mg/kg oral load for 3 days followed by 4 or 6 mg/kg daily maintenance dose	Mean difference in RNFL thickness at 6 months in affected eye compared to baseline RNFL thickness in the unaffected eye	6-month difference of 7.15 μm (95% CI 1.08, 13.22); P=0.021
Cadavid, et al (2017)[87]	Inclusion: first episode of ON, 18–55 years, within 28 days of onset Exclusion: CNS inflammatory disease, ocular disease including high refractive error 2012–2014	Australia, Canada, Europe; multicenter (33)	Double-blind, parallel arms	Intention-to-treat	41, treatment 41, placebo	Opicinumab (anti-LINGO-1 mAb) 100mg/kg infusion once every 4 weeks for 20 weeks following methylprednisolone 1g/day for 3–5 days	Change in full-field VEP latency at 24 weeks	17.3 milliseconds (SE 2.5) vs 20.8 milliseconds (SE 2.5); Difference of 3.5 milliseconds (95% CI −10.6, 3.7); P=0.33
McKee, et al (2019)[88]	Inclusion: first episode of ON, 18–55 years, within 28 days of onset with VA 6/9 or worse Exclusion: sodium or calcium channel inhibitors in the past 2 weeks, ocular disease, immune therapies within 2 months 2013–2015	UK, single center	Double-blind, parallel arms	Intention-to-treat	23, treatment 20, placebo	Amiloride 10mg daily for 5 months with a 1 month wash out	Mean difference in RNFL thickness at 6 months in affected eye compared to baseline RNFL thickness in the unaffected eye using scanning laser polarimetry	6-month difference −0.46 (95%CI −5.02, 4.10); P = 0.840

Legend: IVIg= intravenous immunoglobulin, RNFL= retinal nerve fiber layer thickness, IQR=interquartile range, UK = United Kingdom, USA = United States of America, ON = optic neuritis, VEP = visual evoked potential

[a] Fingolimod[89], lipoic acid[90], and minocycline (no data) terminated early due to lack of recruitment. Clemestine (NCT02521311) currently recruiting. Phase 4 ACTH trial currently recruiting (NCT01838174)

[b] Phase 3 trial completed, but not published (NCT01962571)

Table 4.

Acute and long term treatment strategies for optic neuritis subtypes[13,20,72]

Treatment phase	Multiple sclerosis/ idiopathic[7, 20]	Neuromyelitis Optica Spectrum Disorder[20, 57]	Myelin oligogendrocyte glycoprotein[72]	Glial fibrillary acidic protein[20, 74]
Acute	Consider high dose corticosteroids for 3 days	High dose corticosteroids for 3–5 days and plasma exchange	High dose corticosteroids for 3–5 days followed by a 1 to 3 week corticosteroid taper. Consider plasma exchange if no recovery within 1–2 weeks and vision loss is severe	High dose corticosteroids followed by a corticosteroid taper over weeks-to-months. Consider adding plasma exchange or intravenous immunoglobulin
Long term	Disease modifying therapy	Immunosuppression	Immunosuppression if poor visual recovery or relapsing disease	May require immunosuppression