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REVIEW ARTICLE

Neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein associated disorder-optic neuritis: a comprehensive review of diagnosis and treatment

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Abstract

Optic neuritis (ON) is the most common cause of acute optic neuropathy in patients younger than 50 years of age and is most frequently idiopathic or associated with multiple sclerosis. However, the discovery of aquaporin-4 immunoglobulin G (IgG) and myelin oligodendrocyte glycoprotein (MOG)-IgG as biomarkers for two separate central nervous system inflammatory demyelinating diseases has revealed that neuromyelitis optica spectrum disorder (NMSOD) and MOG-IgG-associated disease (MOGAD) are responsible for clinically distinct subsets of ON. NMOSD-ON and MOGAD-ON both demonstrate tendencies for bilateral optic nerve involvement and often exhibit a relapsing course with the potential for devastating long-term visual outcomes. Early and accurate diagnosis is therefore essential. This review will summarize the current understanding of the clinical spectra of NMOSD and MOGAD, the radiographic and serological findings which support their diagnoses, and the current evidence behind various acute and long-term therapeutic strategies for ON related to these conditions. A particular emphasis is placed on a number of recent multi-centre randomized placebo-controlled trials, which provide the first level I evidence for long-term treatment of NMOSD.

Introduction

Optic neuritis (ON) is a major cause of visual morbidity in children and younger adults, representing the most common cause of acute optic neuropathy in people under 50 years of age [1]. Literally defined, ON encompasses any infectious or non-infectious inflammatory process involving the optic nerve. However, the term is most commonly used to refer to an immune-mediated demyelination of the optic nerve. While most cases of ON are idiopathic or associated with multiple sclerosis (MS), it has become increasingly recognized that certain subsets of demyelinating ON represent wholly distinct clinical entities, with differing long-term prognoses and optimal management strategies.

Our ability to classify ON has greatly benefited from advances in serological antibody testing, in particular live cell-based assays (Fig. 1). The most pivotal advance occurred in 2004 with the discovery of a serum autoantibody associated with neuromyelitis optica (NMO), identified 1 year later as immunoglobulin G (IgG) specific for the central nervous system (CNS) water channel aquaporin-4 (AQP4) [2, 3]. A number of inflammatory demyelinating disorders—a subset of which includes severe ON—now fall under the umbrella of NMO spectrum disorder (NMOSD), in which AQP4-IgG seropositivity is a major diagnostic criterion [4]. More recently, the improved specificity of serological testing for IgG specific for myelin oligodendrocyte glycoprotein (MOG) has identified a discrete class of demyelinating disease known as MOG-IgG-associated disorder (MOGAD). This review will summarize the current understanding of the clinical spectra of NMOSD and MOGAD and the evidence supporting various acute and long-term therapeutic strategies for ON related to these conditions.

Typical idiopathic demyelinating and MS optic neuritis

Our conception of typical ON derives from the landmark optic neuritis treatment trial (ONTT), which enrolled

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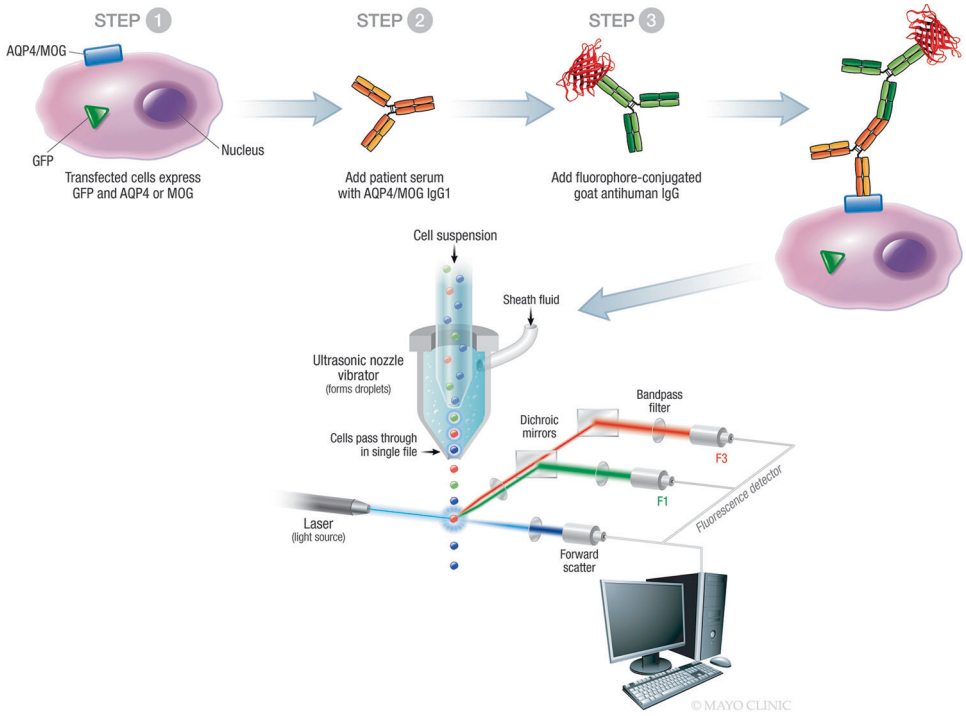

Fig. 1 Live cell flow cytometry-based assay for detecting aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG). Human embryonic kidney cells are transfected with a plasmid resulting in co-expression of green fluorescent protein (GFP; green triangle) and human AQP4 or MOG (blue rectangle) in their native transmembrane conformations (Step 1). Patient serum is added to the cells. If present, IgG specific for AQP4 or MOG will bind to its respective antigen (Step 2). Goat anti-human IgG conjugated to a fluorophore (Alexa 647) is then applied to label bound primary antibody (Step 3). The mixture of transfected and un-transfected cells is then analyzed by flow cytometry, with individual cells simultaneously interrogated for green and red fluorescence. The IgG binding index is calculated by dividing the median fluorescence intensity (MFI) for red signal in the GFP-positive (transfected) population by the MFI in the GFP-negative (un-transfected) population, the latter representing non-specific binding. An IgG binding index ≥2 or ≥2.5 is typically the cut-off for a positive test result. (Illustration by Paul Honermann, Mayo Clinic).

patients with or without a history of MS presenting with acute unilateral ON in a previously unaffected eye [5–7]. The classic presentation is one of vision loss in a young adult, developing over hours or several days, reaching a nadir within 2 weeks, and associated with painful eye movements [5]. The degree of vision loss in typical idiopathic-ON or MS-ON is highly variable and in rare cases can be as severe as no-light perception. Frequently, fundus exam on initial presentation is unremarkable: only 35% of subjects in the ONTT manifested optic disc oedema, while the remainder suffered from retrobulbar ON with a normal optic disc. Although typical ON is inherently a clinical diagnosis, the ONTT demonstrated prognostic utility of magnetic resonance imaging (MRI), using the presence or absence of CNS white matter lesions to risk-stratify patients for future development of clinically definite MS [8]. Although a comprehensive discussion of typical idiopathic-ON and MS-ON is beyond the scope of this review, features of typical ON are highlighted in Table 1 and compared to NMOSD-ON and MOGAD-ON.

Current treatment standards for typical ON [9, 10] originate from the observation in the ONTT that intravenous methylprednisolone (IVMP) given as 1 g/day for 3 consecutive days followed by oral (PO) prednisone dosed at 1 mg/kg/day for 11 days and then tapered over 4 days hastened visual recovery, but did not influence final visual outcome when compared to PO placebo. In contrast, low-dose PO prednisone alone at a dose of 1 mg/kg/day for 14 days and then tapered over 4 days failed to speed visual recovery and was associated with a higher risk of recurrent ON [7]. However, the superiority of IVMP administration has recently been challenged, as new evidence suggests that the IV bioequivalent dose of PO prednisone (1250 mg/day) given over 3 days is non-inferior to IVMP (1 g/day) in hastening visual recovery, with no increased risk of ON recurrence [11]. It has also been posited that optic nerve axon preservation and final visual outcomes in ON may be improved by expeditious initiation of corticosteroids within 48 h of onset; however, this hypothesis awaits formal prospective testing [12].

Table 1 Comparison of typical optic neuritis to NMOSD and MOGAD optic neuritis.

Characteristics	Typical (idiopathic or MS)	NMOSD	MOGAD
Median age	20s	30–40s	30s + children
Sex	Female > Male	Female » Male	Female~Male
Ethnicity	White	Asian/Afro-American	No ethnic bias
ON characteristics			
Pain	+++	++	+++
Optic disc oedema	+	+	+++
Bilateral visual loss	+	++	++
Severe vision loss at nadir	++	+++	+++
Recurrent visual loss	+	++	+++
Steroid dependent	Rare	+	++
Risk of blindness (<20/200)	+	+++	++
Visual recovery	Favourable (Usually complete)	Poor (Usually incomplete)	Favourable (Usually complete but variable)
Other CNS involvement			
ADEM	Rare	Rare	++
Brainstem	+	+	++
Diencephalic symptoms	Rare	++	Rare
LETM	Rare	+++	++
Conus medullaris	+	+	+++
MRI optic nerve enhancement			
Length and location	Short	Long and posterior	Long and anterior
Perineural enhancement	Rare	Rare	++
Optic chiasm involvement	Rare	+++	+
Brain MRI			
Periventricular white matter lesions	+++	+/− (usually peri-ependymal)	+
Other white matter lesions	Juxtacortical and infratentorial	Subcortical, hemispheric, area postrema	Poorly demarcated deep white matter, juxtacortical, brainstem or cerebellar peduncle lesions
CSF findings			
White blood cell count	Normal or mild mononuclear pleocytosis (usually < 10 cells/μl)	Normal or mild/moderate pleocytosis (usually < 50 cells/μl); can be mononuclear or neutrophilic	Normal or mild/moderate pleocytosis (usually < 100 cells/μl) with neutrophilic component
Oligoclonal bands	+++	+	+

Rare or less than 5%, + infrequent, ++ frequent, +++ very frequent.

Modified with permission from: Chen and Bhatti [34].

ADEM acute disseminated encephalomyelitis, *AQP4* aquaporin-4, *CSF* cerebrospinal fluid, *CNS* central nervous system, *IgG* immunoglobulin G, *LETM* longitudinally extensive transverse myelitis, *MOG* myelin oligodendrocyte glycoprotein, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *ON* optic neuritis.

NMOSD-optic neuritis

Pathophysiology and epidemiology

The term 'neuro-myélite optique aiguë' translated into the English 'neuromyelitis optica' was introduced by Eugène Devic in 1894 when he described a case of bilateral blindness and complete paraplegia, in which the post-mortem examination revealed demyelination of both optic nerves and longitudinally extensive demyelination and necrosis of the spinal cord [13]. Subsequent to this definition of NMO as combined ON and transverse myelitis, a longstanding controversy existed over whether NMO represented a geographically limited subtype of MS or an entirely distinct disease. Not until the first decade of the twenty-first century—with the discovery of AQP4-IgG as a novel pathogenic mediator—was NMO definitively proven to be an independent clinical entity [14]. It is now recognized that NMOSD represents a broad spectrum of clinical manifestations and MRI findings (Table 2) [4],

Table 2 Diagnostic Criteria for Neuromyelitis Optica Spectrum Disorder.

Core clinical characteristics	AQP4-IgG positive	AQP4-IgG negative or unknown AQP4-IgG status	Additional MRI requirements in AQP4-IgG negative or unknown AQP4-IgG status
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	1. At least 1 core clinical characteristic 2. Exclusion of alternative diagnoses	1. At least 2 core clinical characteristics occurring as a result of 1 or more clinical attacks and meeting all of the following requirements: a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome b. Dissemination in space (2 or more different core clinical characteristics) c. Fulfilment of additional MRI requirements, as applicable 2. Negative tests for AQP4-IgG 3. Exclusion of alternative diagnoses	1. Acute optic neuritis: a brain MRI showing normal findings (or only non-specific white matter lesions), or an optic nerve MRI with a T2-hyperintense lesion or a T1-weighted gadolinium-enhanced lesion extending over more than one-half the optic nerve length or involving the optic chiasm 2. Acute myelitis: an associated intramedullary MRI lesion extending over either ≥3 contiguous segments (LETM) or ≥3 contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis 3. Area postrema syndrome: associated dorsal medulla/area postrema lesions 4. Acute brainstem syndrome: associated peri-ependymal brainstem lesions

Adapted from Wingerchuk et al. [4].

AQP4 aquaporin-4, *IgG* immunoglobulin G, *LETM* longitudinally extensive transverse myelitis lesions, *MRI* magnetic resonance imaging, *NMOSD* neuromyelitis optica spectrum disorder.

unified by a high rate (73–90%) of AQP4-IgG seropositivity [15, 16].

AQP4 is a transmembrane water channel enriched in the end-feet of perivascular astrocytes of the CNS [17]. Pathological examination of early NMOSD lesions has revealed selective loss of astrocytes and deposition of activated complement, preceding demyelination and apoptosis of oligodendrocytes [18]. Intracerebral administration of purified IgG from AQP4-IgG seropositive NMOSD patients can produce demyelinating lesions in mice, but only when co-injected with human complement [19]. This observation highlights the critical roles of humoral immunity and the complement system in NMOSD pathogenesis, an insight with important therapeutic implications.

NMOSD is a rare disorder, with a reported incidence of 0.4 to 2 per 1,000,000 person-years and a prevalence of 0.5 to 4 per 100,000, largely dependent on the ethnicity of the study population [20]. The median age of onset is 39 years (roughly 10 years later than in MS) [21], and there is a striking female predominance (70–90% of cases) [22, 23]. Unlike MS, NMOSD is more common in people of Asian or African descent than whites [24, 25]. In a large international study, the most common initial manifestation of NMOSD was transverse myelitis (48%) followed closely by ON (42%), with area postrema syndrome (10%) and brainstem, diencephalic, or cerebral syndrome (14%) much less common [23]. The study also found that 63% of patients with NMOSD ultimately developed ON. Compared to MS, the risk of permanent disability is substantially higher in NMOSD [26]. While idiopathic-ON and MS-ON tend to have favourable visual outcomes [7], the natural history of NMOSD-ON is marked by multiple recurrences and significant long-term visual disability, with final visual acuity ≤20/200 in at least one eye in 50–70% of patients [27–30].

Clinical presentation

It can be clinically challenging to distinguish a first episode of NMOSD-ON from other forms of ON (Table 1). Although visual loss at its nadir tends to be quite severe in NMOSD-ON (median visual acuity 20/1250) [31], profound vision loss is also observed in typical ON (the ONTT reported initial visual acuity of 20/200 or worse in 35.9% of participants, including 3.1% with no-light perception) [5]. Furthermore, both MS-ON and NMOSD-ON tend to spare the anterior-most portion of the optic nerve, with optic disc oedema noted in only a minority of cases (5–33% for NMOSD-ON and 9.5–35% for idiopathic-ON/MS-ON) [5, 29, 32]. Although one retrospective series reported a low rate of painful eye movements associated with NMOSD-ON (27%) compared to patients in the ONTT (87%), it is questionable whether this symptom was adequately documented in the reviewed charts [5, 30]. Simultaneous or rapidly sequential bilateral ON are rare presentations of MS and should suggest an alternative aetiology such as NMOSD (or MOGAD; see below) [33, 34].

Assessment and diagnosis

The clinical suspicion for NMOSD-ON may be informed by in-office ancillary testing. Although automated perimetry may demonstrate any pattern of visual field loss, a bitemporal hemianopsia indicative of chiasmal involvement is considered a “red flag” for NMOSD-ON [35]. However, It should be noted that 5% of patients with ON exhibited a bitemporal hemianopsia in the ONTT [36]. Optical coherence tomography (OCT) is of minimal value in distinguishing NMOSD-ON from idiopathic-ON/MS-ON in the acute phase, as the peripapillary retinal nerve fibre layer

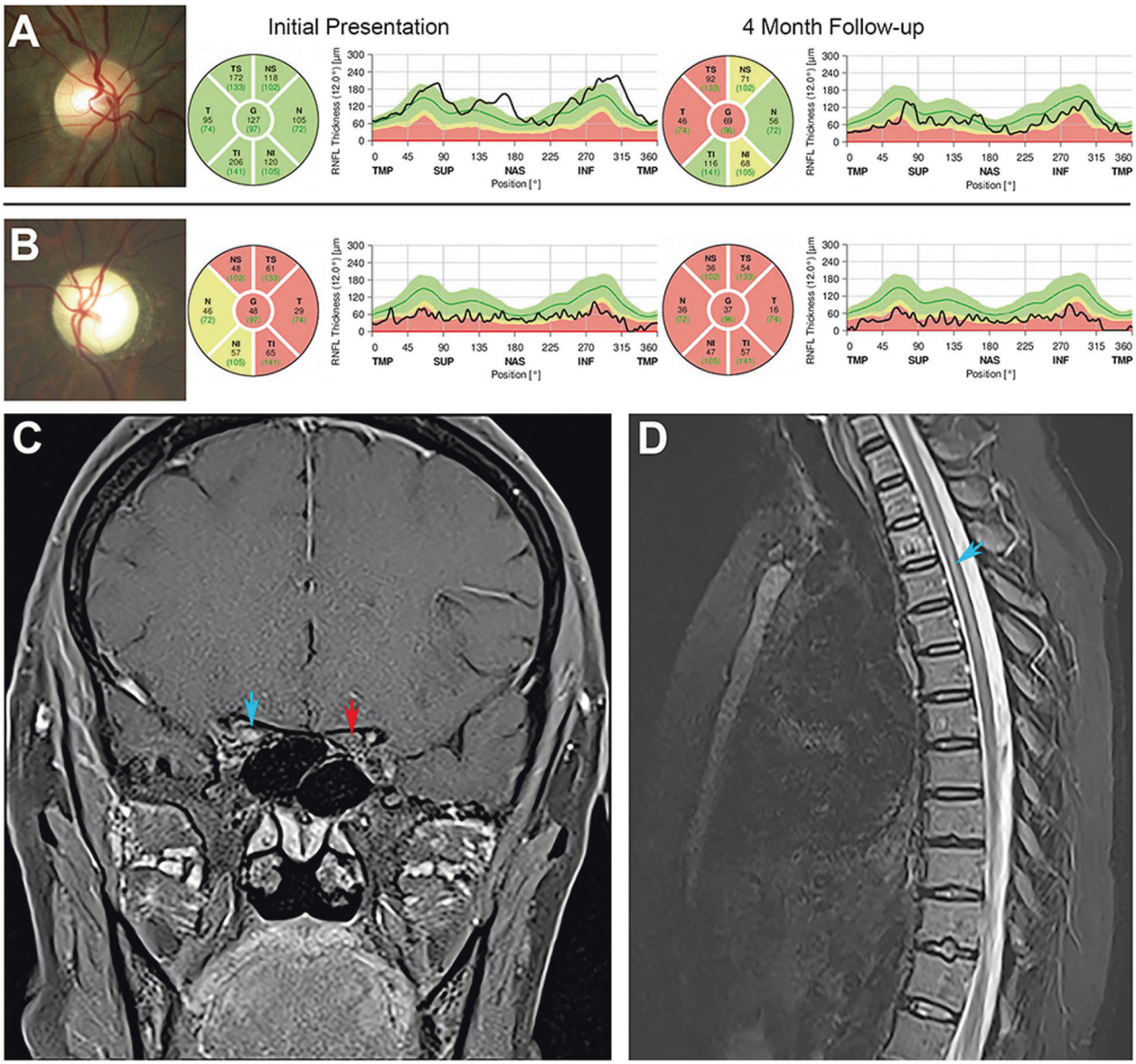

Fig. 2 Clinical presentation of a 49-year-old female with sequential bilateral NMOSD-ON. The patient presented with acute vision loss to hand motions in the right eye, 3 months after having lost vision to no-light perception in the left eye. Visual acuity improved to 20/25 in the right eye following intravenous methylprednisolone and plasma exchange therapy. She was subsequently treated with intravenous rituximab infusions every 6 months. **A** The right optic disc (left panel) appeared normal on presentation, with minimal thickening of the peripapillary retinal nerve fibre layer (pRNFL) on optical coherence tomography (OCT; middle panel). Four months later, substantial pRNFL thinning had developed, particularly in the temporal quadrant (right panel). **B** The left optic disc exhibited considerable pallor, and pRNFL was severely thinned on initial presentation, consistent with profound optic atrophy. Some additional interval thinning was apparent 4 months later. **C** Coronal, post-contrast, T1-weighted magnetic resonance imaging (MRI) of the orbits demonstrated enhancement of the right optic nerve at the level of the orbital apex (blue arrow), while the left optic nerve did not enhance but appeared atrophic (red arrow). The length of optic nerve enhancement was 20.5 mm and involved the posterior orbital, intracanalicular and cisternal segments. **D** Sagittal, T2-weighted, MRI revealed abnormal hyperintense signal of the thoracic spinal cord spanning 3 vertebral segments (blue arrow).

(pRNFL) is normal or only mildly thickened in cases without optic disc oedema. However, in the chronic phase, OCT typically reveals more severe thinning of the pRNFL (Fig. 2A, B) and of the ganglion cell-inner plexiform layer (GCIPL) in NMOSD-ON than in idiopathic-ON/MS-ON, reflecting profound loss of retinal ganglion cell axons and somas, consistent with worse visual outcomes in NMOSD-ON [37–39].

Gadolinium-enhanced MRI reveals optic nerve enhancement in ~94% of cases of acute ON (Fig. 2C) [40]. The findings of longitudinally extensive optic nerve enhancement, chiasmal involvement, and/or bilateral optic

nerve involvement are atypical for idiopathic-ON/MS-ON and should raise suspicion for NMOSD-ON [41–43]. In a retrospective analysis of patients with NMOSD-ON or MS-ON, optic nerve enhancement ≥17.6 mm was 80.8% sensitive and 76.9% specific for NMOSD-ON, and involvement of ≥3 optic nerve segments was 100% specific for NMOSD-ON [44]. Importantly, however, extensive optic nerve involvement does not distinguish NMOSD-ON from MOGAD-ON (see below). For those patients with MRI optic nerve abnormalities suspicious for NMOSD-ON, spine imaging should be performed to assess for longitudinally extensive transverse myelitis, defined as spinal cord involvement >3 vertebral segments (Fig. 2D) [4]. Brain MRI lesions are present in up to 85% of patients with NMOSD, commonly affecting structures with high AQP4 expression such as ependymal cells, the hypothalamus and brainstem [45, 46]. Most brain lesions in NMOSD are non-specific in appearance and rarely have the characteristic periventricular distribution seen in MS [47].

Serological testing for AQP4-IgG is critical in confirming the diagnosis of NMOSD [4]. Serum AQP4-IgG may be tested using a variety of methods, but live cell-based assays (Fig. 1) offer the highest sensitivity, yielding a positive result in three-quarters of NMOSD cases while achieving a specificity >99% [48]. Notably, AQP4-IgG was detected in 20% of 34 patients with recurrent ON who did not otherwise meet clinical criteria for NMOSD, with seropositivity associated with more severe visual loss on presentation, poor visual outcome and subsequent development of transverse myelitis [49].

In contrast to serological testing, cerebrospinal fluid (CSF) analysis is less helpful in NMOSD. Pleocytosis, with either a mononuclear or neutrophilic predominance, is more common in NMOSD than in MS, with CSF cell count >50 cells/μl seen in up to 35% of patients [45]. Oligoclonal bands may be identified in up to one-third of cases and thus their presence does not exclude NMOSD [45]. Detection of AQP4-IgG in the CSF is less sensitive than in the serum [50], although there are rare documented cases of positive CSF AQP4-IgG in seronegative patients with recurrent transverse myelitis [51].

Treatment

Acute visual loss

Treatment of acute flares of NMOSD-ON is imperative to reduce long-term visual morbidity. IVMP is the mainstay of treatment, and early treatment has been shown to correlate with preservation of pRNFL [52]. IVMP treatment typically consists of 1 g/day for 3–5 consecutive days with or without a PO prednisone taper. The use of high-dose (1250 mg) PO prednisone has not been evaluated in NMOSD-ON. Although largely limited to case series and retrospective cohort studies, there is evidence that plasma exchange (PLEX) or immunoadsorption apheresis may be beneficial in the acute treatment of NMOSD, including NMOSD-ON [53–57]. Administered every 48 h for 5–7 cycles, PLEX is often initiated in IVMP-refractory disease, with one series reporting average final visual acuity of 20/50 in NMOSD-ON patients receiving sequential IVMP and PLEX compared to 20/400 in those receiving IVMP alone [55]. In two non-randomized studies of acute NMOSD (including some ON cases), 40–50% of attacks treated with PLEX within 2 days of symptom onset experienced complete recovery, with efficacy decreasing over time and 0–5% recovering fully with PLEX initiation after 20 days [56, 57]. While specific visual outcomes were not reported, these findings support the use of combined IVMP and PLEX as first-line therapy.

Long-term management

The hallmark of NMOSD is a relapsing course (67–90% of patients) [26, 58, 59] with relentless, stepwise progression of neurological disability, including blindness. As such, all patients require long-term immunosuppression with the goal of reducing the frequency of relapses [45]. Chronic immunosuppressive treatment is typically continued indefinitely. Until very recently, therapeutic options were limited to immunosuppressant agents without class I or II evidence (see below).

It is important to correctly diagnose NMOSD and differentiate it from MS because NMOSD may worsen when treated with immunomodulatory therapies developed for MS, such as interferon-β, natalizumab, or fingolimod [60]. Instead, traditional immunosuppressant agents are used as maintenance therapy. Oral corticosteroids commonly serve as a bridge to steroid-sparing maintenance treatments following an NMOSD exacerbation. Table 3 summarizes the results of off-label use of azathioprine, mycophenolate mofetil (MMF) and rituximab for long-term management of NMOSD. Less commonly used agents include methotrexate, intravenous immunoglobulin (IVIG), mitoxantrone and cyclophosphamide [45].

A recent randomized double-blind, placebo-controlled trial demonstrated that rituximab significantly reduced relapses in NMOSD [61]. Two retrospective series demonstrated a greater reduction of the annualized relapse rate (ARR) with rituximab or MMF compared to azathioprine [62, 63]. Similarly, a prospective open-label randomized trial demonstrated superior reduction in ARR by rituximab compared to azathioprine combined with prednisone [64].

As of the time of this writing, three drugs have completed phase 2/3 or 3, randomized, double-blind placebo-controlled

Table 3 Summary of select studies evaluating long-term therapy for NMOSD.

Drug	Mechanism of action	Adverse effects	Study design	Dose	Outcome	Notes
Azathioprine (AZA)	Reduced lymphocyte proliferation via inhibition of purine synthesis	Bone marrow suppression, gastrointestinal disturbance, malignancy, opportunistic infections	Retrospective review of 70 patients with follow-up >12 months [124]	Up to 3 mg/kg/day PO	At dose ≥2 mg/kg/day, ARR decreased from 2.20 to 0.52. At dose <2 mg/kg/day, ARR decreased from 2.09 to 0.82	74% of patients on concurrent prednisone
			Retrospective multi-centre analysis, including 32 patients taking AZA [62]	2–3 mg/kg/day PO	ARR reduction from 2.26 to 0.63; 47% relapse-free; median duration 23.5 months	Some with concurrent prednisone
			Retrospective review, including 49 patients taking AZA [63]	1.75–2.5 mg/kg/day PO	ARR decreased from 1.26 to 0.37; 53% relapse-free; median duration 15 months	69% with concurrent prednisolone
			Prospective, randomized open-label study, 35 patients given AZA [64]	2–3 mg/kg/day PO	ARR decreased from 1 to 0.5; 54% relapse-free at 12 months	Long-term concomitant prednisone (10–20 mg/day)
Mycophenolate mofetil (MMF)	Reduced lymphocyte proliferation via inhibition of guanosine synthesis	Bone marrow suppression, gastrointestinal disturbance, lymphoid malignancies, opportunistic infections	Retrospective series of 24 patients [125]	750–3000 mg/day PO	ARR reduced to 0.09 from 1.3 pre-treatment over a median 27 months	One patient died of disease activity
			Review of 67 patients given MMF as first-line therapy [126]	2 g/day PO	ARR decreased from 1 pre-treatment to 0 post-treatment; 33/67 patients relapse-free at median 24 months	Taken from NOMADMUS cohort (ClinicalTrials.gov Identifier: NCT02850705). Some treated with concomitant steroids.
			Retrospective multi-centre analysis, including 28 patients taking MMF [62]	1–2 g/day PO	ARR decreased from 2.61 to 0.33; 64% relapse-free; median duration 26 months	Some with concurrent steroids
			Retrospective review, including 34 patients taking MMF [63]	1.5–2.0 g/day PO	ARR decreased from 1.54 to 0.18; 65% relapse-free; median duration 26 months	27% with concurrent prednisolone
Rituximab	Monoclonal antibody against CD20, causing B cell depletion	Infusion reaction, opportunistic infections, delayed leukopenia	Meta-analysis of 25 observational studies [127]	375 mg/m^2 IV weekly for 4 times; 1 g IV every 2 weeks for 2 times; or 500 mg IV weekly for 2 times	Mean ARR decreased by 0.79	24/25 studies showed an ARR reduction.
			Retrospective multi-centre analysis, including 30 patients taking rituximab [62]	1 g IV every 2 weeks for 2 times; repeated at 6-month intervals or with CD19 B cell count recovery	ARR reduction from 2.89 to 0.33; 67% relapse-free; median duration 20 months	Some with concurrent prednisone
			Retrospective review, including 55 patients taking rituximab [63]	375 mg/ m^2 IV weekly for 4 times or 1000 mg/m^2 IV every 2 weeks for 2 times; infusion repeated when memory B cell frequency reaches 0.05%	ARR decreased from 1.66 to 0.09; 73% relapse-free; median duration 65 months	27% with concurrent prednisolone
			Prospective, randomized open-label study, 33 patients given rituximab [64]	1 g IV every 2 weeks for 2 times; repeated at 6 months	ARR decreased from 1.30 to 0.22; 79% relapse-free at 12 months	Long-term concomitant prednisone (10–20 mg/day)
			RCT: 38 AQP4-IgG seropositive patients randomized 1:1 to rituximab or placebo [61]	375 mg/m^2 IV weekly for 4 weeks, then 1000 mg IV every 2 weeks for 2 times at weeks 24 and 48	No relapses with rituximab compared to 37% with placebo	All subjects were receiving 5–30 mg/day PO steroids on enrolment; tapered to 2–5 mg/day over the study
Eculizumab	Humanized monoclonal antibody preventing cleavage of complement C5 to inhibit complement activation	Increased meningococcal infection risk, infusion reaction, upper respiratory infection, headache	RCT: 143 AQP4-IgG seropositive patients on stable immunosuppressive therapy, randomized (2:1) to eculizumab or placebo[65]	900 mg IV weekly for four doses, then 1200 mg IV every 2 weeks	Adjudicated relapses in 3% of patients compared to 43% with placebo; ARR decreased from 1.99 pre-enrolment to 0.02 in the eculizumab group and 0.35 in the placebo group.	Baseline immunosuppression included corticosteroids, AZA, MMF, cyclosporine, cyclophosphamide, methotrexate, mizoribine, tacrolimus

Table 3 (continued)

Drug	Mechanism of action	Adverse effects	Study design	Dose	Outcome	Notes
Inebilizumab	Humanized monoclonal antibody against CD19, depleting B cells and plasmablasts	Infusion reaction, upper respiratory infection, urinary tract infection, neutropenia	RCT: 230 patients randomized 3:1 to inebilizumab or placebo [66]	300 mg IV twice, 2 weeks apart	Relapse in 12% of inebilizumab patients and 39% of placebo at 197 days; number-needed-to-treat 3.23	All subjects received 3 weeks of PO corticosteroids; too few AQP4-IgG seronegative patients to determine efficacy
Satralizumab	Humanized monoclonal antibody (IgG2 subclass) against the receptor for pro-inflammatory cytokine interleukin-6	Infusion reaction, urinary tract infection, upper respiratory infection	RCT: 83 patients currently taking azathioprine, MMF, and/or PO corticosteroids randomized 1:1 to additionally receive placebo or satralizumab [67]	120 mg SC every 2 weeks for 3 times, then every 4 weeks subsequently	Relapse in 20% of satralizumab patients (107.4 weeks) compared to 43% of placebo (32.5 weeks); ARR decreased from 1.5 to 0.11 with satralizumab compared to 0.32 with placebo	No definitive efficacy in AQP4-IgG seronegative subset
			RCT: 95 patients randomized 2:1 to satralizumab or placebo [68]	120 mg SC every 2 weeks for 3 times, then every 4 weeks subsequently	Relapse in 30% of satralizumab (92.3 weeks) patients and 50% of placebo (54.6 weeks)	No definitive efficacy in AQP4-IgG seronegative subset
Tocilizumab	Humanized monoclonal antibody (IgG1 subclass) against the receptor for pro-inflammatory cytokine interleukin-6	Infusion reaction, transaminitis, upper respiratory infection, urinary tract infection	Open-label prospective trial of 118 patients randomized 1:1 to tocilizumab or AZA [69]	8 mg/kg IV every 4 weeks	Median time to first relapse of 78.9 weeks (TOCI) vs 56.7 weeks (AZA). 86% relapse-free at 60 weeks (TOCI) vs 57% (AZA)	Too few AQP4-IgG seronegative patients to determine differences in efficacy; AZA dosed at 2–3 mg/day

AQP4-IgG aquaporin-4 immunoglobulin G, *ARR* annualized relapse rate, *AZA* azathioprine, *IV* intravenous, *MMF* mycophenolate mofetil, *NMOSD* neuromyelitis optica spectrum disorder, *PO* oral, *RCT* randomized placebo-controlled trial, *SC* subcutaneous, *TOC* Itocilizumab.

trials for the treatment of NMOSD (Table 3). All three have recently been awarded United States Food and Drug Administration (FDA) approval for long-term treatment of NMOSD; guidance from the National Institute for Health and Care Excellence in the United Kingdom is still under development. The first FDA-approved medication for adults with AQP4-IgG seropositive NMOSD was eculizumab in June 2019. Eculizumab is a humanized monoclonal antibody, which binds to the complement protein C5 and halts activation of the complement cascade. In a phase 3 study of NMOSD patients on stable doses of immunosuppressive therapy, the addition of eculizumab reduced the occurrence of adjudicated relapses to 3%, compared to 43% with placebo, and the adjudicated ARR was 0.02 in the eculizumab group compared to 0.35 in the placebo group [65].

The anti-CD19 monoclonal antibody inebilizumab was tested as monotherapy for NMOSD in a multi-centre, double-blind, randomized placebo-controlled phase 2/3 study [66]. Enrolment was terminated early due to a clear demonstration of efficacy, with the proportion of participants experiencing relapse decreased by more than three-fold. Efficacy in seronegative participants could not be determined due to a low number enrolled. Inebilizumab received FDA approval for use in NMOSD in June 2020.

The second-generation anti-interleukin (IL)-6 receptor monoclonal antibody satralizumab was investigated in two separate randomized, double-blind, placebo-controlled phase 3 trials as adjunct therapy for NMOSD patients stable on immunosuppressant treatment [67] and as monotherapy [68]. Both trials demonstrated reductions in the percentage of patients experiencing relapse and the overall ARR, which was more pronounced when analyzing only AQP4-IgG seropositive NMOSD patients. Neither study demonstrated efficacy in AQP4-IgG seronegative patients. FDA approval for satralizumab was granted in August 2020. Finally, tocilizumab, an older, first-generation IL-6 receptor monoclonal antibody, also recently showed promising results in a phase 2 trial, reducing the number of relapses more effectively than azathioprine [69].

Myelin oligodendrocyte glycoprotein associated disorder (MOGAD)-optic neuritis

Pathophysiology and epidemiology

Autoantibodies against MOG, a cell surface protein expressed by oligodendrocytes, have long been implicated in demyelinating disease based on observations that experimental autoimmune encephalomyelitis can be induced in rodents by infusion of MOG-IgG [70]. In fact, MOG-IgG was incorrectly identified as a biomarker for MS in the early 2000s [71], principally due to lack of specificity

of older enzyme-linked immunosorbent assays [72]. The advent of live cell-based assays using transfected human cell lines to express MOG in its native transmembrane conformation revealed that MOG-IgG is indeed relevant to human demyelinating conditions as a biomarker for MOGAD, a disorder that is distinct from both MS and NMOSD [73, 74].

MOGAD represents a diverse spectrum of clinical manifestations, including ON, transverse myelitis, acute disseminating encephalomyelitis (ADEM) and brainstem encephalitis [75, 76]. Because the current 2015 NMOSD criteria were created before the recognition of MOGAD as a distinct entity, 21–42% of patients with AQP4-IgG seronegative NMOSD will test positive for MOG-IgG [77, 78]. However, MOGAD has a broader clinical phenotype than NMOSD, and only about one-third of patients with MOGAD satisfy the diagnostic criteria for NMOSD [76, 79]. Indeed, the fact that most NMOSD series have not identified AQP4-IgG and MOG-IgG double-positive cases suggests that NMOSD and MOGAD are not mediated by a common pathobiology [77, 78, 80, 81]. Furthermore, MOGAD pathological specimens demonstrate demyelination without astrocyte degeneration, the opposite of NMOSD [82, 83].

The median age of onset of MOGAD in adults is in the early-to-mid 30s, closer to that of MS patients than to NMOSD [84–86]. Unlike AQP4-IgG, MOG-IgG seropositivity is common in children with demyelinating disease (~30% of cases) [87, 88]. In contrast to MS and NMOSD, it appears that there is minimal predilection for females in MOGAD [76, 77, 79]. The national incidence of MOGAD in the Netherlands was recently reported to be 0.16 per 100,000 per year [85].

Clinical presentation

ON is the most common clinical presentation and relapse manifestation of MOGAD in adults (Table 1). In a large United Kingdom study of MOGAD, isolated ON (with bilateral involvement in ~50%) was the initial presentation in 58% of patients, followed by transverse myelitis in 21%, simultaneous ON and transverse myelitis in 12% and an ADEM-like presentation in 9% [76]. Brain-stem involvement, encephalitis, and seizures can also occur in MOGAD [89]. MOGAD presenting at age <9 years is more likely to manifest as ADEM, while older children commonly present with ON or transverse myelitis [85, 90, 91].

The clinical presentation of MOGAD-ON can be atypical in a number of ways. As mentioned above, MOGAD-ON has been reported to be bilateral in 50 to 84% of cases (Fig. 3A, B) [76, 85, 92, 93]. The frequency of bilateral involvement is similar to that seen in NMOSD-ON, but 3–4 times greater than in MS-ON [33, 93–95]. In contrast to NMOSD-ON and MS-ON, MOGAD-ON is commonly (76–86%) associated with optic disc oedema, which can be severe enough to be associated with peripapillary haemorrhages [92, 96, 97]. This fundus appearance may lead to diagnostic confusion with ischaemic optic neuropathy or papilledema, highlighting the importance of eliciting distinguishing features in the patient history (such as painful eye movements [96]), correlating the degree of vision loss to the severity of optic disc oedema (typically worse vision loss in MOGAD-ON than in papilledema) and obtaining an MRI (see below).

Visual loss upon initial presentation with MOGAD-ON can be quite severe, with a median nadir visual acuity of hand motion [96]. While also encountered in MS-ON and NMOSD-ON, central scotomas were observed in a sizeable majority of eyes affected by MOGAD-ON (73%), with an additional 22% demonstrating complete visual field depression (Fig. 3C) [97]. Fortunately, substantial recovery of visual function is quite common in MOGAD-ON, and it is rare to develop permanent severe vision loss after a single episode. Similar to NMOSD-ON, MOGAD-ON has a strong tendency to be recurrent, with at least 50% of patients suffering relapses [76, 98, 99]. While MOGAD patients may enjoy intervals of months or years between ON recurrences, some may relapse during or shortly following completion of a steroid taper, reminiscent of chronic relapsing inflammatory optic neuropathy (CRION). In fact, MOG-IgG seropositivity has been reported in 67–92% of patients previously diagnosed with CRION [100, 101]. Long-term visual outcomes after MOGAD-ON relapses are variable but in general more favourable than NMOSD-ON: 5–20% of MOGAD-ON patients suffer permanent vision loss to 20/200 or worse in at least one eye [76, 92, 96], compared to at least 50% in NMOSD, as detailed above.

Assessment and diagnosis

MOGAD-ON cases presenting acutely with optic disc oedema will demonstrate pRNFL thickening on OCT, whereas all cases will demonstrate progressive pRNFL thinning as optic atrophy develops over the subsequent months (Fig. 3D). Similar degrees of pRNFL and GCIPL thinning have been observed in affected eyes of NMOSD-ON and MOGAD-ON patients; however, the number of attacks required to produce this amount of thinning has been found to be greater in MOGAD-ON than NMOSD-ON [102]. Chronic pRNFL thinning is most prominent in the temporal quadrant representing the papillomacular bundle, consistent with the propensity of MOGAD-ON to produce central scotomas [103].

MRI has great value in distinguishing MOGAD-ON from other aetiologies. Longitudinally extensive enhancement of at least one-half the length of the optic nerve has

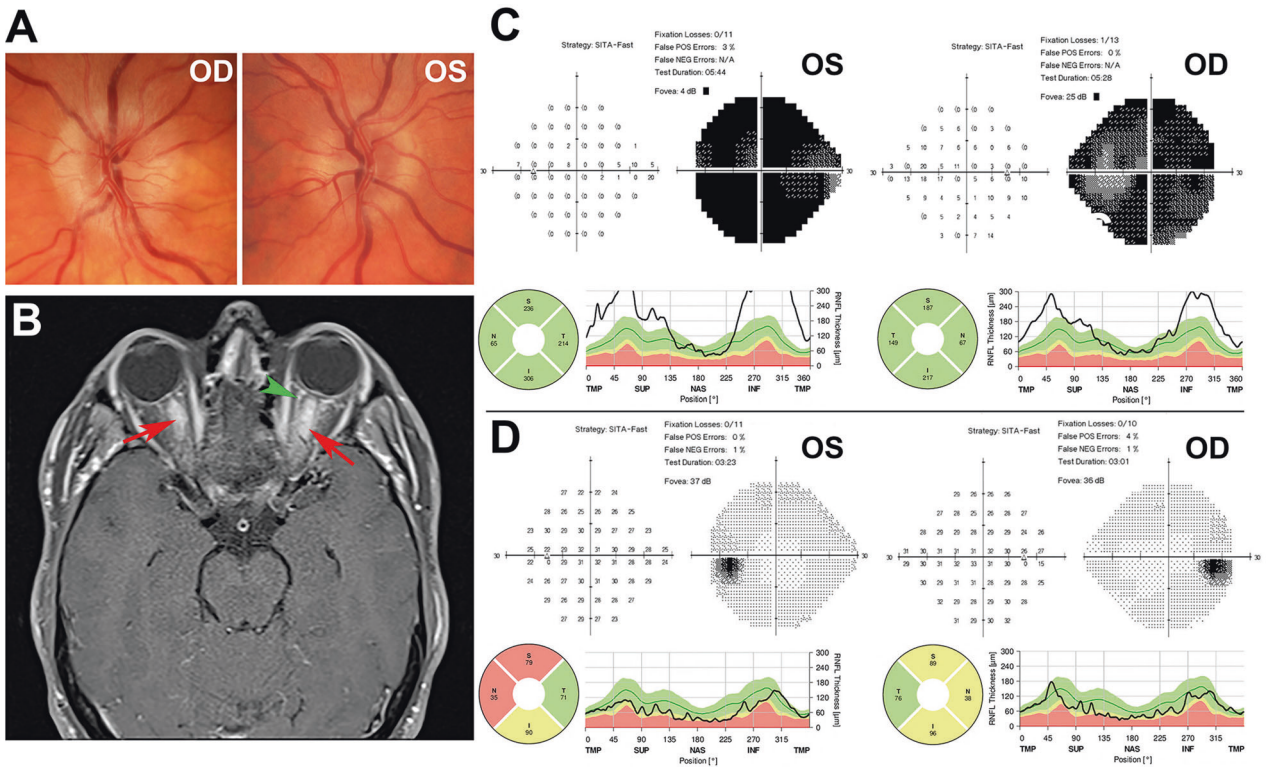

Fig. 3 Clinical presentation of a 53-year-old female with simultaneous bilateral MOGAD-ON. The patient presented with acute loss of visual acuity to 20/50 in the right eye (OD) and hand motion in the left eye (OS). **A** Both optic discs exhibited mild optic disc oedema on initial presentation. **B** Axial, post-contrast, T1-weighted magnetic resonance imaging of the orbits revealed bilateral enhancement of the anterior optic nerves (blue arrows) with co-existing enhancement of the left optic nerve sheath (green arrowhead). The length of enhancement was 21 mm for the right optic nerve and 19 mm for the left, less than 50% of total optic nerve length in both cases. **C** Humphrey visual field testing on initial presentation revealed severe generalized depression of both eyes, while optical coherence tomography (OCT) revealed peripapillary retinal nerve fibre layer (pRNFL) thickening in both eyes, consistent with the presence of optic disc oedema. **D** The patient was treated with intravenous methylprednisolone for 5 days, followed by a prednisone taper over 2 months. At 6-month follow-up, visual acuity had improved to 20/20 in both eyes and visual fields had entirely normalized. OCT revealed the interval development of pathological pRNFL thinning, consistent with partial optic atrophy of both eyes.

been observed in up to 80% of MOGAD-ON cases but is not a pathognomonic sign, as it can also be seen in NMOSD-ON [93, 96]. However, consistent with the high rate of optic disc oedema, MOGAD-ON tends to exhibit enhancement of the anterior portion of the optic nerve, in contrast to the posterior optic nerve/chiasmal involvement common in NMOSD-ON [92, 93, 96]. Nevertheless, MOGAD-ON may affect the optic chiasm in up to 15% of cases [92, 96]. Perhaps most diagnostically useful is the frequent observation of enhancement of the optic nerve sheath (i.e., perioptic neuritis) and adjacent orbital fat, reported in up to 50% of MOGAD-ON, which is not typically seen in NMOSD-ON or MS-ON [79, 96, 104].

MOGAD demyelinating lesions in the brain often have a fluffy appearance and commonly localize to the juxtacortical and deep white matter, brainstem and surrounding the 4th ventricle, unlike the classic ovoid lesions perpendicular to the lateral ventricles in MS [76, 104–106]. Longitudinally extensive transverse myelitis can be seen in MOGAD, but compared to NMOSD, MOGAD-transverse myelitis is more likely to be non-enhancing, multifocal, involving the conus medullaris, and restricted to the grey matter (producing an ‘H sign’) [107].

As in NMOSD, the CSF findings in MOGAD are not diagnostically confirmatory. CSF evaluation may reveal a normal nucleated cell count or demonstrate a pleocytosis (exceeding 100 cells/μl in 28% of cases), sometimes with a neutrophilic component; oligoclonal bands are seen in a minority of cases [108]. Testing for MOG-IgG in the CSF is rarely performed due to a low sensitivity of 60–70% (typically with low titres when positive, suggesting an extrathecal origin of these autoantibodies) [109, 110]. In contrast, autoantibody testing in serum samples is critical to the diagnosis of MOGAD. Based on the recommendations of an international expert panel [75], MOG-IgG testing should be performed exclusively using cell-based assays with either fluorescence microscopy or flow cytometry (Fig. 1). While a fluorescence microscopy-based assay using fixed cells is widely used due to its convenience, live cell-based assays appear to offer higher accuracy [111].

Determining the MOG-IgG titre can help determine the likelihood of a true-positive test, although high titres do not correlate with recurrence risk or final clinical outcome [112]. Serial testing to evaluate the persistence of MOG-IgG seropositivity may have some clinical utility. It has been reported that transient seropositivity is correlated with monophasic disease and persistent seropositivity with a relapsing course [76, 85, 113]. A recent prospective study in children, however, found that while conversion to seronegative status was correlated with a lower (but not zero) risk of relapse, persistent seropositivity had little predictive value for recurrent demyelinating episodes [114]. Whether serological testing should be performed on every patient presenting with acute ON is controversial, as patients with monophasic MOGAD-ON with good recovery do not require chronic immunosuppressive therapy. Many clinicians therefore limit MOG-IgG testing to patients with recurrent or steroid-dependent ON or additional CNS lesions suspicious for MOGAD.

Treatment

Acute visual loss

As the natural history of untreated MOGAD-ON is not well-defined, it is uncertain whether MOGAD-ON differs from typical idiopathic-ON/MS-ON in terms of visual outcome. Notably, a re-analysis of blood samples from the ONTT identified three patients who were MOG-IgG seropositive and recovered to 20/20 visual acuity despite none of them receiving IVMP (two received PO prednisone and the third placebo) [115]. However, a retrospective study of MOGAD from Germany reported that only 7 of 12 untreated MOGAD-ON patients experienced complete or near-complete visual recovery [79]. Another retrospective study reported better visual outcomes in both NMOSD-ON and MOGAD-ON patients in whom IVMP was initiated within 4 days of symptom onset [116]. Given the tendency for corticosteroid-dependence in MOGAD-ON, treatment of acute attacks would seem prudent in most cases.

Acute treatment of MOGAD-ON typically starts with IVMP administered as 1 g/day for 3–5 days, often resulting in rapid visual improvement. The utility of high-dose PO prednisone is not known at this time. Unlike idiopathic-ON/MS-ON, a slow PO prednisone taper over 2–6 months after IVMP may be warranted. This is because a sizeable fraction of patients who will relapse do so early after an attack, with the median time to recurrence of 5 months [108]. It appears that the risk of early recurrence is reduced by a prolonged steroid taper. In a series of 59 patients with relapsing MOGAD (the majority with ON), 146 episodes were treated with a PO prednisone taper, with 28% suffering relapse during the taper (at a median prednisone dose of 10 mg per day) and an additional 42% suffering relapse following the taper (median interval of 2 months) [117]. Notably, among patients with relapse, the median planned duration of the taper was 1.5 months, compared to 5 months in patients who did not relapse. Limited data exists on the efficacy of PLEX in IVMP-refractory MOGAD. In a German study of 25 MOGAD patients with ON or transverse myelitis treated with IVMP and subsequent PLEX or immunoadsorption, 40% experienced complete or near-complete recovery, 56% partial recovery and 4% no recovery [79]. IVIG has not been studied in acute MOGAD-ON, but in two randomized trials, it failed to improve the vision of patients with idiopathic-ON/MS-ON [118, 119].

Long-term management

The necessity of long-term immunosuppressive therapy for MOGAD is less clear-cut than in AQP4-IgG seropositive NMOSD. Roughly half of MOGAD patients experience a monophasic disease course [76] and those who recur often experience substantial recovery after the first relapse. Therefore, for those patients who recovered well after an initial attack of MOGAD, long-term therapy is not needed until relapses occur. Randomized prospective trials of long-term therapy for MOGAD are currently lacking, with only observational studies providing class IV evidence.

As in NMOSD, the disease-modifying MS medications interferon-β and glatiramer acetate were found to be ineffective in MOGAD, while data on natalizumab were ambiguous [79, 120]. MMF, azathioprine, IVIG and rituximab have all been associated with reductions in ARR from ~2 episodes per year pre-treatment to ≤1 with each agent [117, 120]. A recent prospective, non-randomized study found that MMF plus maintenance prednisone resulted in a lower relapse rate than maintenance prednisone alone [121]. IVIG administered every 3–4 weeks has been reported effective in paediatric and adult MOGAD patients [117, 120]. A recent multi-centre retrospective study of 70 MOGAD patients with pre-treatment ARR of 1.6 found only 2 of 10 patients relapsed (median ARR 0) after treatment with IVIG, while other agents were associated with relapse in >50% of patients, including azathioprine (13/22 relapsing; ARR 0.2), MMF (14/19 relapsing; ARR 0.67) and rituximab (22/36 relapsing; ARR 0.59) [122]. Finally, in a case report, tocilizumab was reported to stabilize a patient with recurrent MOGAD-ON [123].

Conclusion

The discovery of AQP4-IgG and MOG-IgG as biomarkers for CNS inflammatory demyelinating diseases distinct from

Table 4 Proposed treatment algorithm for optic neuritis.

Acute treatment	
Idiopathic or MS	○ Consider IV steroids[a] to hasten recovery of vision
AQP4-IgG seropositive	○ IV steroids[a] in all cases
	○ Low threshold for PLEX[b]
MOG-IgG seropositive	○ IV steroids[a]; consider prolonged PO prednisone taper starting at 1 mg/kg/day[c]
	○ Consider PLEX[b] if vision <20/200 at 1–2 weeks or no recovery after IV steroids. Note that PLEX has been evaluated in only one study (see text) and to date no study has evaluated the efficacy of IVIG in acute treatment of MOGAD.
Long-term treatment	
MS	○ Disease-modifying agent
AQP4-IgG seropositive	○ Immunotherapy for all with AQP4-IgG seropositive NMOSD[d]
MOG-IgG seropositive	○ Consider immunotherapy[e] for single attack with significant residual disability.
	○ Immunotherapy[e] for recurrent attacks or steroid dependency

Modified with permission from Chen et al. [128].

IgG immunoglobulin G, *AQP4* aquaporin-4, *MOG* myelin oligodendrocyte glycoprotein, *MS* multiple sclerosis, *IV* intravenous, *PO* oral, *IVIG* intravenous immunoglobulin, *NMOSD* neuromyelitis optica spectrum disorder, *PLEX* plasma exchange, *FDA* United States Food and Drug Administration.

[a]Steroids: IV methylprednisolone 1 g/day for 3–5 consecutive days (±PO prednisone taper).

[b]PLEX: 5–7 treatments every other day.

[c]PO prednisone taper over 2–6 months (not standard of care, but may prevent early recurrence).

[d]Immunotherapy: Eculizumab, inebilizumab and satralizumab are FDA-approved therapies for NMOSD; rituximab, mycophenolate mofetil, and azathioprine may also be considered.

[e]Immunotherapy: IVIG, mycophenolate mofetil, azathioprine, or rituximab.

MS represents a paradigm shift in the field of neuroimmunology. Both NMOSD-ON and MOGAD-ON have the potential for devastating long-term visual disability. Autoantibody seropositivity, clinical manifestations and MRI findings are invaluable in establishing the correct diagnosis of each condition. IVMP is the mainstay of acute treatment for both NMOSD-ON and MOGAD-ON, with PLEX likely beneficial as rescue therapy and potentially as first-line treatment for NMOSD-ON (Table 4). While three new drugs targeting the pathogenic mechanisms underlying NMOSD appear poised to dramatically reduce visual morbidity from recurrent AQP4-IgG seropositive NMOSD-ON, optimal long-term therapy for MOGAD-ON awaits future prospective trials.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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