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Clinical Characteristics and Treatment of MOG-IgG–Associated Optic Neuritis

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Abstract

Purpose of Review Antibodies against myelin oligodendrocyte glycoprotein (MOG) are associated with a unique acquired central nervous system demyelinating disease—termed MOG-IgG-associated disorder (MOGAD)—which has a variety of clinical manifestations, including optic neuritis, transverse myelitis, acute disseminating encephalomyelitis, and brainstem encephalitis. In this review, we summarize the current knowledge of the clinical characteristics, neuroimaging, treatments, and outcomes of MOGAD, with a focus on optic neuritis.

Recent Findings The recent development of a reproducible, live cell–based assay for MOG-IgG, has improved our ability to identify and study this disease. Based on contemporary studies, it has become increasingly evident that MOGAD is distinct from multiple sclerosis and aquaporin-4-positive neuromyelitis optica spectrum disorder with different clinical features and treatment outcomes.

Summary There is now sufficient evidence to separate MOGAD from other inflammatory central nervous system demyelinating disorders, which will allow focused research on understanding the pathophysiology of the disease. Prospective treatment trials are needed to determine the best course of treatment, and until then, treatment plans must be individualized to the clinical manifestations and severity of disease.

Keywords Optic neuritis · Myelin oligodendrocyte glycoprotein (MOG) · Aquaporin-4 (AQP4) · Neuromyelitis optica spectrum disorder (NMOSD) · Acute disseminating encephalomyelitis (ADEM) · Multiple sclerosis

Introduction

Our understanding of inflammatory central nervous system (CNS) demyelinating disorders has significantly expanded over the past 15 years, first with the discovery of antibodies against aquaporin-4 (AQP4), which is a biomarker of neuromyelitis optica spectrum disorder (NMOSD), and more recently with the recognition that antibodies against myelin oligodendrocyte glycoprotein (MOG) are a biomarker for another distinct CNS demyelinating disease process, MOG-immunoglobulin G (IgG)–associated disorder (MOGAD). MOG is a CNS protein expressed on the surface of oligodendrocytes [1]. Antibodies against MOG have been postulated to be involved in demyelination for decades because immunization with MOG in mice causes experimental autoimmune encephalomyelitis, which is one of most commonly utilized animal models of demyelination [2]. In the early 2000s, MOG-IgG was mistakenly thought to be a biomarker of multiple sclerosis (MS) based on non-specific older generation assays using MOG in its denatured form [3]. Recent cell-based assays using MOG transfected in its native confirmation form have found that antibodies against MOG are an excellent biomarker for MOGAD, which has a broad range of clinical manifestations, including optic neuritis (ON), transverse myelitis (TM), acute disseminating encephalomyelitis (ADEM), and brainstem encephalitis [4•, 5, 6••, 7, 8].

The presence of MOG-IgG has been found in many patients that present with AQP4-IgG seronegative NMOSD; however, MOGAD has a wider clinical phenotype and different underlying pathogenesis. Only about one-third of patients

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who are seropositive for MOG-IgG will meet the current 2015 diagnostic criteria for NMOSD [6••, 9, 10••, 11]. While there is clinical overlap between AQP4-IgG positive NMOSD and MOGAD, there are significant differences in terms of histopathology. Pathologic specimens from patients with AQP4-IgG positive NMOSD show astrocytic cell death and secondary demyelination [12]. In contrast, MOGAD tissue shows demyelination with preservation of the astrocytes in a pattern similar to pattern II demyelination of MS [13–15]. The differences in histopathology support the notion that AQP4-IgG positive NMOSD and MOGAD are separate entities. Furthermore, the clinical presentation, response to therapy, and reproducible MOG-IgG live cell–based assay with MOG-IgG almost never seen in patients with MS or AQP4-IgG positivity, all contribute to the recognition of MOGAD as a distinct CNS inflammatory demyelinating entity [4•, 5, 7•, 8]. ON is the most common presentation of MOGAD. In this review, we focus on summarizing the current knowledge of the clinical characteristics, treatments, and outcomes of MOGAD, with a particular focus on ON.

Epidemiology

Our knowledge of the epidemiology of MOG-IgG seropositivity is still evolving. In general, MOGAD is present in greater frequency in younger individuals compared with AQP4-IgG positive NMOSD. However, the incidence and prevalence varies some depending on the cohort studied. A recent study from the Netherlands identified the median age of onset was 32.6 years in adults and 8.7 years in children [16]. In this study, they assessed for the presence of MOG-IgG from all samples of patients with demyelinating disease sent to a national laboratory over 4 years. They found that 7% of patients (92 out of 1277) were positive for MOG-IgG (17% in children, 5% in adults). This provided an overall incidence of 0.16 per 100,000 per year (0.31 per 100,000 children and 0.13 per 100,000 adults per year) [16]. In a nationwide population-based study in Denmark from 2008 to 2018, MOG-IgG was detected in 18% of children with acquired demyelinating syndromes, compared with 4% of children with AQP4-IgG [17].

Unlike MS and AQP4-IgG positive NMOSD, which both have a significant female predominance; most studies have shown that MOGAD equally affects males and females (50–63%). Most studies of MOGAD have involved white cohorts [6••, 7•, 9, 16, 18–21], but it remains unclear if there is a racial predilection of the disease. Studies out of Asia have shown a fairly similar frequency of MOGAD [22–25]. Data on patients of African ancestry are sparse. One study evaluated 42 patients with ON and/or TM at a teaching hospital in Algeria and found that 7.1% (3 out of 42) were positive for MOG-IgG while 14.3% (6 out of 42) were positive for AQP4-IgG which suggests that AQP4-IgG may be more common than MOG-IgG in this population [26], but further studies are required to confirm this finding.

There have not been many epidemiology studies on ON that have incorporated the knowledge of MOGAD. A small Denmark epidemiology study on ON found that 4% (2 out of 51) of cases were positive for MOG-IgG while no cases were positive for AQP4-IgG [27]. In contrast, a recent multicenter Japanese epidemiologic survey of ON between 2015 and 2018 analyzed 531 serum samples and found that 12% were positive for AQP4-IgG, and 10% were positive for MOG-IgG. In total, 77% of samples were negative for either antibody with only one sample positive for both antibodies. Of the 77% double-negative samples, 15% were identified as MS and 4% as clinically isolated syndrome. This study supports the finding that AQP4-IgG is more common in Asian populations than in whites, while MOG-IgG may be equally as common. However, this study did not include all cases of ON in a specified region, and therefore was not entirely population-based.

Clinical Manifestations

The clinical presentation of MOGAD varies based on age at onset. Overall, the most common presentation is ON, which was found to be the presenting symptom in 55% of patients based on a large UK study [6••]. The recent Dutch epidemiology study discussed above found that in younger children, the most common clinical presentation was ADEM, followed by ON, and ON with TM. The study also found that in adults, the most common presentation was ON followed by TM, followed by ON and simultaneous TM. Isolated brainstem syndromes were seen in 10% of cases at presentation. Encephalitis, brain stem involvement, and seizures can also occur in MOGAD [16, 28]. It is important to appreciate that approximately one-third of patients will develop ON, TM, and other combinations of demyelinating phenotypes that will meet the 2015 diagnostic criteria for AQP4-IgG seronegative NMOSD [6••].

Optic Neuritis

ON, defined as inflammation of the optic nerve often associated with pain with eye movements, can be seen in a variety of inflammatory conditions, but can also be isolated or idiopathic. There are several characteristics of ON that should alert the clinician to the possibility of MOGAD (Table 1). MOG-IgG positive ON tends to be more often recurrent, bilateral, and associated with optic disc edema than other causes of acute demyelinating ON. Approximately 50% of patients with MOG-IgG positive ON will develop recurrent ON. Some cases can be steroid dependent and have frequent relapses when steroids are tapered, which follows a chronic relapsing

Table 1 Typical characteristics of optic neuritis in MOG-IgG–associated disorder compared with multiple sclerosis and AQP4-IgG-positive NMOSD

Demographics and characteristics	MOG-IgG	AQP4-IgG	Multiple sclerosis
Median age	30's + children	40's	20's
Sex	Female~male	Female>>male	Female>male
Optic neuritis characteristics			
Bilateral ON	Frequent	Frequent	Infrequent
Severe vision loss at nadir	Very frequent	Very frequent	Frequent
Risk of recurrent ON	Very frequent	Very frequent	Frequent
Steroid dependent	Frequent	Rare	Rare
Risk of blindness (< 20/200)	Infrequent	Very frequent	Infrequent
MRI optic nerve enhancement			
Length and location	Long and anterior	Long and posterior	Short
Perineural enhancement	Frequent	Rare	Rare
Optic chiasm involvement	Infrequent	Frequent	Rare

inflammatory optic neuropathy (CRION)-like phenotype. Recent studies have shown that a large percentage of patients with CRION that were previously thought to be idiopathic are positive for MOG-IgG [29, 30]. About 50% of MOG-IgG positive ON have been reported to present simultaneously in both eyes [4•, 7•, 11•, 23, 31, 32]. It has also been reported that some patients with clinically unilateral ON can have subclinical atrophy in the unaffected eye, which suggests the rate of bilateral ON involvement may be even higher [33].

MOG-IgG positive ON tends to be associated with optic disc edema at presentation more commonly than other forms of ON. Optic disc edema has been reported in up to 86% of cases, which can sometimes be severe with peripapillary hemorrhages (Fig. 1) [4•, 7•, 11•, 19, 23, 31, 32]. Because of the potential to cause severe optic disc edema, patients with MOG-IgG positive bilateral ON are occasionally mistakenly diagnosed with papilledema from raised intracranial pressure, or nonarteritic anterior ischemic optic neuropathy in unilateral cases.

MOG-IgG positive ON typically causes severe vision loss at onset with a median visual acuity of count fingers at nadir. A study out of Japan found that central scotomas or complete visual field loss are present in 95% of patients with MOG-IgG positive ON [19]. Despite the severe vision loss at onset, recovery of vision is common, with only 5–14% of patients having a poor visual outcome of 20/200 or worse [6••, 7•, 22–24, 34]. By comparison, over one-third of patients with AQP4-IgG positive ON have a final visual acuity of 20/200 or worse [22, 23, 34, 35].

Other CNS Manifestations

ADEM is not commonly seen in MS or AQP4-IgG positive NMOSD; therefore, its presence suggests MOGAD, especially if accompanied by ON. Longitudinally extensive TM can be seen in MOGAD and can appear similar to AQP4-IgG positive NMOSD. However, MOG-IgG positive TM more commonly affects the conus medullaris. In addition, the T2 signal abnormality is often restricted to the grey matter, forming a characteristic "H" sign on axial images on MRI [10••, 36–38, 39•].

Cerebrospinal Fluid Characteristics

Characteristics of cerebrospinal fluid (CSF) are neither sensitive nor specific for a diagnosis of MOGAD. Analysis of the CSF can be normal or show a pleocytosis with a wide range of white blood cell counts. The differential can show neutrophil predominance accompanied by increased cytokines and chemokines. Oligoclonal bands are not typically found but can be present in rare cases [6••, 7•, 10••, 35, 40].

Magnetic Resonance Imaging Characteristics

MRI can be instrumental in distinguishing MOGAD from AQP4-IgG positive NMOSD and MS. MOG-IgG–associated demyelinating lesions often have a fluffy appearance and are more commonly located in the brainstem and adjacent to the 4th ventricle, in contrast to the ovoid lesions found adjacent to the lateral ventricles seen in MS. Unlike MS, T1 hypointense lesions are not typically seen in MOGAD [38].

In both MOG-IgG and AQP4-IgG positive ON, the enhancement of the optic nerve exceeds one half of the intraorbital optic nerve length in more than 60% of cases. MOG-IgG positive ON tends to affect the anterior orbital portion of the optic nerve while AQP4-IgG positive ON tends to have more posterior involvement and often involves the optic chiasm [7•, 31]. However, MOG-IgG positive ON can affect the optic chiasm in up to 15% of cases, and therefore, chiasmal involvement is not unique to AQP4-IgG positive ON [7•, 23]. Contrast enhancement of the optic nerve sheath and

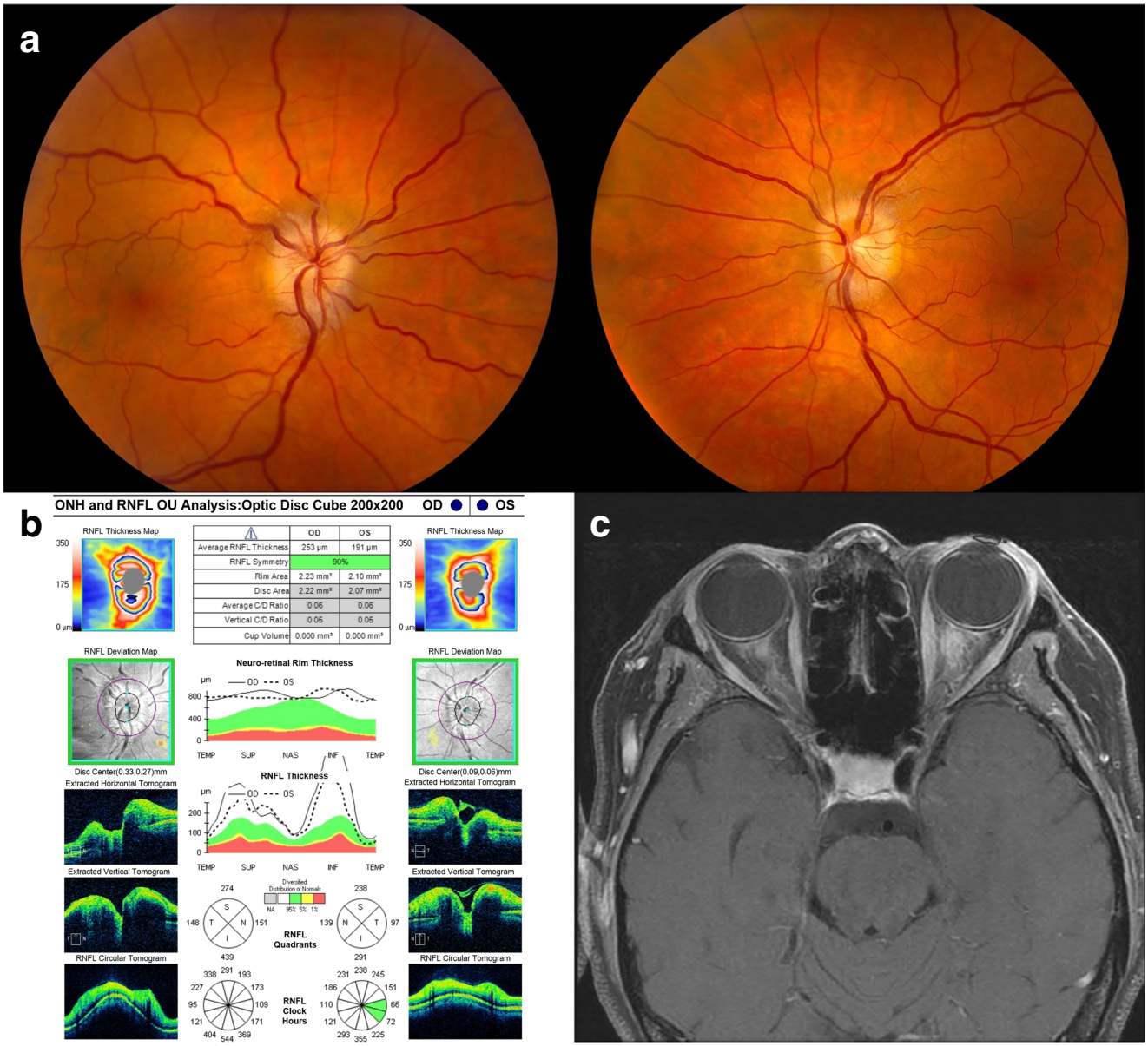

Fig. 1 51-year-old woman with bilateral MOG-IgG positive optic neuritis. **a** Fundus photographs demonstrate bilateral moderate optic disc edema. **b** Optical coherence tomography shows significant thickening of the retinal nerve fiber layer bilaterally. **c** T1-weighted magnetic resonance imaging of the orbits with contrast shows bilateral optic nerve enhancement that extends along the entire optic nerve and involves the optic nerve sheath and peribulbar fat (red arrows)

surrounding orbital fat tissue (perineural enhancement of the optic nerve), which has been reported in up to 50% of MOG-IgG positive ON, is not usually seen in MOG-IgG negative demyelinating ON [7•, 10••, 19, 25, 32, 41] and may be a radiologic signature of MOGAD (Fig. 1).

MOG-IgG Detection and Assay Recommendation

The development of live cell–based assays using MOG transfected in its native conformation has led to the ability to detect MOG-IgG more specifically, which has driven the clinical association between MOG-IgG and the clinical phenotype seen in MOGAD. Multiple studies have demonstrated that MOG-IgG is not usually present in patients with MS or AQP4-IgG positive NMOSD [28, 42]. The current recommendations for MOG-IgG testing have been established based on the current literature and published recommendations from an international expert panel [4•, 43, 44].

Similar to AQP4-IgG, testing for MOG-IgG should be on the serum. Enzyme-linked immunosorbent assays and immunoblotting are not recommended due to the lack of specificity [45•]. Cell-based assays using either flow cytometry or

immunofluorescence are preferred, in which full-length MOG is expressed on human cells. IgG-Fc or IgG1 secondary antibodies should be used for the detection of the IgG since total anti-IgG identifies all antibody subclasses and therefore is less specific. A confirmatory dilution should then be performed to help guide the clinician as to the general likelihood of a false or true positive. There may be utility in repeating testing in a MOG-IgG positive patient since transient positive antibodies have been reported to be associated with a monophasic disease course. Patients with persistently positive MOG-antibodies at 6 months or 1 year may have a higher risk of relapse [6••, 28, 46, 47]. However, patients can have persistent MOG-IgG for many years and remain monophasic [6, 16]. A recent study showed that MOG-IgG antibody titer was associated with a more severe presentation but was not predictive of the risk of relapse or clinical outcome [48].

While it could be argued that testing for AQP4-IgG should be considered for all patients with ON because of the large implications of a positive test, the same cannot be as easily said for MOG-IgG. Testing for MOG-IgG can potentially be more selective because MOG-IgG positivity may not necessarily change management (see below for discussion on treatment). MOG-IgG can therefore be reserved for patients with atypical ON (recurrent, bilateral, severe vision loss, severe disc edema, perineural enhancement on MRI) or in patients with AQP4-IgG seronegative NMOSD or demyelinating disease that is atypical for MS.

Treatment of MOG-IgG Positive Optic Neuritis

Acute Treatment

For acute treatment of MOG-IgG positive ON, 1 g per day of intravenous methylprednisolone (IVMP) for 3–5 days is often used. Patients often show very rapid and dramatic improvement in response to IVMP. A 1–2-month prednisone taper is recommended due to the risk of relapse with abrupt steroid discontinuation. A recent study suggested that earlier treatment with IVMP was associated with better visual outcomes for AQP4-IgG and MOG-IgG positive ON [49]. However, the study was retrospective and only included a small number of MOG-IgG positive ON, and therefore further studies are required to confirm these findings.

The natural history of MOG-IgG ON without treatment is unclear. A recent study found that 3 patients within the optic neuritis treatment trial (ONTT) were positive for MOG-IgG, of which 2 were randomized to low dose oral prednisone, and 1 was randomized to placebo. All 3 recovered to 20/20, which suggests that high dose IVMP may not be necessary in some instances [50]. However, given the severity of vision loss at presentation, limited information on the natural history of MOG-IgG positive ON, and the potential for some cases to be steroid dependent, acute treatment with IVMP is recommended at this time if there is no other medical contraindication.

While early plasma exchange (PLEX) is felt to improve outcomes for AQP4-IgG positive NMOSD [51–53], its utility in MOGAD remains unclear. Because MOG-IgG positive ON is likely an antibody-mediated process, it would be reasonable to add PLEX if the vision loss is severe, and there is no appreciable improvement in 1–2 weeks after IVMP treatment. However, because the outcomes are typically much better with IVMP alone, early PLEX prior to treatment with IVMP is not recommended. Intravenous immunoglobulin (IVIG) is another acute treatment modality that can be used for severe disease if patients do not respond to IVMP.

Long-term Immunotherapy

While all patients with AQP4-IgG positive NMOSD require long-term immunotherapy because of the high rate of relapse and poor recovery, the same is not true for patients with MOGAD. Because approximately 50% of patients with MOGAD will be monophasic and recovery from attacks is much better than AQP4-IgG positive demyelinating attacks, long-term immunotherapy for MOGAD is typically reserved for patients with relapsing disease or in patients with significant disability from a prior demyelinating attack.

There are no prospective trials to guide the choice of therapy for MOGAD. Prednisone is effective in preventing relapse [11], but patients often require higher doses than can be tolerated long-term. Current long-term steroid–sparing immunotherapies for MOGAD are predominantly extrapolated from therapies used in AQP4-IgG positive NMOSD. Retrospective studies have shown that rituximab, azathioprine, mycophenolate mofetil, and IVIG are all associated with a reduction in relapse rate in MOGAD-IgG–associated disorder [10, 11, 20, 54]. Similar to AQP4-IgG positive NMOSD, classic MS disease modifying agents are not effective in preventing relapse in MOGAD [10, 14, 54, 55]. It remains unclear if MS disease modifying agents will worsen MOGAD as can occur with AQP4-IgG positive NMOSD [56]; nevertheless, these should be avoided in MOGAD because of their ineffectiveness.

Therapies for MOGAD will likely diverge from AQP4-IgG positive NMOSD over time. A recent multicenter retrospective study on rituximab demonstrated a reduction of relapses in patients with MOGAD, but not as effectively as seen in AQP4-IgG positive NMOSD patients [57]. While IVIG is rarely utilized for AQP4-IgG positive NMOSD, it has been shown to be fairly effective in preventing relapses in MOGAD, especially in pediatric patients [11, 54, 58]. As the pathophysiology behind MOGAD is better elucidated, targeted therapies are expected to be developed, similar to the recent demonstration of the efficacy of eculizumab, a complement inhibitor, for AQP4-IgG positive NMOSD based on

the knowledge that AQP4-IgG acts through a complement mediated pathway [59].

Conclusions

The reliable detection of MOG-IgG with live cell–based assays has not only allowed for clarity of a unique CNS demyelinating disease entity but also creates separation among previously overlapping syndromes. Future NMOSD diagnostic criteria will certainly separate MOGAD from NMOSD, as knowledge of MOG-IgG was at its infancy at the time of the 2015 international NMOSD criteria. As a result, many cases of MOGAD currently meet the diagnostic criteria for AQP4-IgG seronegative NMOSD despite it being a unique disease process with a different pathophysiology, response to treatment and outcomes. For prompt diagnosis of MOGAD, increased focus should be paid to presentations of ON, as this is the most common initial clinical presentation. MOG-IgG–associated ON tends to be bilateral, recurrent, and often associated with severe optic disc edema and perineural enhancement of the optic nerve on MRI. The decision to initiate long-term immunotherapy for MOGAD is still evolving. Based on current knowledge, unlike MS and AQP4-IgG positive NMOSD, the treatment for MOGAD needs to be individualized based on the severity of attacks, frequency of recurrence, and risks versus benefits of therapy. Future research that prospectively studies patients with different disease severity and treatments are needed to determine the optimal therapy for MOGAD.

Compliance with Ethical Standards

Conflict of Interest Deena A. Tajfirouz, M. Tariq Bhatti, and John J. Chen each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Abbreviations AQP4, aquaporin-4; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis

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