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MOGAD, current knowledge and future trends

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MOGAD, current knowledge and future trends

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Editorial: MOGAD, current knowledge and future trends

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Editorial on the Research Topic
MOGAD, current knowledge and future trends

In the ever-evolving landscape of neuroimmunology, both basic and clinical research, one condition has captured the attention of researchers, clinicians, and patients alike: Myelin Oligodendrocyte Antibody Disease (MOGAD). This enigmatic disorder, characterized by its distinctive serum biomarker and severe central nervous system (CNS) inflammatory attacks, warrants an in-depth exploration of its current understanding and the potential trends shaping its future trajectory.

Similar to Neuromyelitis Optica Spectrum Disorder (NMOSD), MOGAD resides at the intersection of autoimmune disorders and neurology, challenging conventional notions within the realm of demyelinating diseases. Recent advancements in diagnostic tools, particularly the development of sensitive and specific tests for detecting anti-MOG antibodies, have revolutionized our ability to identify and differentiate MOGAD from other similar conditions, such as multiple sclerosis (1, 2). The presence of high titers of this serum antibody in patients with neurological disorders is now a diagnostic cornerstone (3). This heightened accuracy has expanded the spectrum of known clinical manifestations, transcending the common occurrences of optic neuritis, transverse myelitis, and ADEM-like presentations (4). Consequently, this diagnostic precision has led to the formulation of recent diagnostic criteria and, most importantly, earlier diagnoses and more targeted treatment approaches, ultimately enhancing patient outcomes.

In this Research Topic of *Frontiers in Neurology*, we called for original work on the theme of "*MOGAD, Current Knowledge and Future Trends*" In addition to original research on MOGAD. This Research Topic also called for review to collect novel approaches that may help clarify this unique condition.

Refining diagnosis, epidemiology and expanding the clinical spectrum

In this Frontiers in Neurology Research Topic, Lang et al. compared optical coherence tomography (OCT)/OCT angiography (OCTA) measures in patients with NMOSD and MOGAD, revealing that MOGAD patients exhibit reduced superficial vascular plexus density. This suggests distinct pathological processes and underlying macular structural and microvascular impairments. Li et al. described the clinical profiles and treatment responses of a cohort of 93 Chinese patients with pediatric MOGAD. Smith et al. reported excellent

agreement between fixed and live CBA for MOG antibody testing in a real-world clinical cohort of 322 serum samples. Xu et al. documented two cases of cortical encephalitis with high titers of MOG antibodies. Perez-Giraldo et al. reviewed typical and atypical features of transverse myelitis in MOGAD patients. Hor and Fujihara conducted a global review of MOGAD epidemiology, consolidating current knowledge. Vlad et al. analyzed cerebrospinal fluid parameters in 30 adult MOGAD patients and 189 adult patients with Relapsing-Remitting Multiple Sclerosis (RRMS), revealing higher mean QAlb values and a lower presence of OCBs in the MOGAD cohort.

Unraveling the underlying mechanisms

Ongoing research focuses on unraveling the intricate mechanisms driving MOGAD. Scientists are keen to dissect the immune responses involved and decipher the factors triggering antibody attacks on myelin. By doing so, they aim to uncover novel therapeutic targets and interventions. Corbali and Chitnis extensively reviewed the immunological aspects of MOGAD pathophysiology, emphasizing the activation of T cells in the periphery followed by reactivation in the subarachnoid/perivascular spaces by MOG-laden antigen-presenting cells. They also highlighted that abnormal levels of neuroinflammatory biomarkers in MOGAD suggest that most axonal damage occurs during the initial attack. Takai et al. provided a detailed analysis of lesion pathology in MOGAD, noting that perivenous complement deposition is less common than in NMOSD but is observed in myelinated fibers and on myelin degradation products within macrophages. Malli et al. reported a lower frequency of H. Pylori infection in MOGAD and MS patients compared to NMOSD patients, hypothesizing that this infection might serve as a marker of gut hygiene and the onset of autoimmunity. Trentinaglia et al. studied a cohort of 150 MOGAD patients, revealing only two cases with concomitant cancer. They also reviewed an additional 15 case reports in the literature, concluding that MOGAD is unusually associated with a paraneoplastic syndrome. Oertel et al. reviewed appropriate animal models for translational MOGAD research and the current state and prospects of translational research imaging in this disease.

While the progress in MOGAD research is promising, significant challenges remain. Variability in clinical presentations, the complex interplay of immune responses, and the necessity for long-term clinical studies and well-designed randomized-controlled treatment trials present hurdles for researchers and clinicians. MOGAD has transformed from a mysterious entity into a well-defined disorder with targeted diagnostic tools and evolving pathophysiology studies. As we gaze into the future, collaborative research efforts, cutting-edge technology, and a patient-centric approach will likely steer MOGAD toward more accurate and tailored treatments, ultimately improving patient outcomes. The journey to comprehend the complexities of this disorder may be intricate, but the pursuit of unlocking its secrets remains steadfast, driven by the potential to transform lives and redefine our understanding of autoimmune neurology.

Author contributions

SS: Writing—original draft. LP: Writing—original draft. MM: Writing—original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Retinal structural and microvascular changes in myelin oligodendrocyte glycoprotein antibody disease and neuromyelitis optica spectrum disorder: An OCT/OCTA study

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Purpose: To compare the optical coherence tomography (OCT)/OCT angiography (OCTA) measures in patients with neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody disease (MOGAD).

Methods: Twenty-one MOG, 21 NMOSD, and 22 controls were enrolled in our study. The retinal structure [retinal nerve fiber layer (RNFL) and ganglion cell–inner plexiform layer (GCIPL)] was imaged and assessed with the OCT; OCTA was used to image the macula microvasculature [superficial vascular plexus (SVP), intermediate capillary plexus (ICP), and deep capillary plexus (DCP)]. Clinical information such as disease duration, visual acuity, and frequency of optic neuritis and disability was recorded for all patients.

Results: Compared with NMOSD patients, MOGAD patients showed significantly reduced SVP density ($P = 0.023$). No significant difference ($P > 0.05$) was seen in the microvasculature and structure when NMOSD-ON was compared with MOG-ON. In NMOSD patients, EDSS, disease duration, reduced visual acuity, and frequency of ON significantly correlated ($P < 0.05$) with SVP and ICP densities; in MOGAD patients, SVP correlated with EDSS, duration, reduced visual acuity, and frequency of ON ($P < 0.05$), while DCP density correlated with disease duration, visual acuity, and frequency of ON.

Conclusions: Distinct structural and microvascular changes were identified in MOGAD patients compared with NMOSD patients suggesting that the pathological mechanisms are different in NMOSD and MOGAD. Retinal imaging *via* the SS-OCT/OCTA might have the potential to be used as a clinical tool to evaluate the clinical features associated with NMOSD and MOGAD.

KEYWORDS

neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein antibody disease, optical coherence tomography, optical coherence tomography angiography, macula microvasculature

Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein expressed on oligodendrocytes and is a minor component forming the myelin sheath in the central nervous system (1). The immune attack in MOG antibody disease (MOGAD) is associated with myelin and oligodendrocyte damage, resulting in heterogeneous clinical manifestations such as optic neuritis (ON), reduced/loss of vision, myelitis, seizures, brainstem syndromes, and encephalitis (2–4). To date, it is suggested that clinical manifestations in MOGAD differ from multiple sclerosis (MS) (5) but overlap with aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorder (NMOSD AQP4+) (6, 7); optic neuritis and acute myelitis in MOGAD have similarities with clinical manifestations of NMOSD and can only be distinguished by detecting MOG antibodies. Even though testing for MOG antibodies can help differentiate these disorders, MOG testing is time-consuming and not available in most countries; moreover, albeit testing of MOG antibodies is very precise (8), false positives can still arise due to its low prevalence worldwide even in individuals with demyelinating disorders with ON (9, 10). MOGAD and NMOSD have different pathological mechanisms and different target cell damage. Given the different clinical outcomes and treatment strategies between NMOSD and MOGAD, accurate monitoring and evaluation would facilitate optimal treatment decisions and prognosis prediction. Thus, it would be supportive to have other modalities that may help in the quick and early identification of patients with MOGAD and help differentiate it from NMOSD.

Accumulating reports (10, 11) suggested that MOGAD with ON has recurrent and wide-range optic disc edema at the beginning of the disease cascade when compared with NMOSD; these optic nerve head changes cause severe neuroaxonal and microvascular impairment in the retina. Optical coherence tomography (OCT)/OCT angiography (OCTA) can quantify the retinal structural thickness and microvascular density changes and may serve as a reliable tool to differentiate MOGAD from NMOSD.

In this observational cross-sectional study, we utilized the swept-source OCT (SS-OCT) and SS-OCTA to characterize the retinal structural and microvascular changes in NMOSD and MOGAD patients when compared with controls; we also explored the association between OCT/OCTA parameters in MOGAD and NMOSD with their disease duration, disability, and visual acuity.

Methods

This exploratory cross-sectional observational study was approved by the Institutional Review Board of West China Hospital, Sichuan, China, and all participants provided written informed consent before enrolling in our study.

Twenty-two MOGAD and 23 NMOSD patients were recruited from the Neurology Department of West China Hospital. NMOSD patients tested seropositive by cell-based assay (EUROIMMUN AG, Luebeck, Germany) as previously reported (12), and the diagnosis was based on the 2015 International Panel on NMOSD (13), while MOGAD patients tested seropositive by the cell-based assay as previously reported (14) (Figure 1A). Patients with ON less than 6 months before evaluation were excluded from our study. The inclusion criteria for MOGAD and NMOSD patients were as follows: 1) no sudden vision loss or eyeball pain occurred in the past 6 months, 2) long-term follow-up in our hospital with complete data and without a history of seizures, and 3) patients who could cooperate with our study and signed informed consent. The exclusion criteria were as follows: 1) possibly confounding neurological or ophthalmological disorders, 2) eyes with prior ocular surgery or trauma or acute optic neuritis within the preceding 6 months, 3) refractive error of ±6 D (diopters), and 4) inability to cooperate with our study. Clinical variables such as frequency of optic neuritis, visual acuity under illumination, and Expanded Disability Status Scale (EDSS) were assessed and recorded.

For comparison, 22 healthy controls with no history of neurological or neuropsychological diseases were included in our study. Participants with uncontrolled hypertension or diabetes, a history of ocular surgery, glaucoma, and other ophthalmologic diseases were also excluded from our study for all groups.

All participants underwent comprehensive visual acuity using the Snellen chart. Each participant's visual acuity for both eyes was obtained under light and later converted to a logarithm of the minimum angle of resolution (LogMAR).

SS-OCT/SS-OCTA imaging and examination

The SS-OCT/SS-OCTA tool (VG200S; SVision Imaging, Henan, China; version 2.1.016) was used to image the retinal structure and microvasculature for all participants. The specification of this OCT/OCTA tool is well documented in previous reports (15–17). Imaging of the retinal structure was performed with 18 radial B-scans positioned on the fovea. Automatic segmentation of the retinal thickness was done by the OCT tool. Our current study assessed the macular retinal nerve fiber layer (mRNFL) and ganglion cell–inner plexiform layer (GCIPL) in a 3 × 3-mm^2 area around the fovea as shown in Figure 1B. The average thicknesses (measured in μm) of the retinal structure were obtained from the OCT tool.

The OCTA images covered an area of 3 × 3 mm^2 around the fovea. The en-face angiograms of the superficial vascular complex (SVC) and deep vascular complex (DVC) were generated by the OCTA tool. The partition of the SVC and DVC slabs was set in the inner two-thirds and outer one-third border of GCIPL as shown in Figure 1B. The average percentages (%) of the microvasculature in the SVC and DVC were obtained from the OCTA tool.

The OCT/OCTA data displayed in our study followed the OSCAR-IB quality criteria (18) and APOSTEL recommendation (19).

Statistical analyses

The Shapiro–Wilk test was used to test for the normality of our data. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD), while skewed distribution was expressed as medians and interquartile ranges. Categorical variables were presented as frequencies and percentages. SS-OCT/SS-OCTA parameters among the groups were assessed using generalized

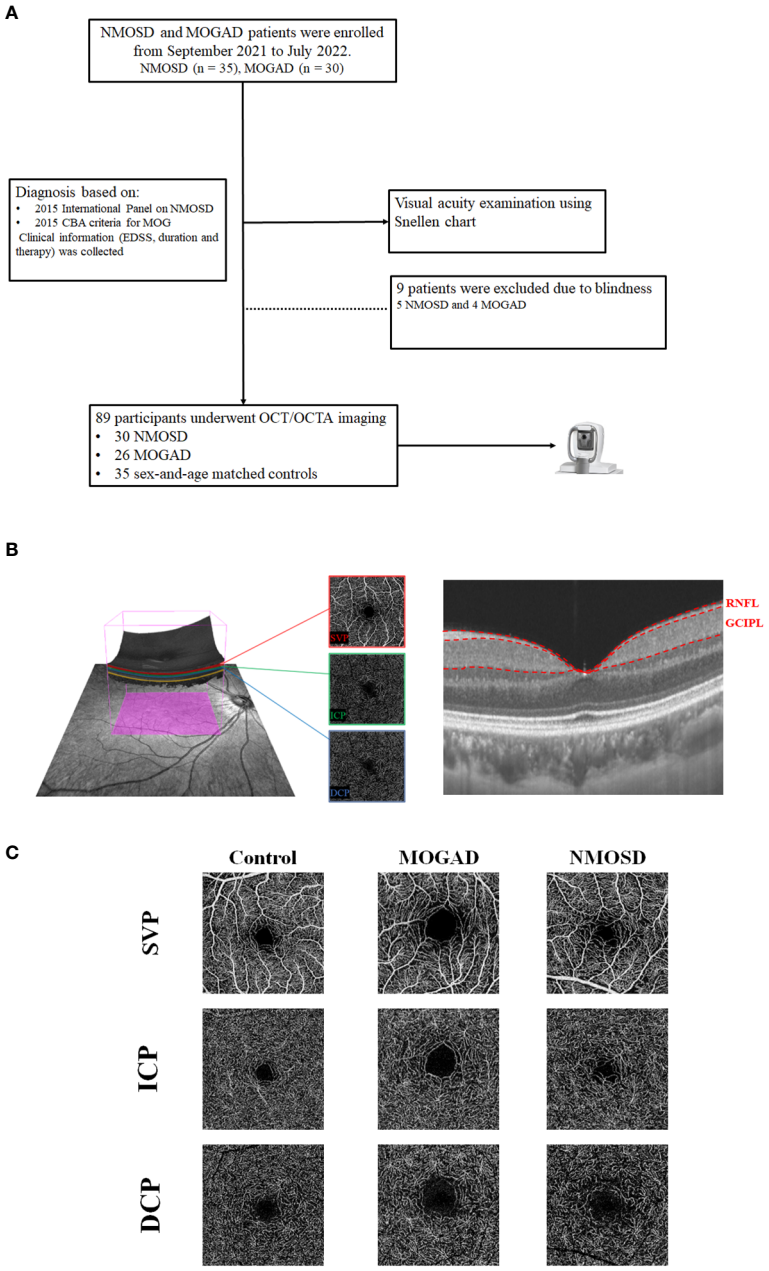

FIGURE 1
The flowchart of our participants and segmentation of OCT/OCTA images. **(A)** The flowchart of the participants in our study. **(B)** The segmentation of three macular microvascular plexuses and the retinal thickness of RNFL and GCIPL in an area of 3 × 3 mm around the fovea. SVP was defined as the microvasculature between the base of the retinal nerve fiber layer (RNFL) to the junction between the inner plexiform layer (IPL) and inner nuclear layer (INL); ICP was the microvessels between the IPL/INL junction to the INL/outer plexiform layer (OPL) junction, while DCP was the microvessels between the INL/OPL junction to 25 μm below the OPL. **(C)** The en face angiograms of our participants.

estimating equations (GEEs) while adjusting for age and gender. The association between SS-OCT/SS-OCTA parameters and the clinical features was performed with GEE while adjusting for risk factors. A comparison between SS-OCTA parameters stratified by history of ON between MOGAD and NMOSD was performed using a linear mixed model while adjusting for risk factors and intereye dependencies. All analyses were performed with SPSS (version 26, SPSS Inc., Chicago, IL, USA). *P*-values less than 0.05 were considered statistically significant. This was an exploratory study, so no adjustment for multiple comparisons was made.

Results

Our final data analyses included 40 eyes from 21 MOGAD patients (mean age = 33.67 ± 11.07 years), 42 eyes from 21 NMOSD patients (mean age = 33.76 ± 11.07 years), and 44 eyes from 22 healthy controls (mean age = 34.18 ± 10.88 years). Age and sex did not differ among the three groups ($P > 0.05$, Table 1). Thirteen MOGAD (61.9%; mean = 1 ON episode) and 11 NMOSD (52.4%; mean = 1 ON episode) patients had a history of ON. Table 1 displays the demographics and clinical information of our participants.

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TABLE 1 Demographic overview.

	HC	MOGAD	NMOSD
Participants (*N*)	22	21	21
Number of eyes (*N*)	44	40	42
Age (years, mean ± SD)	34.18 ± 10.88	33.67 ± 11.07	33.76 ± 11.07
Gender [female, *N* (%)]	17 (77.3)	12 (57.1)	18 (85.7)
EDSS (median, IQR)	–	1.0 (0 - 2.25)	1.5 (1.0 - 3.0)
Patients with a history of ON [*N* (%)]	–	13 (61.9%)	11 (52.4%)
Number of ON episodes (median, range)	–	1.0 (0 - 5)	1.0 (0 - 5)
Disease duration (years, mean ± SD)	–	2.57 ± 2.66	3.17 ± 2.60
VA (LogMAR, mean ± SD)	−0.05 ± 0.10	0.03 ± 0.10	0.18 ± 0.41
Immunotherapy			
None (%)	–	5 (23.8%)	1 (4.8%)
Prednisone (%)	–	7 (33.3%)	1 (4.8%)
Mycophenolate mofetil (%)	–	7 (33.3%)	12 (57.1%)
Azathioprine (%)	–	1 (4.8%)	2 (9.5%)
Rituximab (%)	–	1 (4.8%)	5 (23.8%)

EDSS, Expanded Disability Status Scale; VA, visual acuity; HC, healthy control; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; NMOSD, neuromyelitis optica spectrum disorder; N, number of subjects; ON, optic neuritis.

Comparison of SS-OCT/SS-OCTA measures among the groups

MOGAD and NMOSD patients showed thinner RNFL and GCIPL thicknesses ($P < 0.05$, Table 2 and Figure 2) when compared with controls; compared with NMOSD patients, MOGAD patients had thinner GCIPL thickness ($P = 0.019$, Table 2 and Figure 2).

Figure 1C shows the angiograms of our participants. Compared with controls, MOGAD patients showed reduced SVP ($P < 0.001$, Table 2 and Figure 2) and DCP ($P = 0.012$, Table 2 and Figure 2) densities. Similarly, NMOSD patients showed reduced SVP ($P < 0.001$, Table 2 and Figure 2), ICP ($P = 0.022$, Table 2 and Figure 2), and DCP ($P < 0.001$, Table 2 and Figure 2) densities and enlarged FAZ area ($P = 0.001$, Table 2 and Figure 2) when compared with controls.

MOGAD patients showed reduced SVP density ($P = 0.023$, Table 2) and thinner GCIPL thickness ($P = 0.019$, Table 2) when compared with NMOSD patients; the FAZ area was larger ($P = 0.034$) in NMOSD patients than in MOGAD patients.

Supplementary Figure 1 shows the correlation between OCT and OCTA measures in both MOGAD and NMOSD patients. Supplementary Figure 1A shows the correlation in MOGAD patients, while Supplementary Figure 1B shows the correlation in NMOSD patients.

Table 3 shows the SS-OCTA measures among the groups stratified by history of ON. Compared with controls, MOG-ON eyes showed reduced SVP ($P < 0.001$, Table 3) and ICP ($P < 0.001$, Table 3) densities and enlarged FAZ area ($P = 0.02$, Table 3), while MOG-NON eyes showed reduced SVP ($P < 0.001$, Table 3) and DCP ($P < 0.001$, Table 3) densities. MOG-ON eyes showed significantly reduced ($P < 0.05$, Table 3) SVP, ICP, and DCP densities when

TABLE 2 Comparison of OCT/OCTA parameters.

	HC	MOGAD	NMOSD	*P* (MOGAD vs. HC)	*P* (MOGAD vs. NMOSD)	*P* (NMOSD vs. HC)
FAZ, mm^2	0.273 ± 0.089	0.328 ± 0.095	0.377 ± 0.115	0.135	0.034*	0.001*
SVP, %	42.636 ± 3.195	31.705 ± 8.576	32.495 ± 8.359	<0.001*	0.023*	<0.001*
ICP, %	37.048 ± 4.288	32.376 ± 6.253	32.413 ± 6.582	0.172	0.304	0.022*
DCP, %	17.361 ± 5.091	14.911 ± 4.813	12.379 ± 4.924	0.012*	0.558	<0.001*
RNFL, μm	19.285 ± 1.039	17.206 ± 2.412	18.270 ± 3.582	<0.001*	0.057	0.017*
GCIPL, μm	74.985 ± 5.543	60.006 ± 13.880	60.087 ± 16.205	<0.001*	0.019*	0.001*

FAZ, foveal avascular zone; SVP, superficial vascular plexus; ICP, intermediate capillary plexus; DCP, deep capillary plexus; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell and inner plexiform layer; HC, healthy control; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; NMOSD, neuromyelitis optica spectrum disorder.
*P < 0.05.

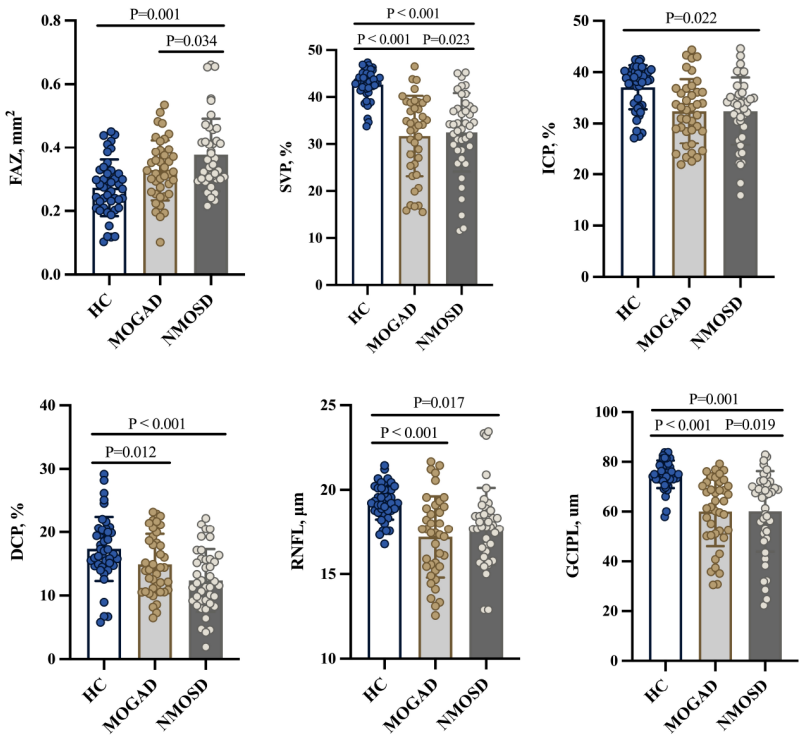

FIGURE 2
Comparison of OCT/OCTA parameters. FAZ, foveal avascular zone; SVP, superficial vascular plexus; ICP, intermediate capillary plexus; DCP, deep capillary plexus; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell and inner plexiform layer; HC, healthy control; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; NMOSD, neuromyelitis optica spectrum disorder.

compared with MOG-NON eyes. NMOSD-ON eyes and NMOSD-NON eyes showed reduced microvascular densities and thinner retinal thicknesses when compared with controls. Importantly, NMOSD-ON eyes showed an enlarged FAZ area (P = 0.036, Table 3) when compared with MOG-ON eyes; NMOSD-NON eyes showed significantly reduced DCP density (P = 0.048, Table 3) when compared with MOG-NON eyes.

Figure 3 shows the association between SS-OCT/SS-OCTA measures in MOGAD and NMOSD patients and their clinical features. RNFL thickness was significantly correlated with EDSS (P < 0.001) (Figure 3A), disease duration (P = 0.004) (Figure 3C), and frequency of ON (P = 0.001) (Figure 3G), while GCIPL correlated with reduced visual acuity (P < 0.001) (Figure 3E) and frequency of ON (P = 0.001) (Figure 3G) in MOGAD patients. GCIPL thickness in NMOSD patients significantly correlated with EDSS (P < 0.001) (Figure 3B), disease duration (P < 0.001) (Figure 3D), and frequency of ON (P < 0.001) (Figure 3H).

Supplementary Figure 2 shows the correlation between OCT/OCTA measures and clinical features in the eyes of patients with MOGAD-ON and the eyes of patients with NMOSD-ON.

TABLE 3 OCTA results in MOGAD and NMOSD patients stratified by history of ON.

	MOG-ON	MOG-NON	NMOSD-ON	NMOSD-NON	*P* MOG-ON vs. MOG-NON	*P* MOG-ON vs. HC	*P* MOG-NON vs. HC	*P* MOG-ON vs. NMOSD-ON	*P* MOG-NON vs. NMOSD-NON	*P* NMOSD-ON vs. HC	*P* NMOSD-NON vs. HC
Number of eyes	18	22	18	24							
FAZ, mm^2	0.336 ± 0.098	0.322 ± 0.095	0.420 ± 0.132	0.345 ± 0.090	0.862	0.020*	0.065	0.036*	0.829	<0.001*	0.001*
SVP, %	25.727 ± 6.996	36.597 ± 6.424	26.878 ± 8.667	36.707 ± 5.084	<0.001*	<0.001*	<0.001*	0.892	0.620	<0.001*	<0.001*
ICP, %	29.202 ± 5.817	34.972 ± 5.434	28.179 ± 7.113	35.589 ± 3.906	0.001*	<0.001*	0.495	0.054	0.626	<0.001*	0.008*
DCP, %	18.696 ± 3.892	11.814 ± 2.905	15.585 ± 5.043	9.972 ± 3.214	<0.001*	0.170	<0.001*	0.054	0.048*	0.139	<0.001*

FAZ, foveal avascular zone; SVP, superficial vascular plexus; ICP, intermediate capillary plexus; DCP, deep capillary plexus; HC, healthy control; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; NMOSD, neuromyelitis optica spectrum disorder.
*P < 0.05.

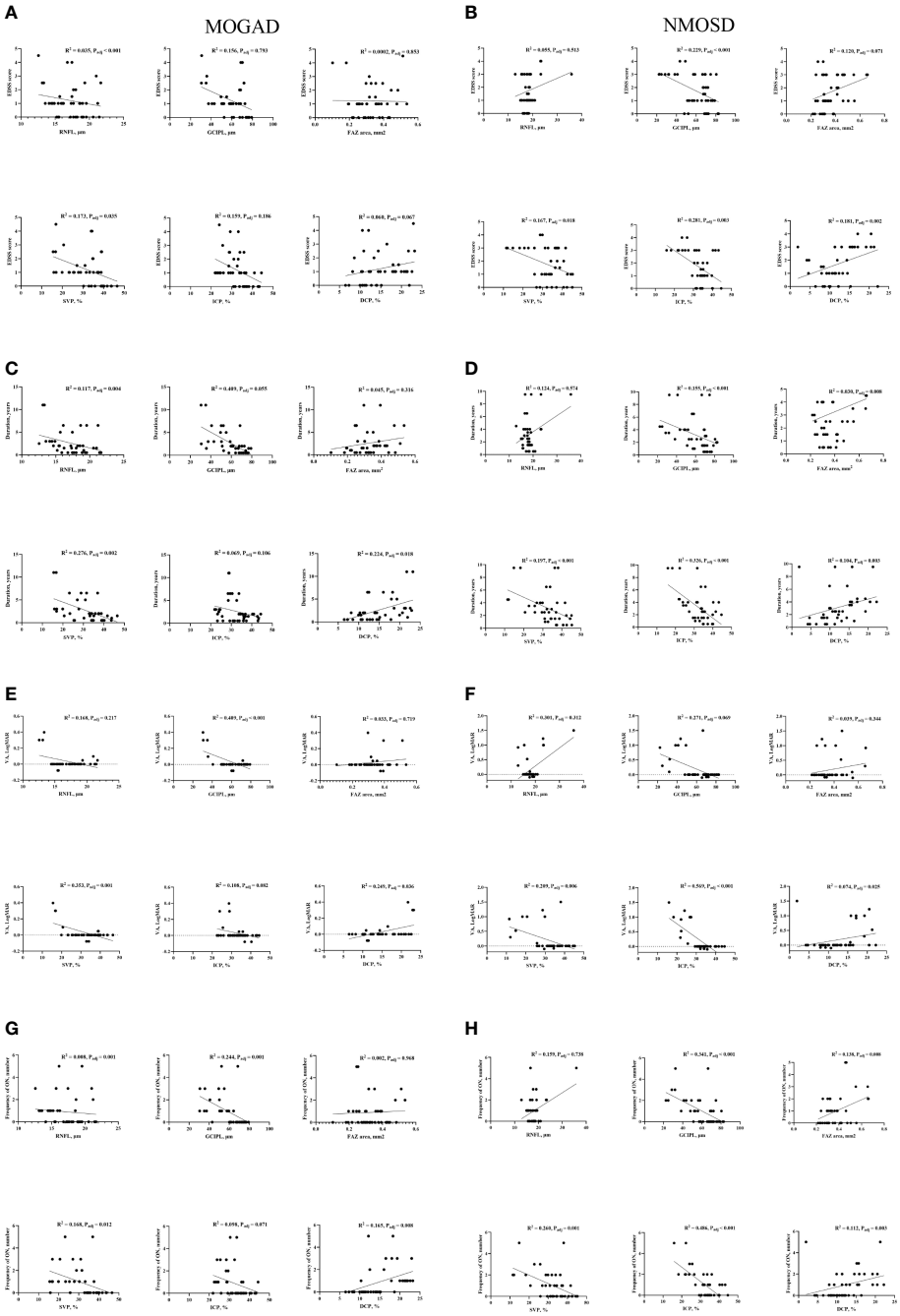

FIGURE 3
Correlation between clinical features and OCT/OCTA parameters in MOGAD and NMOSD patients. EDSS, Expanded Disability Status Scale; VA, visual acuity; FAZ, foveal avascular zone; SVP, superficial vascular plexus; ICP, intermediate capillary plexus; DCP, deep capillary plexus; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell, and inner plexiform layer; HC, healthy control; MOGAD, myelin oligodendrocyte glycoprotein antibody disease; NMOSD, neuromyelitis optica spectrum disorder. Association of retinal parameters and EDSS **(A)**, Duration **(C)**, VA **(E)** and Frequency of ON **(G)** in MOGAD patients. Association of retinal parameters and EDSS **(B)**, Duration **(D)**, VA **(F)** and Frequency of ON **(H)** in NMOSD patients

Supplementary Figures 2A, B show the correlation between OCT/OCTA measures with visual acuity (measured in LogMAR) and frequency of ON in MOGAD-ON, while Supplementary Figures 2C, D show the correlation between OCT/OCTA measures with visual acuity (measured in LogMAR) and frequency of ON in NMOSD-ON.

In MOGAD patients, EDSS correlated (P = 0.035) with SVP, disease duration correlated with SVP (P = 0.002) and DCP (P = 0.018), and reduced visual acuity and frequency of ON significantly correlated ($P < 0.05$) with SVP and DCP, respectively, as shown in Figure 3. In NMOSD patients, EDSS, disease duration, reduced visual acuity, and frequency of ON correlated ($P < 0.05$, Figure 3) with retinal microvascular changes in the three plexuses.

Discussion

Our current report showed retinal thinning and reduced microvascular densities in NMOSD and MOGAD patients

compared with controls which are congruent with previous OCT/OCTA reports (20–23) indicating that neurodegeneration and microvascular impairment occur during the disease cascade. Our study showed thinner GCIPL thickness and reduced SVP density in MOGAD patients compared with NMOSD patients. In MOGAD patients, SVP density correlated with EDSS, disease duration, frequency of ON, and visual acuity, while DCP correlated with disease duration, visual acuity, and frequency of ON; RNFL thickness in MOGAD patients correlated with EDSS, disease duration, and frequency of ON. In NMOSD patients, SVP and ICP densities correlated with EDSS, disease duration, visual acuity, and frequency of ON, while GCIPL thickness correlated with EDSS, disease duration, and frequency of ON.

The novel findings in our study were significantly thinner GCIPL thickness and reduced SVP density in MOGAD compared with NMOSD. The SVP, located in the GCIPL, is responsible for the metabolic supply of neurons in these layers (24), where reduced thicknesses have been reported in both MOGAD and NMOSD (11, 22, 23). With regard to retinal neurodegeneration, it is suggested that retinal thinning in NMOSD is as severe as in MOGAD (25); similarly, a recent report showed that microvascular impairment in MOGAD and NMOSD was similar (23). However, a recent study showed that retinal thinning was more severe in MOGAD than in NMOSD which is congruent with our structural report (26). Our findings of thinner GCIPL thickness and reduced SVP density in MOGAD compared with NMOSD patients included patients with a history of optic neuritis. ON in MOGAD is often bilateral and characterized by retinal edema (27). During retinal edema, it suggested that GCIPL experiences severe neurodegeneration during the ensuing months (22, 27, 28). This structural thinning amasses with each added ON episode which occurs recurrently in MOGAD (25, 29). Although a single episode of ON does not lead to a devastating impairment (26), the highly frequent ON attacks accrue with GCIPL thinning. This is analogous to NMOSD, which is characterized by less frequent ON episodes. Due to the highly recurrent ON attacks in MOGAD, GCIPL thinning and reduced SVP density compared with NMOSD may reflect severe neurodegeneration and microvascular impairment.

In line with previous reports (30, 31), we found enlarged FAZ area as a unique characteristic in NMOSD patients but not in MOGAD patients irrespective of ON. We also showed that NMOSD eyes without ON showed reduced microvascular densities compared with controls. This development may be linked with the pathology of AQP4 antibodies since the parafoveal areas of the retina comprise the highest density of astrocytic Muller cells, which express AQP4 and have shown to be the targets of anti-AQP4 antibodies in NMOSD (32, 33). Enlarged FAZ area and reduced microvascular densities in NMOSD eyes without ON suggest that some activities occur during the subclinical phase in NMOSD and may initiate relapse-independent disease progression.

Concerning microvascular changes after ON, our current study did not find any significant difference between NMOSD-ON and MOG-ON patients which is in line with a previous report (23). It is suggested that ON in MOGAD is acute and severe which is similar to ON in NMOSD; however, the long-term prognosis is better in MOGAD compared with NMOSD. Thus, it is plausible to suggest that microvascular impairment after ON in MOGAD patients may be as severe as in NMOSD patients.

Although NMOSD and MOGAD patients presented with similar clinical features, dissimilar clinical associations were shown in MOGAD and NMOSD which may suggest different pathological processes and underlying macular structural and microvascular impairment. In NMOSD, reduced macula microvascular densities and GCIPL thinning significantly correlated with clinical disability, implying that the potential force of underlying neurodegeneration and microvascular impairment may lead to clinical disability measured by EDSS (34). Moreover, reduced macula microvascular densities and GCIPL thinning significantly correlated with disease duration and frequency of ON, while reduced microvascular densities significantly correlated with reduced visual acuity, which is consistent with OCT/OCTA reports (34–36). These findings were different from those in MOGAD, where clinical correlations were most identified with the SVP and DCP of the macula suggesting the pathological mechanisms are different in NMOSD and MOGAD. The differential association pattern demonstrated indicates that retinal imaging markers might have the potential to be used as a clinical tool to evaluate the clinical features associated with NMOSD and MOGAD.

We would like to acknowledge some limitations in our study. The exploratory and cross-sectional study design of the study limits the understanding of the results concerning the cause and effect. Secondly, our study focused on quantitative retinal microvasculature, while other central nervous system tissues such as the brain, spinal cord, and optic nerve were not evaluated; further studies with a comprehensive assessment of the central nervous system in both NMOSD and especially MOGAD are needed. Thirdly, the clinical relevance of macula microvasculature was assessed with clinical disability (EDSS), visual acuity, disease duration, and frequency of optic neuritis; further study is warranted to assess its value to cognition and treatment response. The data from our study were obtained from our hospital cohort which limits the generalizability of the data to the general population. There was a possibility of a selection bias caused by the exclusion of individuals with retinal abnormalities (high myopia) and unmatched gender among groups. This may have led to an underestimation of the observed correlations.

In conclusion, we showed that GCIPL thinning and reduced SVP density are severe in MOGAD than in NMOSD. We also showed that microvascular changes after ON in NMOSD may be as severe as in MOGAD. Importantly, we showed that enlarged FAZ area and reduced microvascular densities occur as unique features during the subclinical phase of NMOSD but not during MOGAD. Taken together, our study suggests that the OCT/OCTA tool can help facilitate the differentiation of MOGAD from NMOSD in settings with overlapping clinical features.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of West China Hospital, Sichuan, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL: methodology, data curation, formal analysis, writing—original draft, and writing—review and editing. WK: methodology, data curation, formal analysis, writing—original draft, and writing—review and editing. LK: investigation and data curation. ZS: investigation and formal analysis. XW: investigation and formal analysis. QD: investigation and data curation. BW: conceptualization, methodology, validation, writing—review and editing, and supervision. HZ: conceptualization, methodology, validation, funding acquisition, writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1029124/full#supplementary-material

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Pathophysiology of myelin oligodendrocyte glycoprotein antibody disease

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Myelin Oligodendrocyte Glycoprotein Antibody Disease (MOGAD) is a spectrum of diseases, including optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, and cerebral cortical encephalitis. In addition to distinct clinical, radiological, and immunological features, the infectious prodrome is more commonly reported in MOGAD (37–70%) than NMOSD (15–35%). Interestingly, pediatric MOGAD is not more aggressive than adult-onset MOGAD, unlike in multiple sclerosis (MS), where annualized relapse rates are three times higher in pediatric-onset MS. MOGAD pathophysiology is driven by acute attacks during which T cells and MOG antibodies cross blood brain barrier (BBB). MOGAD lesions show a perivenous confluent pattern around the small veins, lacking the radiological central vein sign. Initial activation of T cells in the periphery is followed by reactivation in the subarachnoid/perivascular spaces by MOG-laden antigen-presenting cells and inflammatory CSF milieu, which enables T cells to infiltrate CNS parenchyma. CD4+ T cells, unlike CD8+ T cells in MS, are the dominant T cell type found in lesion histology. Granulocytes, macrophages/microglia, and activated complement are also found in the lesions, which could contribute to demyelination during acute relapses. MOG antibodies potentially contribute to pathology by opsonizing MOG, complement activation, and antibody-dependent cellular cytotoxicity. Stimulation of peripheral MOG-specific B cells through TLR stimulation or T follicular helper cells might help differentiate MOG antibody-producing plasma cells in the peripheral blood. Neuroinflammatory biomarkers (such as MBP, sNFL, GFAP, Tau) in MOGAD support that most axonal damage happens in the initial attack, whereas relapses are associated with increased myelin damage.

KEYWORDS

MOGAD, T cells, MOG (myelin oligodendrocyte glycoprotein), blood brain barrier (BBB), MOG-IgG, autoantibodies, pathophysiology-contemporary knowledge

Introduction

MOG is a transmembrane protein found on the outer surface of the central nervous system myelin and a marker of mature oligodendrocytes (1, 2). It constitutes only a small portion of the myelin (0.05%), and its possible roles include cell adhesion, microtubule stability, and receptor function (1, 3, 4).

High titers of autoantibodies targeting MOG are identified in various demyelinating diseases, including optic neuritis, transverse myelitis, acute disseminated encephalomyelitis (ADEM), and cerebral cortical encephalitis. These are now recognized as a spectrum of diseases associated with MOG antibodies, MOGAD (5). Despite heterogeneous presentation and clinical overlap between MOGAD, multiple sclerosis (MS), and neuromyelitis optica

spectrum disease (AQP4-IgG+, NMOSD), distinctive radiologic, pathological, lab, and clinical features of MOGAD have been identified (Table 1), and most recently an international MOGAD diagnostical criteria has been proposed (63).

Autoimmunity in MOGAD starts at the periphery by activation of T cells and production of autoantibodies and eventually transfer of these immune mediators into the CNS (5, 38). How humoral immunity and cellular immunity cooperate in MOGAD pathogenesis is an intriguing subject. This review will highlight major distinctive clinical, radiological, and histopathological features of MOGAD and summarize how different immune compartments contribute disease pathogenesis. For this purpose, we will use evidence from human and animal studies such as MOG-induced experimental autoimmune encephalomyelitis (EAE) models, as some of these models closely resemble MOGAD compared to MS due to relapsing and remitting course (vs. progressive disease) and MOG as the autoimmune trigger (64–66).

Distinctive features of MOGAD

Distinctive clinical, radiological, and histopathological features and laboratory findings of MOGAD are summarized below (Table 1).

Clinical findings

MOGAD most commonly presents as bilateral optic neuritis, transverse myelitis, ADEM, or, less commonly, cerebral cortical encephalitis. Brainstem demyelination could also occur in MOGAD; however, area postrema syndrome or internuclear ophthalmoplegia is associated with NMOSD or MS, respectively (5, 67).

The monophasic course is more common in MOGAD (40–50%), and the remaining half of the MOGAD cases experience a relapsing course, which is associated with persistent high titers of MOG-IgG (15, 16). In contrast, most NMOSD patients (90%) have a relapsing course (6). In MS, most patients first experience a relapsing-remitting phase (90%), half of which develop secondary progressive disease (17). Progression in MOGAD or NMOSD is relapse dependent; however, progression independent of relapse activity is well-established with MS (20, 21).

Pediatric MOGAD is not more aggressive than adult-onset MOGAD. The overall annualized relapse rate (ARR) in MOGAD, excluding the first attack, is 0.23 in pediatric and 0.35 in adult MOGAD patients (5). This is different from MS, where pediatric MS patients display a more inflammatory phenotype and therefore have higher ARR than adult-onset MS patients, with an ARR of 1.13 in pediatric-onset vs. 0.40 in adult-onset MS (18).

An infectious prodrome (at least once during the disease course) is commonly reported with MOGAD, varying from 37 to 70% (7–10). MOG-IgG+ optic neuritis patients had 37% and 67% preceding infection in two series (3/8 and 6/9) (7, 8). In MOG-IgG+ ADEM patients preceding infection was present in 70% (12/17, including three patients with vaccinations) (9). Jarius et al. reported an infectious prodrome in 40% (15/37) of MOGAD patients, which included mostly optic neuritis or myelitis patients but also some ADEM or cerebellitis cases (10). In NMOSD, the infectious prodrome is reported in 15–35% (6, 11, 12). Earlier studies with multiple sclerosis showed that 27–48% of all MS relapses were associated with infections if patients followed longitudinally (13, 14).

Radiological findings

Optic neuritis is bilateral and lengthier (compared to MS), and the anterior optic pathway is more commonly involved (vs. posterior in NMOSD) in MOGAD (Figure 1) (22, 23, 68). Optic nerve head swelling and perineural sheath enhancement are other typical features of MOGAD, indicating increased blood—optic nerve barrier breakdown (22, 68).

Spinal cord involvement is seen as longitudinal extensive transverse myelitis (LETM) in MOGAD and NMOSD (22, 24, 25). Multiple spinal cord lesions are frequent in MOGAD and MS (both >60%) (24). Gray matter restricted (H sign) or central cord involvement is a typical appearance of MOGAD lesions on axial MRI (24, 25). On the other hand, shorter and dorsal/lateral spinal cord lesions are more typical of MS (25). Conus medullaris involvement is seen in MOGAD or MS (22).

Typical brain involvement in MOGAD is ADEM-like fluffy lesions (25). The number of supratentorial lesions is fewer in MOGAD and NMOSD than in MS (22). High AQP4 expressing regions such as diencephalon (hypothalamus and thalamus) or dorsal midbrain (area postrema) are commonly affected in NMOSD (26). In MS, more supratentorial lesions are typically found in cortical, juxtacortical, or periventricular areas (27).

Contrast (Gadolinium) enhancement is a measure of BBB breakdown commonly found in MOGAD lesions. Within 4 weeks of the symptom onset, ON has enhancing pattern in most MOGAD (94%), NMO (100%) and MS (75%) patients (23). Myelitis, on the other hand, has an enhancement rate of 27–70% of MOGAD patients and around 75% of NMO or MS patients within 4 weeks of the symptom onset (24, 28).

Leptomeningeal enhancement, an indicator of leptomeningeal inflammation, was less frequently reported in MOGAD than in MS (29–31, 69). Gadde et al. reported the presence of LME in 33% (7/21) of a pediatric cohort. In comparison, Cobo-Calvo et al. reported in 6% (3/49) of their adult cohort (29, 30). Further studies are needed to determine if LME prevalence is higher (using 7T MRI) and if LME presence is associated with relapse activity in MOGAD. In MS, LME presence is reported as 79% with 7T MRI, while with lower field (1.5 or 3T MRI), prevalence is 21% (31). In NMOSD, it is also infrequent (6%) (31).

Central vein sign, defined as lesions with central vein identifiable by MRI, is commonly seen in MS (>40%), while their frequency is much lower in MOGAD (≈10%) or NMOSD (<10%) (22).

Slowly expanding lesions are not present in MOGAD, while present in MS (25, 32). Paramagnetic rim lesions (PRL) associated

TABLE 1 Distinctive features of MOGAD.

	MOGAD	NMOSD	MS
Clinical findings			
Presentation at onset	Optic neuritis	Optic neuritis	Optic neuritis
	Transverse myelitis	Transverse myelitis	Transverse myelitis
	Brainstem demyelination	Brainstem demyelination	Brainstem demyelination
	ADEM	Area postrema syndrome	Internuclear ophthalmoplegia
	Cerebral cortical encephalitis		
Infectious Prodrome (6–14)	37.5–70% (at least once)	15–35% (at least once)	27–48% (of all relapses)
Course (6, 15–17)	Monophasic (40–50%)	Monophasic (10%)	Relapsing Remitting (90%)
	Relapsing (50–55%)	Relapsing (90%)	Secondary Progressive (half of relapsing remitting patients develop secondary progressive disease)
			Primary Progressive/Relapsing Progressive (10%)
Annualized Relapse Rate (excluding the first attack) (5, 18, 19) [Overall: treated and untreated]	0.23 (pediatric, overall) 0.35 (adult, overall)	0.91 (adult, untreated) 0.18 (adult, treated)	1.13 (pediatric, overall) 0.40 (adult, overall)
Progression independent of relapse activity (PIRA) (20, 21)	No	No	Yes
Radiology			
Optic nerve (22, 23)	Bilateral	Bilateral	Unilateral
	Lengthier	Lengthier	Shorter
	Anterior optic pathway involvement	Posterior optic pathway involvement	
	ON head swelling		
	Perineural sheath enhancement		
Spinal cord (22, 24, 25)	LETM	LETM	Shorter lesions
	Multiple lesions	Central cord	Multiple lesions
	H-sign (gray matter restricted lesion)		Dorsal/lateral lesions
	Central cord		Conus medullaris
	Conus medullaris		
Brain (22, 26, 27)	Less supratentorial lesions	Less supratentorial lesions	More supratentorial lesions
	ADEM-like lesions	Diencephalon (i.e., hypothalamus and thalamus)	Cortical/juxtacortical lesions
		Dorsal midbrain (i.e., area postrema)	
Contrast Enhancement rate within 4 weeks of the attack (Indication of BBB damage) (23, 24, 28)	ON (94%) Myelitis (26–70%)	ON (100%) Myelitis (78%)	ON (75%) Myelitis (75%)
Leptomeningeal enhancement (29–31)	33% (Pediatric)	6%	21% (1.5 or 3 T field)
	6% (Adult)		79% (7 T field)
Central Vein sign (average CVS+ rate) (22)	≈10%	<10%	>40%
Slowly expanding lesions (25, 32)	No	Not studied	Yes
Paramagnetic rim lesions (32–34)	Not studied	Rare	Yes (due to iron laden microglia/macrophage)
Lab			
Serum ab test (35–37)	High Mog-IgG titer	High AQP4-IgG titer	Low Mog-IgG titer possible
Longitudinal ab testing (38–40)	Some patients become seronegative	Rarely becomes seronegative	NA

(Continued)

TABLE 1 (Continued)

	MOGAD	NMOSD	MS
Oligoclonal bands (30, 41–46)	5–13%	10–16%	95%
Increased Qalb rate (% higher than the age normal; indication of Blood-CSF barrier damage) (10, 45–48)	32–35% (all patients)	ON (15%) myelitis (64%)	25% (all patients)
CSF pleocytosis (during acute attack) (42, 45, 47)	Optic neuritis: 34% Myelitis: 85% Brain/Brainstem: 60%	Optic neuritis: 24% Myelitis: 65%	50%
Pathology			
White matter lesions (49)	Perivenous confluent around small veins	Perivenous confluent/focal	Focal lesions around large veins
	Deep white matter	High AQP4 expressing regions (hypothalamus, area postrema), but also supratentorial	Periventricular
	Chronic active lesions absent		Chronic active and slowly expanding lesions
	Iron rim lesions absent		Iron rim lesions present
Cortical lesions (50–54)	Perivenous confluent intracortical demyelination	No cortical demyelination	Band-like subpial demyelination underneath the meningeal inflammation
		Neuronal loss in cortical layers II-IV	Ectopic meningeal lymphoid follicles
Dominant T cell type (50, 55–57)	CD4	Increased activated CD4 T cells (OX40+) reported	CD8
Activated complement deposition (49, 50, 58)	Present	Present	Present
Astrocytes (49, 50, 58–61)	Relative sparing	Pronounced loss	Activated and contribute to inflammation
	Normal GFAP (CSF)	Increased GFAP (CSF)	Increased GFAP (CSF and serum) in progressive MS
Oligodendrocytes (49, 50, 58, 62)	Variable loss	Variable loss	Variable loss (Type III demyelination)
	Preserved progenitor cells		

with iron-laden microglia and macrophages, are present in MS; however, they have not been investigated in MOGAD (32–34).

Histopathological findings

White matter lesions in MOGAD exhibit a confluent pattern around small veins, while in MS, focal lesions form around larger veins detectable by MRI (central vein sign) (50). Chronic active or slowly expanding lesions and iron rim lesions are absent in MOGAD while present in MS (50).

Cortical lesions in MOGAD also have perivenous confluent patterns and intracortical demyelination (50). In MS, subpial demyelination underneath the meningeal inflammation is common (51, 52). There are also ectopic lymphoid follicles found in MS, which are important aspect of chronic and progressive inflammation. In NMOSD, there is no cortical demyelination, while there is a neuronal loss in cortical layers II-IV (53, 54).

The dominant T cell type is CD4 in MOGAD, whereas CD8 is in MS (50, 55, 56). Astrocytes are spared in MOGAD, while pronouncedly decreased in NMOSD, and activated and proinflammatory in MS (49, 50, 58). Differential astrocyte involvement in these three diseases is also supported by GFAP levels in serum and CSF (59–61). GFAP-CSF levels are increased in the NMOSD patients but not in MOGAD compared to HC (60). In MS, progressive patients have higher GFAP both in serum and CSF compared to RRMS and HC (59). Conversely, oligodendrocytes are variably lost in all three diseases, while in MOGAD, progenitor cells are preserved as they do not yet express MOG (49, 50, 58, 62).

Laboratory findings

Oligoclonal band presence is low in MOGAD (5–13%), similar to NMOSD (10–16%) (30, 41–43, 45, 46). In MS, however, OCB positivity is found in the majority of the cases (95%) (44).

CSF pleocytosis in MOGAD is quite common during relapses and even higher in the spinal cord (85%) or brain/brainstem (60%) involvement compared to optic neuritis (34%) (42). In NMOSD, a similar trend is present, with CSF pleocytosis in 24% of optic neuritis and 65% of myelitis (45). In MS, 50% of the patients have pleocytosis during relapses (47).

Increased albumin CSF/serum ratio (QAlb), a measure of blood-CSF barrier dysfunction, is also a feature of MOGAD. In two separate studies, almost one-third of MOGAD patients (32 and 32.4%) had increased albumin CSF/serum ratio (QAlb) (10, 46). This ratio was even higher in patients with a history of a spinal cord, brain, or brainstem involvement (10/21; 47.6%) (10). Elevated

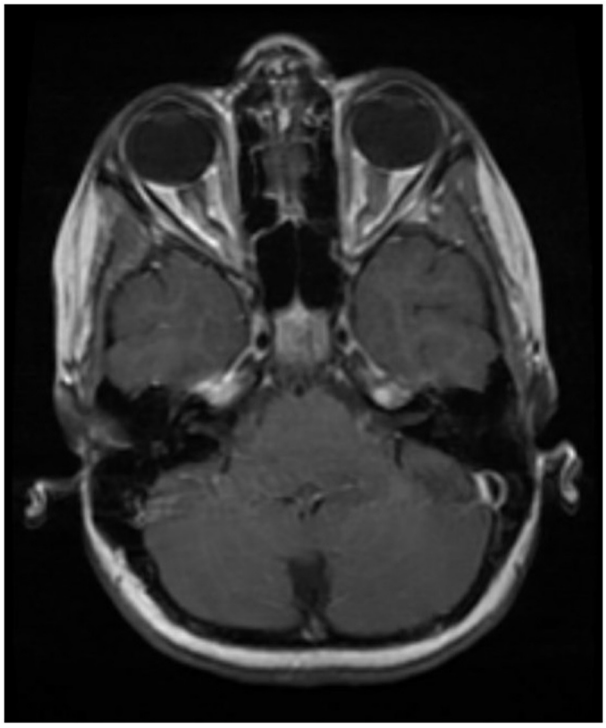

FIGURE 1
Typical optic nerve involvement in MOGAD. Bilateral and longer lesions involving anterior parts of the optic nerve.

QAlb values are reported at a similar frequency with MS (29.5%, $n = 606$) (70). On the other hand, QAlb levels are reported variably for NMOSD (increased in up to 50–80% of patients), which implies implying blood-CSF barrier dysfunction in MOGAD may not be as severe as it is in NMOSD (45, 46, 71).

CSF cytokine/chemokine profile of MOGAD shows increased proinflammatory cytokines (Figure 2, created with BioRender.com), including Th1 (TNF-α, IFNγ), Th2 (IL13), Th17 (IL6, IL8, G-CSF, GM-CSF), Treg (IL10) and B cell (CXCL12, APRIL, BAFF, CXCL13, CCL19) related and other (IL-1ra, MCP-1, MIP-1a) cytokines/chemokines (72, 73).

Autoimmune etiology of MOGAD

The prevailing concept for autoimmunity in MOGAD is the outside-in model, where autoantibodies and activated immune cells in the peripheral blood cross the blood-brain barrier at the time of attack/relapse (Figure 2) (41, 74).

The central tolerance toward MOG may not be well developed in the thymus, preventing the elimination of MOG reactive T cells by negative selection (1, 75, 76). In the thymus, the expression of a self-antigen in the epithelial cells eliminates lymphocytes with a strong affinity to a self-antigen (central tolerance) and also allows some self-reactive T cells to develop into Tregs (peripheral tolerance) (77). MOG expression in the human thymus is variably reported. In two studies analyzing the thymus, MOG RNA was not detected, while in another study, MOG was detected in isolated medullary thymic epithelial cells (78–81). There is no protein-level study assessing MOG expression in human thymic tissue. Even if MOG expression in the thymus is low or present, central tolerance is not a perfect process, and peripheral tolerance mechanisms are needed to suppress self-reactive lymphocytes. Peripheral tolerance mechanisms include anergy or apoptosis of self-reactive T cells through the absence of costimulatory molecules or the presence of inhibitory molecules (such as PD1 or CTLA) and regulatory T cells (77). From MOG-induced EAE models and human MOGAD, we know that tolerance against MOG could be disrupted.

MOG reactive T cells, present due to a compromised tolerance against MOG, could be activated upon antigen-specific or non-specifically through mechanisms such as MOG peptide presentation, molecular mimicry, or bystander activation. MOG peptides could be present in the periphery, such as in cervical lymph nodes draining CNS, or rarely in a tumor expression MOG (82, 83). MOG antibodies, on the other hand, could facilitate recognition of trace amounts of MOG present in the periphery leading to T cell activation (84). Infections could cause bystander activation and molecular mimicry. Milk protein Butyrophilin and small Hepatitis B surface antigen are reported to have cross-immunoreactivity with MOG; however, pathophysiological consequences of these molecular mimicries have not been established (85, 86).

Immunogenetics

Genetic risk factors associated with the autoimmune etiology of MOGAD are not widely explored. HLA genotyping studies did not identify a significant allele in two Dutch and UK cohorts (87, 88). However, a study in the Chinese Han cohort observed that DQB1*05:02 and DRB1*16:02 alleles and DQB1*05:02-DRB1*16:02 haplotype were more frequent in pediatric-onset MOGAD patients and DQB1*05:02-DRB1*16:02 haplotype was associated with higher initial EDSS and relapse risk (89).

Role of infections in MOGAD

An infectious prodrome is commonly reported in MOGAD patients (37.5 to 70%) (7–10). An infectious prodrome could stimulate the underlying autoimmune processes by bystander activation, molecular mimicry, and epitope spreading. Infections could also disrupt peripheral tolerance by increasing costimulatory molecules and MHC-II expression on antigen-presenting cells (APCs) (90). This would lead to increased avidity of the interaction between APCs and self-reactive CD4+ T cells, which would otherwise go to anergy or apoptosis due to weak T cell stimulation.

Bystander activation of self-reactive B and T cells is one mechanism that could explain infectious prodrome commonly preceding attacks. In fact, pro-inflammatory cytokines that increase during infections, such as IL6 and TNFα, are also found to increase in CSF of MOGAD patients (38, 72, 73). In addition, Toll-Like receptor (TLR) activation caused by viruses could convert MOG-specific B cells into MOG-ab secreting plasmablasts (91). Separately, infections could directly or indirectly affect BBB as well (92, 93).

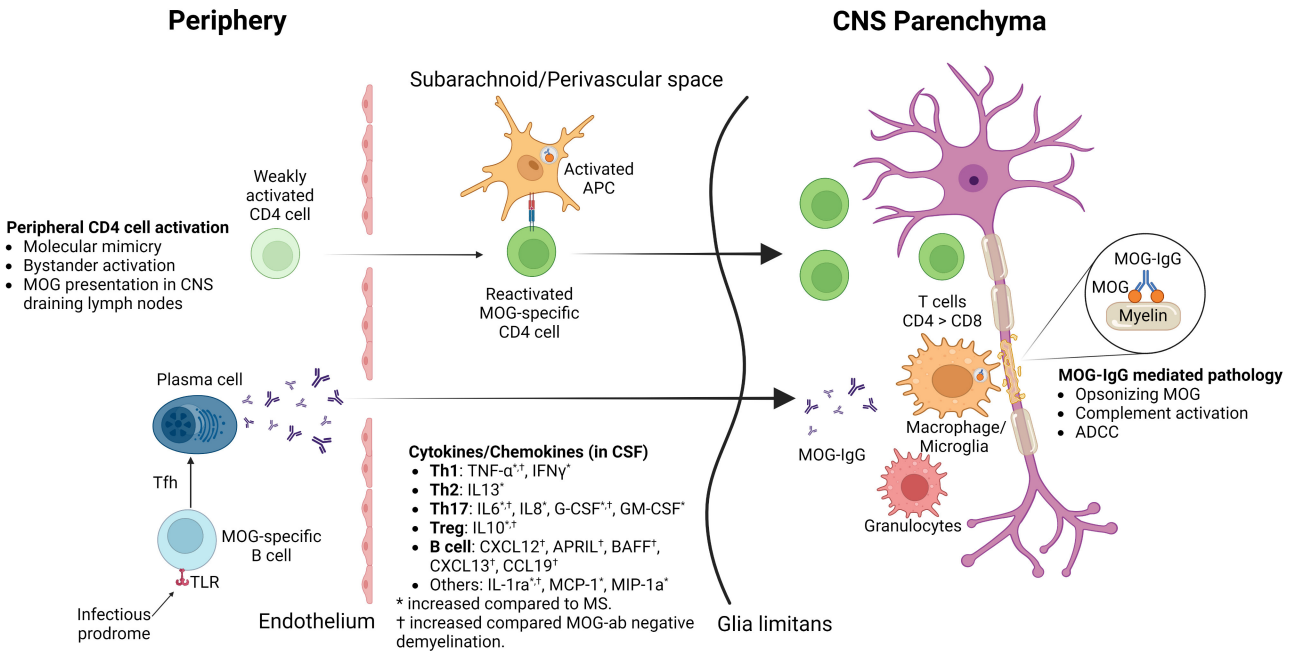

FIGURE 2
Pathophysiological actors in MOGAD.

Since the COVID-19 breakout, multiple case studies reported COVID-19 infection preceding MOGAD onset (94, 95). The median time between COVID-19 to MOGAD diagnosis was 6 days (range: −7 to 45 days), while in a few cases, MOGAD diagnosis preceded or was concomitant with COVID-19 (94, 95). Further studies will show if the MOGAD incidence rate has increased after the pandemic.

Anti-MOG IgG

The serum level of MOG IgG is an essential diagnostic and clinical biomarker. There is no consensus cut-off value for a diagnostic titer, which changes from center to center (35). Autoantibodies detected in MOGAD patients are of IgG1 type (96). MOG IgM levels do not correlate with anti-MOG IgG levels and could provide false positive results (96, 97). Persistent MOG-IgG positivity is associated with increased relapse risk (9). In monophasic MOGAD, MOG-IgG titers decrease over time, whereas in relapsing MOGAD, MOG-IgG titers tend to stay high (98).

Paired serum and CSF MOG-IgG positivity is found in more than half (56%) of the MOGAD patients (99). Some MOGAD patients are MOG-IgG seronegative and CSF positive, and CSF-restricted MOG-IgG may not always coexist with OCB positivity or elevated IgG index in the CSF (71). Therefore, in a strong clinical context (such as seronegative NMOSD or ADEM), CSF testing could help with MOGAD diagnosis (99, 100). Furthermore, CSF MOG-IgG positivity is associated with worse outcomes (99).

Detection of MOG-IgG antibodies in the serum by a live cell-based assay is the gold standard for diagnosis (35). Patient serum samples are incubated with live HEK293 cells expressing full-length MOG protein on their membrane, followed by secondary staining with anti-human IgG (H+L or Fc) or IgG1 (Fc) secondary antibodies. The analysis is done either by immune fluorescence microscopy or flow cytometry (35, 36).

Antibody response to MOG could be monoclonal or polyclonal. Mayer et al. tested the human MOG IgG binding pattern for seven different mutant human MOG proteins and mouse MOG proteins (101). They found that half of the patients showed decreased binding only to P42S (Proline to Serine) mutant, whereas about a third of the patients showed decreased binding to multiple mutants. These results indicated that an epitope containing P42 (proline at position 42) is the primary target of MOG IgG in half of the patients, and many patients have a polyclonal antibody response. Interestingly, immunoreactive epitopes are temporally stable, and there is no evidence of intramolecular epitope spreading (96, 101).

Pathogenicity of patient-derived purified MOG-IgGs was shown by Spadaro et al. by intrathecally injecting human MOG IgGs in an adoptive transfer EAE model (induced by MBP or MOG-specific T cells transferred to Lewis rats) (102). In this experiment MOG-antibodies were not pathogenic alone, and provided a second hit when interacted with T cells. When coupled with MBP-specific T cells, which are alone encephalitogenic and disrupt BBB, MOG abs mediated MS type II demyelination, characterized by complement (C9neo) and immunoglobulin deposition. On the other hand, when coupled with MOG-specific T cells, which do not induce clinical disease by themselves, MOG abs enhanced T cell recruitment and activation.

The source of the MOG abs in the CNS is mostly peripheral, although sometimes intrathecal production might be possible (41, 71, 74, 100). Through an impaired BBB (provided by activated T cells, infections, coexisting autoantibodies etc.), these MOG antibodies could enter the perivascular spaces and CNS, where they could contribute to disease pathology.

Suggested mechanisms for MOG antibody pathogenicity include opsonization of MOG, complement activation, antibody-dependent cellular cytotoxicity (ADCC), and anti-MOG ab-induced intracellular signaling cascade (3, 50, 84, 103, 104).

MOG-IgG opsonizes MOG and could activate myeloid antigen-presenting cells (APC) through Fc receptor binding (84, 104). These activated APCs can further stimulate MOG-specific T cells in the periphery or in perivascular spaces in the CNS (56).

The role of complement activation in MOGAD is still debated. IgG1 is a complement-fixing subtype, and there is evidence of C9neo deposition in the MOGAD histopathology (50). Furthermore, oligodendrocytes express relatively less surface complement regulatory proteins such as CR1, MCP, and HRF, making them more vulnerable to complement activation (106). In a multinational cohort study, serum-activated complement proteins (C3a, C5a, and Bb) were elevated in MOGAD patients compared to control groups (107). However, there was no correlation between activated complement protein levels in the serum and the clinical presentation (relapsing vs. monophasic or ADEM vs. ON vs. TM). On the other hand, complement activation in MOGAD is to a lesser extent, compared to AQP4 NMO (108). This might be because MOG-IgG has a bivalent binding pattern (both Fab subunits should bind to MOG), whereas AQP4-IgG has a monovalent binding pattern, which activates complement more efficiently (103, 108–111). This also indicates that anti-complement therapy may not be as successful as in NMO for MOGAD.

Another pathogenic mechanism is ADCC. Brilot et al. showed that MOG IgG binding to MOG induces Natural Killer cell-mediated killing of MOG-expressing cells *in vitro* (104).

MOG abs also have a direct downstream effect on oligodendrocytes (3). When Mog ab binds alone, it activates MAPK and AKT survival pathways and increases intracellular calcium levels, whereas cross-linking of the MOG abs leads to the activation of stress-related pathways and reduced cytoskeletal integrity.

B cells

B cells are part of the disease pathogenesis through the production of MOG antibodies; however, there is much to discover about their contribution to the MOGAD. For example, anti-CD20 therapy is relatively ineffective in most patients. In a large cohort, rituximab decreased the relapse rate by 37%, and only 33% of patients remained relapse-free after 2 years (105). Failure of B cell depleting therapy suggests alternative pathogenic mechanisms in these patients, which could be used for enhanced T cell activation and MOG ab production. Serum MOG ab levels and circulating MOG-specific B cells did not correlate in MOGAD patients, raising the possibility of different MOG ab sources (for example, CD20-plasma cells) (91).

CXCR4 expression is increased in CD19+ B cells in PBMCs from MOGAD patients (112). Interestingly, CXCL12 (also called stromal cell-derived factor 1), a ligand of CXCR4, is also found increased in the CSF (compared to MOG ab- demyelination) and serum (compared to MS) of MOGAD patients (73, 113). As, CXCL12/CXCR4 axis is related with chemotaxis, increased CXCL12 could contribute immune cell infiltration (such as T, B, and monocytes) in the MOGAD (114). B cells are present in the lesions of MOGAD, although fewer than T cells (56). However, the source of MOG-IgGs is presumably the periphery, except in some patients with intrathecal production or CSF-restricted positivity (41, 50, 56, 71, 74, 100). Therefore, it is not certain if B cells cross BBB during MOGAD relapses and contribute to lesion formation within the CNS.

Altered regulatory B cells in MOGAD are reported in a study (115). Decreased Breg/Bmem ratio and decreased IL10+ CD19+ cell frequency are accompanied by increased circulating follicular T helper cells in MOGAD (115).

T cells

T cells play a key role in MOGAD pathogenesis. First, MOG abs are IgG1 phenotype, so follicular T helper cells are essential for MOG-specific B cell class switching (96). Second, MOG abs are not pathogenic alone unless they are coupled with MOG-specific or encephalitogenic T cells (102). CD4+ T cells are the dominant inflammatory cell type in the lesions and have an essential role in disrupting BBB and creating a proinflammatory environment (50, 116).

MOG-specific T cells are first activated peripherally (90). Due to inadequate tolerance toward MOG, MOG-specific T cells could be present in the blood. Infections, molecular mimicry, and MOG peptide presentation could facilitate the activation of self-reactive T cells. Then, peripherally activated CD4+ T cells cross BBB and are reactivated by the MOG-laden APCs in the perivascular or subarachnoid spaces (56). This reactivation is followed by endothelial and microglial activation, allowing more T cells and autoantibodies to enter the perivascular space (90, 116).

The strength of T cell reactivation and chemokines in the CNS can facilitate parenchymal infiltration of the CD4+ T cells (90, 117, 118). Anti-MOG abs help APCs (such as macrophages) to present native MOG protein to T effector cells and enhance the reactivation of effector T cells in the CNS (84, 119). T cells could be reactive to different epitopes of MOG protein. Most immunogenic MOG epitopes were previously determined in EAE models and tested MS patients (120, 121). These include p35–55, p119–130, p181–195, and p186–200. The following study tested nine different MOG peptides (p1–20, p35–55, p64–80, p81–96, p99–107, p119–130, p181–195, p186–200, and p205–214) in MOGAD, AQP4+ NMO, MS, and HC, but didn't find a difference of MOG-specific T cells between any groups based on CFSE assay (122). This could be explained by the lack of central tolerance and, therefore, the presence of MOG reactive T cells even in HC. Another

possibility is that native full MOG protein is required for an optimal T-cell response.

Th17 responses are higher in MOGAD patients. Our lab used different MOG peptides for *in vitro* stimulation and showed MOGAD patients had more IL17+ and IL17+IFNγ+ (double positive) central memory cells than healthy controls (123). When relapse and remission MOGAD samples were compared, there was an increased proportion of IL17+, IFNγ+, and IL17+IFNγ+ CMCs after stimulation with several individual MOG peptides in MOGAD patients at the time of relapse (123). Later, Horellou et al. stimulated PBMCs with recombinant full-length MOG protein (rhMOG) and observed increased IL17+ CD4 T cells in non-relapsing (monophasic) MOGAD patients upon rhMOG stimulation, but not in relapsing MOGAD or MS (124).

Tregs play an important role in peripheral immune tolerance. Horellou et al. reported an increased CD4+ Foxp3+ Treg population in the non-relapsing MOGAD group and decreased CD45RA-Foxp3+ Treg population in MOGAD relapsing group upon rhMOG stimulation (124). They hypothesized that this opposite response to MOG stimulation could contribute to the relapse mechanism. Besides, we don't know if Tregs are functional in MOGAD; however, inflammatory milieu (high IL6 and TNF) in MOGAD could render Tregs ineffective with suppressing (72, 113, 125).

Innate immune cells

Macrophage (CD68+) and granulocyte (hematoxylin-eosin) infiltration is reported in MOGAD lesions, especially in the perivascular demyelinating areas (50, 56). The presence of phagocytic macrophages indicates active demyelination, and MOG-laden macrophages could further activate T cells in the perivascular spaces (56).

IL-1β and IL-12p70, monocyte or dendritic cell-related cytokines, are increased in the serum of MOGAD patients (126). IL-1β levels were highest in the acute stage and lower in the chronic phase, indicating monocyte/macrophages play a role in the acute demyelinating stage (126). IL-1β also affects the permeability of endothelial cells *in vitro* human BBB model (127).

In a recent study of three patients (1 MOGAD, 1 RRMS, and 1 Healthy control), single-cell RNA sequencing of PBMCs revealed changes in monocyte signature in MOGAD compared to RRMS or HC, however, a larger, age and sex-matched cohort is needed to confirm these findings (112).

The increased neutrophil-to-lymphocyte ratio (NLR) in serum is also reported in MOGAD, with relapse samples having higher NLR values than the remission sample (128). This biomarker requires caution as many confounding factors, such as hospitalization and steroid treatment, could affect NLR.

Coexisting antibodies

Epitope spreading is not established in MOGAD, however, coexisting antibodies have been investigated. Kunchok et al. tested 17 neuronal IgGs in the CSF and serum of pediatric and adult MOGAD patients and found NMDA-R-IgG is the most frequent coexisting autoantibody (4% in children and 7% in adults) (129). On the other hand, anti-Aqp4 IgG and anti-MOG IgG rarely coexist (0.06%) (130).

Serum-IgG from demyelinating animal models or patients could also affect BBB permeability by affecting pericyte function and lymphocyte adhesion molecule (LAM) expression on endothelial cells (131, 132). Interestingly, anti-GRP78 antibodies were reported to be commonly present in acute MOGAD patients (10/15, 67%) and caused BBB dysfunction through increased LAM expression in endothelial cells and NF-κB activation (133).

In summary (Figure 2), MOGAD pathophysiology is driven by acute attacks during which T cells and MOG antibodies cross BBB. Initial activation of T cells in the periphery is followed by reactivation in the subarachnoid/perivascular spaces by MOG-laden APCs and inflammatory CSF milieu, which enables T cells to infiltrate CNS parenchyma. CD4 T cells, unlike CD8 in MS, are the dominant T cell type found in lesion histology. Granulocytes, macrophages/microglia, and activated complement are also found in the lesions, which could contribute to demyelination during acute relapses. MOG antibodies potentially contribute to pathology by opsonizing MOG, complement activation, and antibody-dependent cellular cytotoxicity. Stimulation of peripheral MOG-specific B cells through TLR stimulation or T follicular helper cells might help B cells differentiate into MOG antibody-producing plasma cells in the peripheral blood.

Lesion topography in MOGAD

Different clinical presentations and lesion distribution seen in MOGAD is an intriguing topic. What is the difference between MOG-IgG-related optic neuritis, transverse myelitis, and tumefactive lesions in ADEM?

Higher antibody levels in serum can favor spinal cord involvement against the optic nerve. Jarius et al. reported that MOG antibody titers are higher during relapses compared to remission, and relapses involving myelitis have higher titers of MOG antibodies compared to isolated optic neuritis (48).

Expression levels of MOG protein across different parts of the CNS could contribute to differential lesion involvement. For example, Bettelli et al. reported that 2D2 TCR transgenic mice, which have MOG-specific T cell receptors, developed spontaneous autoimmune optic neuritis but not spinal cord lesions, which they associated with higher MOG expression in the optic nerve compared to the spinal cord (134). Comparative expression of human MOG protein in optic nerve and CNS has not been reported, although MOG expression in different parts of the human brain and spinal cord has been variably reported in the human protein atlas (80, 135). Consequently, we do not know if the most common lesion location (optic nerve in adults, brain in children) relates to MOG expression level in those tissues.

The Th17:Th1 ratio could affect lesion topography. PBMCs from MS patients were stimulated with MOG or MBP proteins, and higher Th17:Th1 upon MOG (recombinant human) stimulation was associated with spinal cord involvement (136). Interestingly, epitope-specific T cell functional avidity help determine Th17:Th1

ratio in MOG peptide-induced EAE model (C3HeB/Fej mice, p35–55, p79–90, p97–114 MOG peptides) (137). So, maybe also in MOGAD, different epitope/TCR reactivity in T helper cells brings differential Th17:Th1 balance, affecting the lesion topography.

The quantitative relationship between inflammatory T cells and autoimmune antibodies could explain the size and structure difference of lesions in MOGAD (50, 138). Lassmann et al. tested this hypothesis with encephalitogenic T cells (MBP-specific) and MOG antibodies in an EAE model. Higher numbers of T cells in the presence of MOG abs induced an ADEM-like phenotype with ubiquitous perivenous demyelination all over the brain stem and spinal cord and partly in the brain. In contrast, low T cell and high MOG ab titer induced focal demyelinating plaques like in MS.

Biomarkers and therapeutic mechanisms

Potential biomarkers investigated with MOGAD are listed below (Table 2). First, MOG-IgG is both a diagnostical and prognosis biomarker. High titers are needed for MOGAD diagnosis, and seronegative conversion is associated with decreased relapse risk (9). Furthermore, relapsing MOGAD patients have higher MOG-IgG titer at remission compared to monophasic MOGAD (139). Treatments such as IVIG, Plasmapheresis, or FcRn blockers target pathogenic antibodies in the blood, including MOG-IgG. IVIG has been used commonly for maintenance treatment in MOGAD, and potential therapeutic mechanisms include increasing clearance of pathogenic antibodies by saturating neonatal FcR (FcRN) and blockade of activating FcγRs (144). Similarly, anti-FcRn antibodies also increase the pathogenic ab clearance, and currently, rozanolixizumab, an anti-FcRn agent, is in phase 3 clinical trial for relapse prevention in MOGAD (NCT05063162).

Serum NfL (sNfL) level is a biomarker for axonal damage and correlates with relapse activity in MS. A recent study evaluated longitudinal sNfL values from 18 MOGAD patients and found that median sNfL levels at the onset are higher compared to age-matched HC (140). Most follow-up sNfL values stayed stable or decreased over time, including relapse serum samples of 6 patients. In the following study, sNFL levels were not different between relapse and remission MOGAD samples (141). This observation supports that significant axonal damage happens in the first clinical attack (30, 140).

Increased MBP (CSF) and Tau levels (serum) in MOGAD suggest that there is myelin and oligodendrocyte damage (60, 141). Increased Tau levels in the relapse, but not sNFL, may support that the source of Tau could be damaged oligodendrocyte processes, not axons (141).

Serum GFAP levels are stable during relapses in MOGAD (141). This finding is compatible with the spared astrocytes seen in the biopsy. In NMOSD, astrocyte damage is pronounced and serum GFAP levels are increased during relapses (141). In MS, increased GFAP is seen with progressive disease (145).

IL6 and TNFα levels are increased during relapses in the CSF of MOGAD patients (43, 44). Recently, increased serum IL6 levels are also reported in MOGAD (113). Increased IL6 is associated with Th17 differentiation through IL6-STAT3 pathway and impaired BBB (142). Recently, a multinational study showed that IL6 receptor blockade with tocilizumab is therapeutically effective and safe in MOGAD and NMOSD (146). Increased TNFα, on the other hand, could also affect BBB permeability through

TABLE 2 Biomarkers investigated with MOGAD.

Potential biomarkers		MOGAD disease activity	Significance/implications	Therapeutic mechanism
MOG-IgG titer (9, 98, 139)	Serum	High titers required for diagnosis	Seronegative conversion indicates decreased relapse risk	FcRn blockers, IVIG, Plasmapheresis
NfL (140, 141)	Serum	Increased mostly in the first attack, then stay stable throughout the course	Significant axonal damage happens mostly in the first attack	
MBP (60)	CSF	Increased	Marker of demyelination	
GFAP (60, 141)	Serum	Stay stable during relapses	Spared astrocytes	
Tau (141)	Serum	Increased during relapses	Synthesized in axons and oligodendrocytes	
IL6 (72, 73, 113, 142)	CSF, serum	Increased in the CSF during relapses	Increased STAT3 activation could cause increased Th17	IL6 receptor blockers
			Impair BBB	
TNFα (42, 43, 143)	CSF	Increased in the CSF during relapses	May affect BBB through increased cell adhesion molecule expression (such as ICAM-1 and VCAM-1)	
A20/TNFAIP3 (123)	Serum	Decreased in the serum during relapses (individual level)	Increased NFKB activation	Steroids (increase)
	Intracellular		Steroid increase A20 expression in T cells	
N/L ratio blood (128)	Blood	Increased ratio during relapses	Could help differentiating relapse from pseudo-relapse	

leukocyte adhesion molecule expression such as ICAM-1 and VCAM-1 (143). Although, steroids may decrease TNFα synthesis, we do not have information about targeted therapies such as TNF receptor blocking, while few cases in the literature are diagnosed with MOGAD while on anti-TNF treatment due to preexisting other autoimmune diseases (147, 148).

We recently reported that A20, a negative regulator of the NF-κB pathway, is decreased in the serum during relapses on an individual level (123). Interestingly, steroids increase A20 expression in CD4 T cells. As well known, MOGAD patients are quite steroid-responsive, and it is difficult to taper steroids following relapses (149). In addition to inhibiting the NF-κB pathway through A20, steroids improve BBB and decrease activation of T cells, thereby minimizing the migration of lymphocytes into the brain (150–152).

NLR is increased in MOGAD patients during relapse, supporting high inflammatory activity in the periphery (128). However, this biomarker should be utilized carefully as factors such as hospitalization and steroid treatment affect NLR.

Micro RNAs (miRNAs) have not been fully explored in MOGAD. Only, a study measured miR-17, miR-18a, miR-20a, and miR-92a-1 in PBMCs (12 MOGAD, 12 HC) *via* qPCR and found them increased in MOGAD (153). In the EAE model, miRNA-17 increased Th17 and miRNA-20a decreased Treg fraction (153, 154). Further miRNA screening studies (serum or PBMCs) are needed to confirm these miRNAs and identify other miRNAs.

Developing a peripheral immune tolerance against MOG is a promising therapeutic method. For example, intradermal MOG vaccination increased MOG-specific Tregs and improved clinical outcomes in the macaque EAE model (rhMOG induced) (155). More recently, Ugur Sahin et al. used an mRNA vaccine to induce tolerance in a mouse EAE model (C57BL/6 mice, MOG p35-55 induced) (156). This mRNA vaccine provided a self-antigen presentation in a non-inflammatory context, expanded MOG-specific Tregs, and increased expression of inhibitory molecules such as PD-1 and CTLA4. Furthermore, when the mRNA vaccine was administered on days 7 and 10 after immunization with MOG p35–55, the development of EAE was prevented, and administration after the EAE onset alleviated the symptoms.

Discussion

Frequent infectious prodrome and high IL6/IL17 associated cytokine-chemokine signature are important components of MOGAD (113). Within this inflammatory milieu in the peripheral blood, MOG-specific T cells, especially CD4+, are activated through bystander activation, molecular mimicry, or maybe MOG peptide presentation in CNS-draining lymph nodes. Peripherally activated T cells further open blood-brain barrier through reactivation in the perivascular spaces, allowing autoantibodies, complement, and more immune cells to enter to perivascular spaces and CNS (90, 116). In addition to CD4+ T cells, granulocytes, macrophages/microglia, and activated complement are also found in the lesions contributing to demyelination (50, 56).

In addition to being diagnostical and prognostic biomarker, MOG antibodies potentially contribute to pathology by opsonizing MOG, complement activation, and antibody-dependent cellular cytotoxicity. MOG antibodies enhance T cell-mediated inflammation in the CNS, however, MOG antibodies alone are not pathogenic (102). MOG-IgG is detected in the CSF of more than half of the MOGAD patients and associated with worse outcomes compared to CSF negative MOGAD patients (99). Since MOG antibodies require BBB dysfunction to enter CNS, a trigger involving T cell activation and BBB dysfunction is important for the onset.

BBB and blood-CSF barrier dysfunction in MOGAD is evidenced by contrast enhancing lesions and increased albumin quotient (32%) (10, 46). Increased pro-inflammatory cytokines (such as IL6, TNFα, IL-1β, MCP-1) could also contribute to BBB dysfunction (72, 73, 113). Available treatments such as plasmapheresis, IVIG (or FcRn blockers), steroids, and IL6 receptor blockers may affect BBB directly or indirectly through decreasing inflammatory cytokines and coexisting autoantibodies in the plasma.

Neuroinflammatory biomarkers (such as MBP, sNFL, GFAP, Tau) in MOGAD support that most axonal damage happens in the initial attack, as evidenced by increased sNFL (140, 141). Demyelination associated with myelin and oligodendrocyte damage is evidenced by increased MBP (CSF) and Tau levels (serum, during relapse) [51, 135].

Understanding the autoimmune etiology of MOGAD will help us to identify biomarkers, predict prognosis, and find targeted therapies. For example, therapeutic mechanisms targeting IL6, MOG-IgG (FcRn blocking or IVIG), or improving peripheral tolerance (Treg-inducing MOG-vaccine) are new avenues that will benefit our patients.

Author contributions

The first draft of the manuscript was written by OC. All authors commented on previous versions of the manuscript, contributed to the manuscript conception and design, read, and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Helicobacter pylori infection may influence prevalence and disease course in myelin oligodendrocyte glycoprotein antibody associated disorder (MOGAD) similar to MS but not AQP4-IgG associated NMOSD

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Background: *Helicobacter pylori* (*Hp*) persists after colonizing the gut in childhood, and potentially regulates host immune system through this process. Earlier studies have shown that *Hp* infection in childhood, may protect against MS in later life. Such an association was not seen with AQP4-IgG positive NMOSD, while the association with MOGAD is unclear.

Objective: To evaluate frequency of *Hp IgG* among patients with MOGAD, MS, NMOSD and matched controls and its effect on disease course. To ascertain whether childhood socio economic factors were linked to prevalence of *Hp* infection.

Methods: In all, 99 patients diagnosed to have MOGAD, 99 AQP4 IgG+ NMOSD, 254MS and 243 matched controls were included. Patient demographics, diagnosis, age at disease onset, duration and the last recorded expanded disability status scale (EDSS) were obtained from our records. Socioeconomic and educational status was queried using a previously validated questionnaire. Serum *Hp*IgG was detected using ELISA kits (Vircell, Spain).

Result: Frequency of *Hp* IgG was significantly lower among MOGAD (28.3% vs 44%, p-0.007) and MS (21.2% vs 44%, p-0.0001) but not AQP4-IgG+ NMOSD patients (42.4% vs 44%, p-0.78) when compared to controls. Frequency of *Hp* IgG in MOGAD & MS patients combined (MOGAD-MS) was significantly lower than those with NMOSD (23.2% vs 42.4%, p- 0.0001). Seropositive patients with MOGAD- MS were older (p-0.001. OR -1.04, 95% CI- 1.01- 1.06) and had longer disease duration (p- 0.04, OR- 1.04, 95% CI- 1.002- 1.08) at time of testing. Educational status was lower among parents/caregivers of this study cohort (p-0.001, OR -2.34, 95% CI- 1.48-3.69) who were *Hp* IgG+.

Conclusions: In developing countries *Hp* infection may be a significant environmental factor related to autoimmune demyelinating CNS disease. Our preliminary data suggests that *Hp* may exert a differential influence - a largely protective role for MS-MOGAD but not NMOSD and may influence disease onset and course. This differential response maybe related to immuno-pathological similarities between MOGAD and MS in contrast to NMOSD. Our study further underscores the role of *Hp* as a surrogate marker for poor gut hygiene in childhood and its association with later onset of autoimmune diseases.

KEYWORDS

Helicobacter pylori, environmental factor, MS, MOGAD, NMOSD

Introduction

Traditionally recognized as a human pathogen, *Helicobacter pylori (Hp)*is a gram-negative microaerophilic bacterium that colonizes the human gut in early childhood and persists most often for life (1). Infection may be acquired through oral-oral or faecal- oral transmission. Improving hygienic conditions and socio economic status has reduced *Hp* status in developed/industrialised nations. This declining trend was noted to be associated with an increase in autoimmune disorders in the developed world (2, 3) and supports the "hygiene hypothesis". The latter refers to the inverse relationship between infection and atopy that was first proposed by Strachan (4) in 1989. He observed an increased frequency of allergic rhinitis and atopic dermatitis among first born children who were less likely to have been exposed to infection compared to younger siblings. The term "hygiene hypothesis" coined in 2000 (5), laid emphasis on the broader environmental infection burden that showed a negative correlation between overall infection frequency and a substantial increase in frequency of allergic and autoimmune diseases, observed in industrialized countries. A variety of pathogens, parasites and commensal microorganism have been observed to protect against different autoimmune conditions and includes *Hp* (6).

Helicobacter pylori infection in childhood possibly contributes to the development of the immune system and may be protective against later onset of some autoimmune diseases such as atopy, allergy and MS. Despite high prevalence in the developing world, < 10% develop a chronic inflammatory state which leads to symptomatic gastroduodenal disease later in the life of the human host (7). This phase of *hp* infection is also associated with extra-gastric diseases including certain autoimmune disorders such as rheumatoid arthritis, inflammatory bowel disease (8) and NMOSD (9, 10). Several studies have reported the protective role of *Hp* in MS, including from Japan (9, 10,) Iran (11), India (12) and Australia (13). There were two studies that failed to show this protective effect, one of which had included patients with opticospinal MS along with conventional MS (14). The other study had a poorly designed control arm (15, 16). Recently 2 meta analysis which included several new studies also concurred with the protective role of *hp* in MS (17, 18). As early as 2007, there were reports of a higher frequency of *Hp* among opticospinal form of MS (which in all probability was NMOSD) when compared to conventional MS patients (9, 14) This was confirmed by one of the authors (14) in a later study that incorporated AQP4-IgG assay that showed an association with NMOSD but not MS.

Myelin oligodendrocyte glycoprotein antibody associated disorders (MOGAD) have been recently discovered. Antibodies targeting MOG which is a surface expressed protein in myelin results in demyelination similar to MS (19) with which it also shares pathological similarity (20). The association of *Hp* with MOGAD has not been reported before. The present study explores the frequency of *Hp* in all three primary autoimmune demyelinating CNS disorders in a developing country where there is high *Hp* seroprevalence, to determine its possible association.

Materials and methods

Four hundred and fifty two patients, which included all 99 myelin oligodendrocyte glycoprotein antibody associated disorder (MOGAD) (21), all 99 aquaporin-4 antibody positive (AQP4 IgG+) NMOSD (22) and 254 consecutive patients with MS (23) from the Mangalore demyelinating disease registry [MANDDIR]were selected. Two hundred and forty three healthy volunteers matched by age and gender were included as controls for this study. Patient demographics, diagnosis, age at disease onset, duration and the last recorded expanded disability status scale (EDSS) was obtained from our data base. Socioeconomic and educational status (24) was queried using a previously validated questionnaire (12). Testing for serum *Hp* IgG was done using Vircell (Granada, Spain) ELISA kits as per manufacturer's instructions. Antibody index was determined (by dividing optical density values of samples by optical density for cut-off control samples, multiplied by 10). Antibody index was positive if >11, equivocal if between 9 -11 and negative if < 9. All equivocal results were retested and if found to remain equivocal reported as negative for *Hp* IgG. All patients were tested for both AQP4 IgG (25) and MOG IgG using "in house" cell based assays. This study was

approved by the institutional ethics committee and patients and healthy volunteers signed an informed consent form.

Statistics

Categorical variables were expressed in percentages and continuous variables as mean and standard deviations. Patients and controls were stratified by *Hp*serology. Frequency of *Hp* in different subtypes of demyelinating disorders were compared with matched controls and then amongst each sub group using Chisquare test. Univariate analysis was performed on following variables namely age at onset,disease duration, gender, EDSS, socio economic and educational state and area of living.Independent variables that showed a p value of ≤ 0.20 were included in the multivariate analysis. A p value < 0.05 was taken to be significant. Strength of association was expressed as odds ratios (OR) and 95% confidence intervals (CI). Analysis was performed on SPSS statistical software program (IBM, USA).

Results

Clinical and Demographic features are listed in Table 1. Patients in the MS group were predominantly of the relapsing remitting (RR). The non MS group comprised of equal number of AQP4IgG + NMOSD and MOGAD patients. Patients were predominantly female among MS and NMOSD patients. All patients had comparable age and disease duration at time of *Hp* serology testing.

Frequency of Hp IgG serology

Helicobacter pylori antibody frequency was significantly low in MOGAD (28.3% vs 44% p- 0.007) and MS patients (21.2% vs 44%, p- 0.0001) when compared to matched controls. Comparison of NMOSD patients did not show a difference from controls (42.4% vs 44% p=0.78).Seroprevalence of *Hp* was similar between MS and MOGAD (p- 0.16) while it was significantly different for both subtypes when compared to NMOSD (Supplementary Table 1).

Hp serological prevalence and disease association

For determining association with potential disease modifying variables, MOGAD and MS patients were combined together (MOGAD-MS) and analysed after stratification based on *Hp* serology. In univariate analysis (Supplementary Table 2), age at disease onset was significantly higher in seropositive patients (p-0.001, OR- 1.03, 95% CI -1.01-1.05) who were also less educated (p-0.009, OR-1.99, 95% CI -1.18- 3.36). In multivariate analysis- age at disease onset (p-0.001, OR-1.04, 95% CI- 1.01-1.06), duration of disease (p-0.04, OR-1.04, 95%CI- 1.002- 1.08) and educational status (p-0.02, OR- 2.12, 95% CI- 1.11-4.06) were significant association after controlling for gender, disability measured by EDSS, socioeconomic status and area of living (Supplementary Table 3). Among NMOSD patients, seropositive patients showed a trend for greater disability (p- 0.08, OR-1.14, 95%CI – 0.97-1.33) compared to seronegative patients. Lower socioeconomic status was significantly associated with *Hp* seropositivity (p=0.01, OR-3.83, 95% CI – 1.31 -11.23). Age of disease onset did not differ between the groups. Though statistically insignificant, our data suggested that seropositive patients may have had an early disease onset. Multivariate analysis did not show any variable to be significant (data not shown).

Hp serology and association with socioeconomic and educational status

We combined all patients and controls, to determine whether there were commonalities among those harbouring *Hp* in our study cohort. In univariate analysis a significant number of seropositive patients had low educational levels(p- 0.001, OR-2.3, 95% CI 1.57-3.38) and lived in rural areas(p- 0.002, OR 1.79, 95% CI – 1.23-2.61). After adjusting for other variables, (Tables 2, 3) multivariate analysis showed that educational background of care givers and patients (p- 0.001, OR -2.34, 95% CI- 1.48-3.69)was a significant determinant that differentiated seropositive patients and controls from their seronegative counterparts.

TABLE 1 Clinical and demographic features.

	MS (254)			Non MS disorders (198)		Healthy control
	RRMS (174)	SPMS (73)	PPMS (7)	AQP4-IgG+ (99)	MOGAD (99)	243
Gender (Female)	126(72.4%)	44(60.3%%)	5(71.4%)	90(90.9%)	44(44.4%)	149(61.3%)
Age (Mean ± SD)	35.18 ± 10.9	45.3 ± 11.36	45.7 ± 10.0	41.6 ± 12.6	33.06 ± 14.5	35.2 ± 11.23
Disease Duration (Mean ± SD)	8.58 ± 5.63	13.2 ± 6.13	11.7 ± 10.54	10.9 ± 7.2	6.81 ± 5.84	–
EDSS (Mean ± SD)	1.46 ± 0.97	5.41 ± 2.42	6.0 ± 3.0	4.27 ± 3.28	1.68 ± 2.02	–
*Hp*IgG +	35 (64.8%)	16(29.6%)	3(5.6%)	42 (42.4%)	28(28.3%)	107(44.03%)

HpIgG +, Helicobacter pylori antibody positive; EDSS, Expanded disability status scale; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive MS; PPMS, primary progressive MS, AQP4-IgG += Aquaporin-4 antibody positive, MOGAD= myelin oligodendrocyte glycoprotein antibody associated disease.

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TABLE 2 Association of socioeconomic status and *hpylori* status among the study cohort.

	Hp+	*Hp -*	p value	Odds ratio	95%CI
Gender					
Male	77(33.3%)	159(34.3%)	0.801	0.95	0.68-1.34
Female	154(66.6%)	305(65.7%)			
Education					
Basic education	115(68.8%)	197(51%)	**0.001**	2.3	1.57-3.38
Graduation and above	52(31.2%)	189(49%)			
Socioeconomic status					
Low	81(46.8%)	167(42.6%)	0.35	1.18	0.82-1.69
High	92(53.2%)	225(57.4%)			
Area of living					
Rural	109(64.5%)	192(50.3%)	**0.002**	1.79	1.23-2.61
Urban	60(35.5%)	190(49.7%)			

(Univariate analysis for all cases and controls combined). Bold value indicates a significant p value of < 0.05.

Discussion

Helicobacter pylori prevalence remains high in developing nations and offers an opportunity to study its association with autoimmune demyelinating CNS disorders in these regions. This is particularly relevant for Indian MS patients in whom there were no definitive environmental associations detected that were traditionally associated among white populations. These include Epstein Barr virus infection (26), smoking (12), obesity (12) and Vitamin D deficiency (27). In an earlier study we reported that *Hp* infection was protective against MS patients (12) and we have currently replicated the results in a larger cohort. Seropositive patients with MS- MOGAD had a later age of disease onset in our study. A similar delay in disease onset was reported in *Hp* seropositive patients with bronchial asthma (28). Despite a longer duration of disease, seropositive patients had disability that was comparable with seronegative patients (Supplementary Table 2). Previously two case control studies have reported similar results in *Hp* seropositive MS patients (9, 11). Our study also suggests that *Hp* infection may confer a protective effect against MOGAD similar to MS. In contrast, *Hp* infection was detected to be frequent in NMOSD patients. An effect on disease onset and course could not be clearly determined in the latter.

The differential association of CNS autoimmune disorders with *Hp* infection may in part be due to the differential immune response mounted by *Hp* in the human host (29). It is evident from human gut mucosal studies that *Hp* behaves as a commensal in early infection with a potential for pathogenicity in later life. Compared to adults, gastric mucosa in paediatric patients showed minimal inflammation, increased T regulatory (reg) cells and elevated levels of Treg related cytokines namely transforming growth factor- beta (TGFβ) and interleukin 10 (IL10) (30). Limited studies in experimental allergic encephalitis (EAE) models demonstrated that prior infection with *Hp* induced Foxp3^{+}Treg cell upregulation (31) and inhibition of MOG specific Th1 and Th17 responses (32). In adult patients, peptic ulceration was noted to be associated with reduced Tregs (33).

We have hypothesised possible mechanisms by which *Hp* infection could modulate the host immune response. Recent insights (34) suggest that *Hp* may possess inflammasone ligands that trigger caspase- 1 activation in dendritic cells lining the gastric lumen (Figure 1). Activation of the Toll like receptor2/Nucleotide-Binding Domain, Leucine-Rich–Containing Family, Pyrin Domain–Containing-3/Caspace1/Interleukin-18 axis (TLR2/NLRP3/CASP1/IL-18) axis may promote IL18 mediated Treg upregulation in the early phase of infection. The resulting immune tolerance may be the basis for protection against allergy and possibly autoimmune disorders such as MS and MOGAD. On the other hand, chronic gastritis is characterized by upregulated T helper 17(Th17) response, neutrophil recruitment and expression

TABLE 3 Association of socioeconomic status and *hpylori* status among the study cohort.

Variables	p value	Odds ratio	95%CI
Education status	**0.001**	2.34	1.48-3.69
Area of living	0.14	1.38	0.89-2.13
Socioeconomic status	0.37	0.82	0.54-1.25

(Multivariate analysis for all case and control combined). Bold value indicates a significant p value of < 0.05.

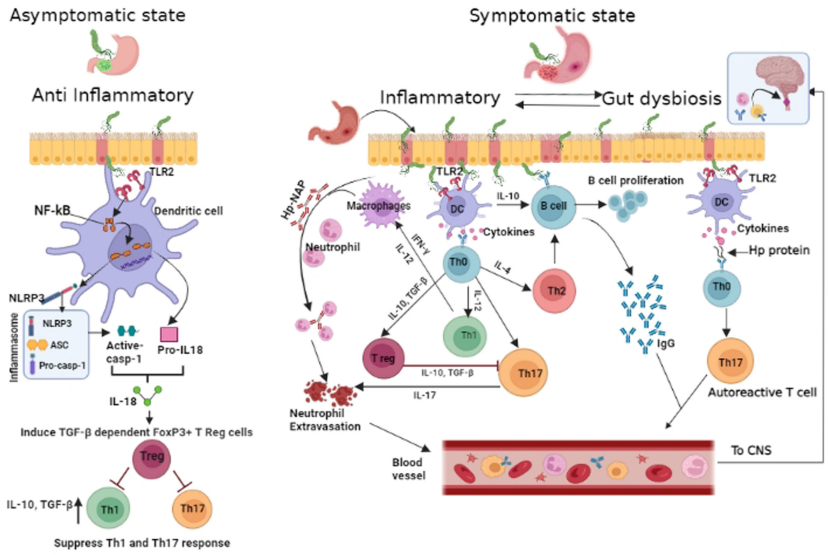

FIGURE 1
Proposed schematic of *Helicobacter pylori* mediated modulation of host immunity: In early phase of *Hp* infection(depicted on left of cartoon), *Hp*triggers Nucleotide-Binding Domain, Leucine-Rich–Containing Family, Pyrin Domain–Containing-3(NLRP3)inflammasome and caspace 1 activity in antigen presenting cell([APC]dendritic cells and macrophages) *via* Toll like receptor2 (TLR2) and Nuclear factor kappa B(NF-kB). Processing of pro interleukin -18 (pro-IL-18) and release of mature IL-18 results in T regulatory (Treg) cell differentiation and production of anti inflammatory cytokines – Interleukin-10 (IL10) and transforming growth factor Beta (TGF-β) with further expansion of Treg cells, resulting in immunosuppression. In the inflammatory state (depicted on right),APCafter processing *Hp*,signals naïve Tcells to differentiate (through release of cytokines - IL12 &IL17) into T helper (Th1 &Th17) cells andB cells are driven by interleukin 10 (IL10)to generate *Hp*-specific antibodies. Th17 induced neutrophil recruitment is further enhanced by *Hp*– neutrophil activating protein (NAP). Gut derived antibodies with potential for cross reaction with neural elements, *Hp* specific autoreactive T cells, neutrophils and *Hp* specific antibodies may target the central nervous system and induce/aggravate CNS inflammation. Created in BioRender.com.

of B cell activating factor (BAFF) in macrophages (35, 36). Chronic *Hp* infection has also been noted to be associated with gut dysbiosis and associated pro inflammatory state (37). We have postulated that pro- inflammatory state of chronic gastritis accompanied by gut dysbiosis may upregulate Th1/Th17 driven immune response initially in the gut and later systemically, facilitating the development of NMOSD in later life. The role of gastric derived antibodies that cross react with neural elements cannot be excluded. A previous publication from our group has shown this to be a potential pathway for disease pathogenesis in NMOSD (38). *Helicobacter pylori* related pro-inflammatory proteins particularly neutrophil activating protein (NAP) may contribute to AQP4 –IgG associated neural damage and severity of disease.In a recent study a significant correlation was noted between seropositive AQP4 IgG + NMOSD, *Hp*- NAP and disability (10). Bacterial virulence genes of *Hp* have not been studied in detail in the context of CNS autoimmune disorders. An association between *Hp*- cytotoxin associated gene A (cag-A) and autoimmune thyroiditis (39) and asthma was previously reported (28). Additionally the underlying genetic susceptibility for autoimmune disorders is also important.

We reviewed the relevance of hygiene hypothesis in a low middle income (LMIC) setting in relation to *Hp* infection and CNS autoimmune disorders. For this purpose,we analysed educational status and income levels of patients and primary caregivers in childhood in order to correlate poor sanitary conditions in childhood with early *Hp* colonization in the gut. Our study showed a significant association between lower educational status among all cases and controls stratified by *Hp* serology. Our hospital caters to patients from lower economic status which may explain the lack of difference in economic status between the two groups.

In conclusion, in developing countries *Hpylori* may be a significant environmental factor associated with autoimmune demyelinating disorders. Our study was limited by the small number of study participants and the cross sectional nature of the analysis. It is not clear at this time whether analysis of risk/benefit has to be carefully undertaken before *Hp* eradication is contemplated, in populations harbouring high *Hp* seroprevalence. Therefor the role of *H pylori* in modulating human immunity and its protective/ deleterious effects need to be understood through larger studies that will additionally evaluate the role of *Hp* virulence genes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Central Ethics Committe, Nitte University. The

patients/participants provided their written informed consent to participate in this study.

Author contributions

LP developed the concept, study design, analysis, interpretation, drafting and revising the work. CM contributed to study design, data acquisition, analysis, interpretation of results, manuscript drafting and revision. AD'C contributed to data acquisition, analysis and manuscript drafting. AS contributed to data collection, data analysis and interpretation. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1162248/full#supplementary-material

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Pediatric myelin oligodendrocyte glycoprotein antibody-associated disease in southern China: analysis of 93 cases

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Objective: To study the clinical features of children diagnosed with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) in southern China.

Methods: Clinical data of children diagnosed with MOGAD from April 2014 to September 2021 were analyzed.

Results: A total of 93 children (M/F=45/48; median onset age=6.0 y) with MOGAD were involved. Seizures or limb paralysis was the most common onset or course symptom, respectively. The most common lesion locations in brain MRI, orbital MRI, and spinal cord MRI were basal ganglia and subcortical white matter, the orbital segment of the optic nerve, and the cervical segment, respectively. ADEM (58.10%) was the most common clinical phenotype. The relapse rate was 24.7%. Compared with the patients without relapse, relapsed patients had a longer interval from onset to diagnosis (median: 19 days VS 20 days) and higher MOG antibody titer at onset (median: 1:32 VS 1:100) with longer positively persistent (median: 3 months VS 24 months). All patients received IVMP plus IVIG at the acute phase, and 96.8% of patients achieved remission after one to three courses of treatment. MMF, monthly IVIG, and maintaining a low dose of oral prednisone were used alone or in combination as maintenance immunotherapy for relapsed patients and effectively reduced relapse. It transpired 41.9% of patients had neurological sequelae, with movement disorder being the most common. Compared with patients without sequelae, patients with sequelae had higher MOG antibody titer at onset (median: 1:32 VS 1:100) with longer persistence (median: 3 months VS 6 months) and higher disease relapse rate (14.8% VS 38.5%).

Conclusions: Results showed the following about pediatric MOGAD in southern China: the median onset age was 6.0 years, with no obvious sex distribution difference; seizure or limb paralysis, respectively, are the most common onset or course symptom; the lesions of basal ganglia, subcortical white matter, the orbital segment of the optic nerve, and cervical segment were commonly involved in the CNS MRI; ADEM was the most common clinical phenotype;

most had a good response to immunotherapy; although the relapse rate was relatively high, MMF, monthly IVIG and a low dose of oral prednisone might effectively reduce relapse; neurological sequelae were common, and possibly associated with MOG antibody status and disease relapse.

KEYWORDS

MOG antibody associated disease (MOGAD), clinical features, relapse, prognosis, children

1 Introduction

Myelin oligodendrocyte glycoprotein (MOG) is found on the myelin surface, and acts as a cellular adhesive molecule to regulate the stability of the oligodendrocyte microtubule (1). In humans, the MOG only is expressed exclusively in the central nervous system (CNS) (2). Antibodies against MOG have been associated with a wide variety of clinical phenotypes, including acquired demyelinating syndromes such as optic neuritis, myelitis, acute disseminated encephalomyelitis (ADEM), neuromyelitis optical spectrum disorder (NMOSD), encephalitis, and aseptic meningitis. Its clinical features and immunopathological mechanisms are distinct from both classic multiple sclerosis (MS) and aquaporin-4 (AQP4)-IgG-positive NMOSD, and being considered as a disease entity in its own, i.e. MOG antibody-associated disease (MOGAD) (3, 4). MOGAD is commonly seen in pediatric patients and can overlap with other autoimmune diseases in the central and peripheral nervous systems (5, 6). In addition, some clinical features of MOGAD differ between children and adults (7). In the present article, we retrospectively investigated 93 pediatric MOGAD patients and focused on their clinical manifestation, radiological presentation, treatment response, relapse rate, maintenance immunotherapy, outcome, and prognosis.

2 Article types

Original Research.

Abbreviations: ADEM, acute disseminated encephalomyelitis; AQP4, aquaporin-4; BAEP, brainstem auditory evoked potential; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; IQR, interquartile range; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LETM, longitudinally extensive transverse myelitis; MMF, mycophenolate mofetil; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG antibody-associated disease; MRI, magnetic resonance image; MS, multiple sclerosis; NMDAR, N-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorders; OCB, oligoclonal bands; ON, optic neuritis; RTX, rituximab; VEP, visual evoked potential; WBC, white blood cell count.

3 Manuscript formatting

3.1 Subjects and methods

3.1.1 Subjects

Children diagnosed with MOGAD from April 2014 to September 2021 in the Department of Neurology of Guangzhou Women and Children's Medical Center were included. This study was approved by the Ethics Committee of Guangzhou Women and Children Medical Center (Approval No: [2019]40701). Clinical features including demographic data, prodromal events, clinical manifestations, laboratory investigations, neuroelectrophysiological data [electroencephalogram (EEG), visual evoked potential (VEP), brainstem auditory evoked potential (BAEP)], brain magnetic resonance image (MRI), treatment, outcomes, and prognosis were retrospectively reviewed. Neurological disability was assessed by an expanded disability status scale (EDSS). The EDSS was assessed before and after immunotherapy and at the end of follow-up, respectively.

3.1.2 Methods

3.1.2.1 Inclusion criteria

Patients were involved if they were younger than 18 years old and met the diagnostic criteria of MOGAD proposed by Jarius S et al., defined as 1) Monophasic or relapsing acute optic neuritis (ON), myelitis, brainstem encephalitis, or encephalitis, or any combination of these syndromes; 2) MRI or electrophysiological (VEP in patients with isolated ON) findings compatible with CNS demyelination; 3) Seropositivity for MOG-IgG as detected using a cell-based assay employing full-length human MOG as target antigen (8). Encephalitis was diagnosed according to international criteria for inflammatory or infectious encephalitis (9). ADEM was diagnosed according to the criteria proposed by the International Pediatric MS Study Group (IPMSSG) 2013 (10). Acquired demyelinating syndromes were classified according to IPMSSG criteria (10), but MS and NMOSD followed with the more recent criteria (9, 11). An uncategorized MOGAD clinical phenotype was defined as any MOGAD not falling into the clinical phenotype of ADEM, ON, NMOSD, and encephalitis. Anti-NMDAR encephalitis was diagnosed according to the criteria proposed by Graus et al. (12). Acute phases include initial attack at onset and subsequent

initial attack at relapses. Relapse was defined as the development of new neurological symptoms one month after the onset of the initial attack or, in the case of ADEM, three months after the onset of the last attack (6, 13, 14), except for the patients with anti-NMDAR encephalitis which were defined as the new onset or symptomatic deterioration occurring after at least two months of improvement or stabilization (15).

3.1.2.2 Exclusion criteria

Patients were excluded if they presented poisoning, infectious, genetic, metabolic, vascular, or neoplastic central nervous system disease, or they failed to complete follow-up.

3.1.2.3 Antibodies test

MOG IgG and AQP4 IgG in serum were detected by the fixed cell-based assay commercial kit (Shaanxi Maiyuan Biotechnology Co., Ltd, Shanxi, China). Anti-NMDAR IgG in serum and cerebrospinal fluid (CSF) were detected by fixed cell-based assay (EUROIMMUN, Lübeck, Germany). These antibodies test was performed by an independent medical agency during acute attacks or follow-up visits. These methods had been reported in detail in our previous study (7, 16). The cut-off value for being MOG positive in the commercial assay was a titer of 1:10.

3.1.3 Neuroelectrophysiological examination

Neuroelectrophysiological examinations including EEG, VEP, and BAEP were performed by neuro-electrophysiologist. The results of EEG, VEP, and BAEP were judged and interpreted by two neuro-electrophysiologists in our hospital. Abnormalities of EEG included: 1) abnormal frequency, amplitude, waveform, distribution, symmetry, stability, and reactivity of the basic rhythm; 2) The amplitude of each frequency band (α, β, θ, δ waves) and the correlation and distribution between the amplitudes are abnormal; 3) Physiological reactions disappear or abnormal reactions appear. 4) Increased slow activity (θ, δ waves); 5) The appearance of pathological waves. Abnormalities of BAEP included: 1) the incubation period of I wave, III wave, and V wave is prolonged; 2) the interphase period of I~ III, III~ V, and I ~ V wave is prolonged; 3) the waveform is poorly differentiated or disappears; 4) the single or bilateral I wave, III wave, and V wave all disappear. Abnormalities of VEP included: 1) the P100 wave disappearing; 2) the latency of the P100 wave prolonging with or without amplitude decrease.

3.1.3.1 Treatment

At the onset and for an acute attack, all patients received intravenous methylprednisolone (IVMP) with a high dose of 15-30 mg/kg/d for 3 to 5 days tailed to oral prednisone (2 mg/kg, reduced 2.5-5 mg every one to two weeks, tapered off within 3 to 6 months or more) in combination with intravenous immunoglobulin (IVIG) administered at 2 g/kg divided into 2-3 days. Patients responding poorly to the IVMP combination with IVIG treatment or severe attack received plasma exchange (n=3) or rituximab (RTX) (n=1) For relapsed patients, maintenance immunotherapy included maintaining mycophenolate (MMF) (0.25 g, once to three times a day), monthly IVIG (400 mg/kg), and maintained a low dose of oral prednisone (initial dose was 2 mg/kg/d, reduced 2.5-5 mg/d every two weeks until dose reached 5 mg/d, 5 mg/d for one to two months and reduced to 2.5 mg/d for two months, and then 2.5 mg every other day for two months) for about 10 to 12 months. The definition described the recovery from onset based on the EDSS score at six months after onset according to Demuth et al. (17) was: classifying the recovery as "complete" if the 6-month EDSS score reached the score before the attack, "partial" if recovery was incomplete, and "absent" if there was no improvement or clinical deterioration.

3.1.3.2 Follow-up

All patients were followed up either by a neurologist in the neurological clinic or by a neurologist *via* telephone contact.

3.1.3.3 Statistical analysis

Statistical analysis was performed using SPSS IBM 20.0. Quantitative data with normal distribution was described by mean ± SD, otherwise median with the interquartile range (IQR). The qualitative data was described by frequency and percentage. Person Chi-Square, Likelihood Ration, or Fish exact test was used to compare the qualitative data. The quantitative data with normal distribution were compared using the independent t-test, otherwise using Mann-Whitney U or Kruskal-Wallis H test. The p-value <0.05 (two-sided) was considered significant. Figures were graphed using GraphPad Prism 7.01 (GraphPad Software Inc., US).

3.2 Results

3.2.1 Demographics

A total of 93 children (male: female 45:48) diagnosed with MOGAD came from different regions of southern China, including the provinces of Hunan, Jiangxi, Guangdong, Guangxi, Hainan,and so on. All were of Han Chinese ethnicity. The median onset age was 6.0 years (IQR 4.0-8.0 years). There was no significant difference on onset age between boys and girls [Girl: 6.0 years (IQR 4.0-8.0 years) VS Boy: 6.0 years (IQR 3.5-8.0 years)]. The median interval from onset to diagnosis was 19.0 days (IQR 12.0-28.5 days). There was no significant difference in the median interval from onset to diagnosis between boys and girls [Boy: 20.0 days (IQR 12.0-35.0 days) VS Girl: 19.0 days (IQR 12.0-25.0 days)].

3.2.2 Prodromal events

A slight majority – 51.6% (48/93) – of patients had prodromal events within one month before onset, among which 45.2% (42/93) were infectious events, with acute respiratory infection being the most common (n=40); other events included acute gastroenteritis (n=1) and urinary tract infection (n=1). Four patients had a history of vaccination about 2-14 days before the onset, including live-attenuated oral poliovirus vaccine (n=1), meningococcal meningitis vaccine (n=1), influenza vaccine (n=1), and Streptococcus pneumonia vaccine (n=1). Two patients suffered a head fall before onset. Their head CT scanning showed no abnormality and needed no further treatment.

3.2.3 Neurological symptoms

The most common initial neurological symptom at onset was seizure (22.6%, 21/93), followed by headache (18.3%, 17/93), limb paralysis (17.2%, 16/93), and visual deficits (15.1%, 14/93). The less common initial neurological symptoms included ataxia (9.7%, 9/93), bowel and bladder dysfunction (2.2%, 2/93), speech disorder (2.2%, 2/93), and sensor dysfunction (1.1%, 1/93). While during the whole course, the most common neurological symptoms were limbs paralysis (47.3%, 44/93), followed by seizure (43.0%, 40/93), headache (40.9%, 38/93), visual deficits (31.2%, 29/93), ataxia (29.0%, 27/93), speech disorder (18.3%, 17/93), bowel and bladder dysfunction (15.1%, 14/93), and cranial nerve palsy (10.8%, 10/93). The less common neurological symptoms included respiratory failure due to brainstem involvement (5.4%, 5/93), sensor dysfunction (4.3%, 4/93), and dysphagia (4.3%, 4/93). Bilateral visual deficits were more common than unilateral (20.4% VS 10.8%). Other common symptoms included fever (50.5%, 47/93) and vomiting (29.0%, 27/93).

3.2.4 Laboratory investigation outcome

3.2.4.1 MOG antibody test result

All patients underwent serum MOG antibody tests at onset and acute attack. At the onset, the medium MOG antibody titer was 1:32 (IQR 1:32-1:100). Meanwhile, the serum AQP4 antibody was negative in all patients. At follow-up, patients underwent a MOG antibody test at least on the first, second, and third follow-up per patient every three months after discharge. The median duration of persisting MOG antibody positive was six months (IQR 3-6 months), ranging from 2 to 36 months (Figure 1A).

3.2.4.2 Co-existing autoantibodies

Forty-six patients underwent CSF anti-NMDAR antibody tests, and 23.9% (11/46) of them were co-positive for anti-NMDAR antibodies. Seven among these eleven patients have been reported in our previous study (16).

3.2.4.3 CSF test result

All patients underwent CSF examination through lumbar puncture at the onset. The median CSF white blood cell count (WBC) at the first lumbar puncture was 40.0×10^6/L (IQR 10.0-89.5×10^6/L), ranging from 1 to 790×10^6/L, and in which the lymphocyte was dominant. CSF pleocytosis was seen in 72.0% (67/93) of patients. The glucose and chloride levels of CSF were normal. The median protein level in CSF was 0.37 g/L (IQR 0.26-0.50 g/L) and ranged from 0.15 to 2.44 g/L. CSF protein was raised in 47.3% (44/93) of patients. Positive oligoclonal bands (OCBs) was seen in 10.8% (10/93) of patients, including positive in both CSF and serum seen in 8.6% (8/93) of patients and only positive in CSF seen in 2.2% (2/93).

3.2.5 Neuroimaging examination

MRIs were performed for clinical purposes either at acute neurological presentation or at follow-up. All patients underwent brain, orbital, and spinal MRI at onset, and 97.8% (91/93) were abnormal. Meanwhile 39.8% (37/93) of patients showed gadolinium enhancement lesions. In brain MRI, the basal ganglia and subcortical white matter were the common lesion locations, observed in 45.2% (42/93) of patients (Figures 2A, C). While cortical gray matter, cerebellum, brainstem, and deep white matter were preferentially involved (Figure 2D). However, periventricular white matter, corpus callosum, and leptomeninges were the less frequently involved locations (more details in Table 1, Figures 2B, G). Nearly three-quarters (72.0%, 67/93) of patients had large (diameter >2 cm) lesions with unclear boundaries in brain MRI, among which three patients had a tumefactive demyelinating lesion (Figure 2E), and two patients had a leukodystrophy-like demyelinating lesion (Figure 2F). It was also found 19.4% (18/93) of patients had small subcortical patchy lesions with unclear boundaries in brain MRI (Figure 2A). In orbital MRI, 19.4% (18/93) of patients were abnormal with optic nerve swelling and gadolinium enhancement (Figure 2H). Abnormal Orbital MRI in unilateral was seen in 38.9% (7/18) of patients, and bilateral was seen

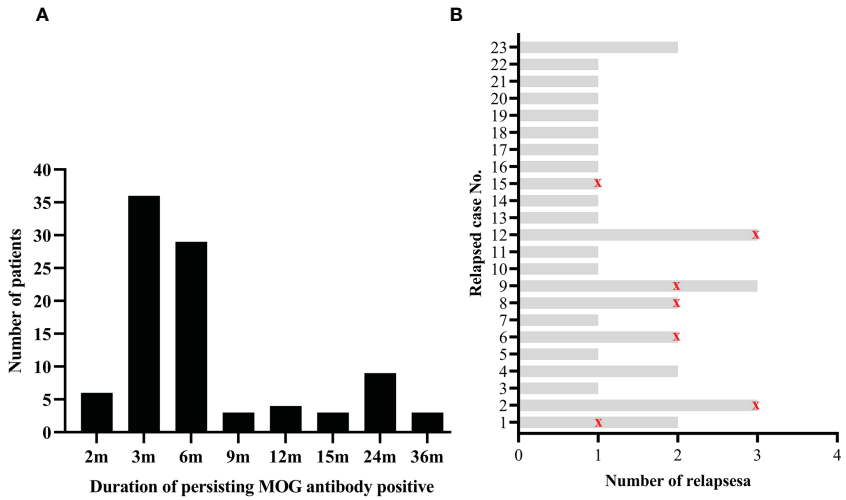

FIGURE 1
Serum MOG antibody during the disease course. **(A)** Numbers of patients with different duration of persisting MOG antibody positive; **(B)** Status of serum MOG antibody in recurrent patients. The red marks indicate that the serum MOG antibody turned negative during this relapse.

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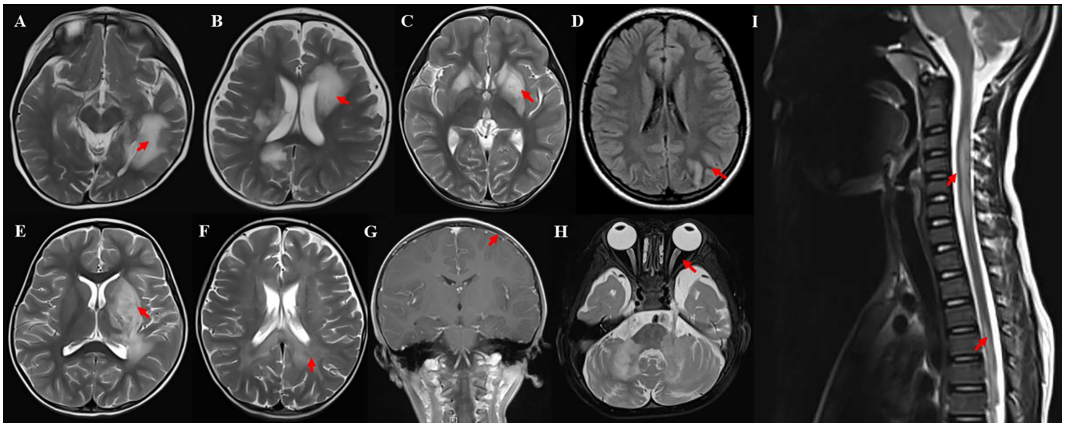

FIGURE 2
Example of MRI of MOGAD patients. **(A)** Large, poorly demarcated in subcortical white matter; **(B)** MS-like lesion around in periventricular; **(C)** Bilateral basal ganglia obvious edema, similar to EBV encephalitis; **(D)** Left occipital and temporal cortex edema with T2WI-hyperintense lesions along the gyrus; **(E)** Tumefactive lesion in left basal ganglia; **(F)** Symmetric white matter lesions around the posterior horn of lateral ventricle (leukodystrophy-like); **(G)** Local leptomeningeal gadolinium enhancement in T1WI; **(H)** bilateral optic edema; **(I)** longitudinally extensive transverse myelitis in the cervical and thoracic spinal cord.

TABLE 1 Clinical features of different clinical phenotypes in pediatric MOGAD.

	ADEM n=54	Encephalitis n=19	ON/NMOSD n=12	Uncategorized MOGAD n=8	*P*
Onset age (median (IQR), years)	5.24(4.0)	8(6.5)	7.5(2.8)	3.8(4.1)	0.007
Clinical presentation					
Fever (N (%))	26(48.1)	15(78.9)	2(16.7)	4(50)	0.005
Headache (N (%))	19(35.2)	12(63.2)	5(41.7)	2(25)	0.142
Seizure (N (%))	18(33.3)	10(52.6)	1(8.3)	1(12.5)	0.029
Visual deficits (N (%))	14(25.9)	2(10.5)	12(100)	1(12.5)	<0.001
Limbs paralysis (N (%))	28(51.9)	7(36.8)	2(16.7)	7(87.5)	0.007
Ataxia (N (%))	18(33.3)	3(15.8)	1(8.3)	5(62.5)	0.026
Laboratory investigation outcome					
MOG antibody titer (median (IQR))	32(68)	32(22)	100(288)	21(200)	0.018
Duration of persistent MOG antibody positive (median (IQR), months)	6(3)	3(3)	6(17)	5(15)	0.031
OCB (Positive, N (%))	5(9.3)	5(26.3)	0(0)	0(0)	0.041
Lesions in MRI					
Cortical gray matter (N (%))	26(48.1)	10(52.6)	1(8.3)	1(12.5)	0.008
Subcortical WM (N (%))	33(61.1)	4(21.1)	4(33.3)	1(12.5)	0.002
Deep WM (N (%))	25(46.3)	0(0)	1(8.3)	1(12.5)	<0.001
Periventricular WM (N (%))	9(16.7)	0(0)	2(16.7)	0(0)	0.043
Corpus callosum (N (%))	8(14.8)	0(0)	0(0)	0(0)	0.026
Basal ganglia (N (%))	33(61.1)	4(21.1)	2(16.7)	3(37.5)	0.002
Brainstem (N (%))	27(50)	0(0)	0(0)	2(25)	<0.001
Cerebellum (N (%))	26(48.1)	0(0)	3(25)	3(37.5)	<0.001

(Continued)

TABLE 1 Continued

	ADEM n=54	Encephalitis n=19	ON/NMOSD n=12	Uncategorized MOGAD n=8	*P*
Optic nerve (N (%))	7(13)	0(0)	11(91.7)	0(0)	<0.001
Spinal cord (N (%))	14(25.9)	0(0)	4(33.3)	2(25)	0.013
Leptomeninges (N (%))	2(3.7)	7(36.8)	0(0)	0(0)	0.001
Lesion size (>2cm, N (%))	49(90.7)	9(47.4)	4(33.3)	5(62.5)	<0.001
EDSS at onset (median (IQR))	6.5(2.5)	6(2.5)	5(0.8)	8(2)	0.011
EDSS after acute treatment (median (IQR))	2(1)	1(2)	2(0)	3.5(3.5)	0.009
Follow-up and prognosis					
Duration of follow-up (median (IQR), months)	14(19)	7(10)	12(27)	8(44)	0.134
EDSS at last follow-up (median (IQR))	0(1)	0(1)	1(1)	1(1.5)	0.134
Relapse (N (%))	12(22.2)	5(26.3)	2(16.7)	4(50)	0.084
Sequalae (N (%))	20(37)	6(31.6)	7(58.3)	6(75)	0.097

ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; IQR, interquartile range; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance image; MOGAD, MOG antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorders; OCB, oligoclonal bands; ON, optic neuritis; WBC, white blood cell; WM, white matter.

in 61.1% (11/18). Within the optic nerves, lesions were divided into the five segments with the T2 hyperintensity: orbital (100%,18/18), intracanalicular (88.9%, 16/18), pre-chiasmal (22.2%, 4/18), chiasmal (11.1%, 2/18), and optic tracts (0.0%, 0/18), with the orbital segment being the most commonly involved. In spinal cord MRI, 21.5% (20/93) of patients were abnormal. Among them, 20.0% (4/20) presented with short myelitis (SM) and 80.0% (16/20) presented with longitudinally extensive transverse myelitis (LETM), in which four patients showed cervical, thoracic, and lumbar spinal cord were involved. The cervical segment was the most frequently involved, followed by the thoracic segment, which mostly involved was the upper thorax (T1-T6) (Figure 2I). Four patients had lumbar spinal cord involvement, and two (10%, 2/20) had conus involvement (more details in Table 1). Meanwhile, 15.0% (3/20) of these patients had spinal nerve root gadolinium enhancement.

Analyzing MRI recovery, at the last follow-up, lesions completely absorbed were observed in 49.5% of patients (46/93), with mostly absorbed in 31.2% (29/93), partially absorbed in 14.0% (13/93), and partially absorbed with residual neuron necrosis in 5.4% (5/93). MRI lesions in the patients with ON/NMOSD or with uncategorized MOGAD were more likely to be completely absorbed. In contrast, lesions in the patients with ADEM were more likely to be partially absorbed with residual neuron necrosis (Figure 3A). Moreover, lesions in patients achieving complete recovery were more likely to be completely absorbed. In contrast, lesions in patients absent of recovery were more likely to be partially absorbed with residual neuron necrosis (Figure 3B).

3.2.6 Neuroelectrophysiological examination

All patients underwent EEG examination during the acute stage at onset, and 64.5% (60/93) had abnormal EEG. The slow background activity seen in 88.3% (53/60) was the most common abnormality followed by focal epileptiform discharges seen in 25.0% (15/60). Eighty-one patients underwent BAEP examination during the acute stage at onset, and 18.5% (15/81) had abnormal BAEP including prolonged latency of the BAEP waves (n=12) and BAEP waves without differentiation (n=3). Eighty-four patients underwent VEP examination during the acute stage at onset, among which 40 patients younger than 6 years or could not cooperate with the pattern reversal VEP underwent the flash-

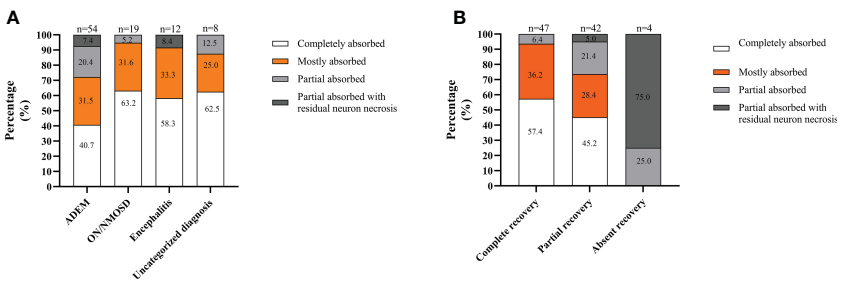

FIGURE 3
MRI recovery at the last follow-up in the South China cohort. **(A)** Depending on the onset attack phenotype; **(B)** In different recovery groups. The total number of patients in each group is shown above the bar.

VEP, and the other 44 patients underwent the pattern reversal VEP. Another 20.0% (8/40) of patients had abnormal flash VEP and 63.6% (28/44) of patients had abnormal pattern reversal VEP. In flash-VEP, bilateral abnormalities were more common than unilateral (n=5 in bilateral VS n=3 in unilateral), so as in pattern reversal VEP (n=18 in bilateral VS n=10 in unilateral). The most common abnormality in flash-VEP was the latency of the P100 wave prolongation with amplitude decrease (50.0%, 4/8), likewise in pattern reversal VEP (39.3%).

3.2.7 Clinical phenotype

At the onset, ADEM (58.10%, 54/93) was the most common clinical phenotype, followed by isolated ON or NMOSD, encephalitis, and the uncategorized MOGAD (more details seen in Table 1). Patients with different clinical phenotypes varied in the onset age, clinical and radiological features, MOG antibody titer, duration of persisting MOG antibody positive, the ratio of OCB positive, and EDSS in acute stage at onset and after treatment (more details seen in Table 1).

3.2.8 Clinical course and relapse

After a median follow-up of 10 months (IQR 5.0-24.5), 23 (24.7%) of the 93 patients had a relapse and 34 episodes in total. The median follow-up duration for the 23 relapsed patients was 24 months (IQR 8.0-43.0), and the median relapse interval was 12.0 months (IQR 8.0-17.3). For 34 relapsed attacks in total, 79.4% (27/34) of attacks occurred with persistent MOG antibody positive, while only 20.6% (7/34) of attacks occurred when MOG antibody turned negative (Figure 1B). Regarding the 34 episodes, ADEM was the most frequently relapsing clinical phenotype observed in 44.1% (15/34), followed by ON 20.6% (7/34), encephalitis 20.6% (7/34), brainstem encephalitis 8.8% (3/34) and other uncategorized MOGAD 5.9% (2/34). 23.5% (8/34) of relapsing episodes occurred post-infection, and 26.5% (9/34) happened during the steroid less than 5 mg/d or within three months after steroid withdrawal. Compared with patients without relapse, relapsed patients had a longer interval from onset to diagnosis, higher MOG antibody titer at onset, longer duration of persisting MOG antibody positive, higher EDSS at last follow-up, and a higher ratio of sequelae (more detail seen in Table 2).

3.2.9 Treatment and outcome

At the onset and for an acute attack at relapse, all patients received IVMP with a high dose of 15-30 mg/kg/d for 3 to 5 days tailed to oral prednisone (2 mg/kg, tapered off within 3 to 6 months or more) combination with IVIG administered at 2 g/kg divided over 2-3 days. The median course of IVMP and IVIG treatment was one (IQR 1-1). Most patients (73.1%, 68/93) achieved remission after only one IVMP and IVIG treatment course. However, 10.8% (10/93) of patients received one IVMP and two IVIG treatment courses and remission. Eight patients received two IVMP and two IVIG treatment courses to achieve remission. Three patients received three IVMP and three IVIG treatment courses to achieve remission. Three patients with severe attacks who responded poorly to IVMP and IVIG treatment received plasma exchanges followed by one course of IVMP and IVIG treatment, subsequent remission.

TABLE 2 Comparison of clinical features between patients with relapse and without relapse.

	Relapse-free n=70	Relapsed n=23	*P*
Onset age (median (IQR), years)	5.7(4.5)	6(3.5)	0.170
Interval from onset to diagnosis (median (IQR), days)	19(14)	20(350)	0.008
Laboratory investigation outcome			
CSF WBC (median (IQR), x10^6/L)	40(80)	29(69)	0.786
CSF Protein (median (IQR), g/L)	0.36(0.21)	0.44(0.33)	0.705
MOG antibody titer (median (IQR))	32(90)	100(288)	0.000
Duration of persistent MOG antibody positive (median (IQR), months)	3(3)	24(12)	0.000
OCB (N (%))	8(11.4)	2(8.7)	1.000
Anti-NMDAR antibody (Positive, N (%))	7(10)	4(17.4)	0.456
MRI Lesion size (>2cm, N (%))	49(70)	18(78.3)	0.444
Gadolinium enhancement MRI lesions (N (%))	25(35.7)	12(52.2)	0.162
EDSS at onset (median (IQR))	6.5(3)	6(2.5)	0.676
EDSS after acute treatment (median (IQR))	2(1)	2(1)	0.115
Duration of follow-up (median (IQR), months)	10(17)	24(35)	0.002
EDSS at last follow-up (median (IQR))	0(1)	1(2)	0.009
Sequalae (N (%))	24(34.3)	15(65.2)	0.009

CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; IQR, interquartile range; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance image; NMDAR, N-methyl-D-aspartate receptor; OCB, oligoclonal bands; WBC, white blood cell.

Moreover, one patient did not achieve remission after four IVMP and IVIG treatment courses and responded to rituximab treatment. According to the definition of recovery, 50.5% (47/93) of patients achieved complete recovery at the onset, 45.1% (42/93) achieved partial recovery, and 4.3% (4/93) were absent from recovery. Regarding the onset attack phenotype, patients with ON/NMOSD or ADEM were more likely to achieve complete recovery, while patients with the uncategorized MOGAD were more likely to be absent of recovery (Figure 4A). Regarding the onset age, patients aged 9 to 12 years were more likely to achieve complete recovery, while those under six years were more likely to be absent of recovery (Figure 4B). For all patients, the median duration of oral prednisone at the first attack was 6.0 months (IQR 4.0-7.0 months) and there was no significant difference in duration of oral prednisone between patients with or without relapse (6.0 months (IQR 4.0-8.0 months) VS 5 months (IQR4.0-6.3 months)), P=0.380).

3.2.10 Maintenance immunotherapy

For 23 relapsed patients, the initial maintenance immunotherapy included maintaining MMF (n=10), monthly IVIG (n=7), and maintaining a low dose of oral prednisone (n=6). Half (5/10) of patients who received MMF treatment became relapse-free with a median follow-up of 32 months (IQR 20.0-39.5 months), while the remaining 50% (5/10) of patients who still relapsed became relapse-free after receiving monthly IVIG treatment with a median follow up for 46 months (IQR 26-25 months). Of patients who received monthly IVIG treatment, 57.1% (4/7) became relapse-free with a median follow-up of 12 months (IQR 7.5-25 months), while the remaining 42.9% (3/7) of patients who still relapsed became relapse-free after receiving MMF treatment with follow-up of 12 months, 18 months, and 30 months respectively. Six relapsed patients received maintenance of a low dose of oral prednisolone for 12.2 ± 1.8 months, three patients became relapse-free with follow-ups of 12 months, 14 months, and 20 months respectively, while the remaining three patients who still relapsed became relapse-free after receiving monthly IVIG treatment with follow-up of 10 months, 15 months, and 18 months. There was no significant difference in the frequency of patients who became relapse-free in these three maintenance immunotherapies used alone (P=1.000).

3.2.11 Prognosis

No patients were lost to follow-up and the median duration of follow-up was 10 months (IQR 5.0-24.5 months). At the last follow-up, 41.9% (39/93) of patients had one to three items of neurological sequelae including movement disorder (25.6%, 10/39), mild visual impairment without affecting daily life (23.1%, 9/39), irritability (12.8%, 5/39), speech disturbance (12.8%, 5/39), learning difficulties (12.8%, 5/39), seizure (10.3%, 4/39), and headache and sleep disorder (7.7%, 3/39). Compared with patients without sequelae, patients with sequelae had higher MOG antibody titer at onset, longer duration of persisting MOG antibody positive, more IVMP treatment courses, higher EDSS after acute treatment and at last follow-up, higher relapse rate, and less ratio of thalamus involvement (more detail seen in Table 3).

3.3 Discussion

MOGAD is now recognized as a separate disease with distinct clinical and paraclinical features from other CNS inflammation diseases like AQP4 NMOSD and MS (4). Moreover, some clinical features of MOGAD differ between children and adults (7). In the present article, we reported the clinical features and investigation of 93 pediatric MOGAD patients with relatively large case numbers.

Demographically, our patients were similar to the previous studies from other regions in China and other countries in terms of the onset age (6.0 years VS 5.7-7 years) and balanced sex distribution (51.6% female to 49%-57%) (13, 18–22). According to the previous studies, the onset age of pediatric MOGAD patients was younger than patients with AQP4 NMOSD (9.8 years) and MS (14.4 years) (23). While the female ratio of pediatric MOGAD patients was lower than patients with AQP4 NMOSD (71.4%-92.9% female) (24–27) and MS (64% female) (25).

In our study, 51.6% of patients had prodromal events within one month before onset, among which more than 90% were acute respiratory infection and vaccination. Furthermore, the majority of positive pathogenic examination results were viral infections. The ratio of patients with prodromal events was nearly two times higher than that in Zhou et al.'s study, in which it was 26.9% (28). This difference may be caused by the different subjects involved. In our

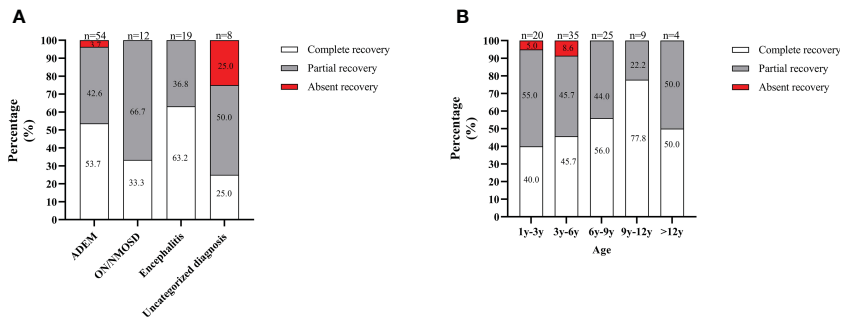

FIGURE 4
Recovery from the onset attack in the South China cohort. **(A)** Depending on the onset attack phenotype; **(B)** In different age groups. The total number of patients in each group is shown above the bar.

TABLE 3 Comparison of clinical features between patients with sequelae and without sequelae.

	Non-sequelae n=39	With sequelae n=54	*P*
Onset age (median (IQR), y)	6(3.5)	5(4)	0.111
Interval from onset to diagnosis (median (IQR), days)	19(13)	19(13)	0.330
Clinical presentation			
Seizure (N (%))	15(27.8)	15(38.5)	0.277
Dysphagia (N (%))	2(3.7)	2(5.1)	0.738
Unilateral visual deficits (N (%))	4(7.4)	6(15.4)	0.311
Bilateral visual deficits (N (%))	12(22.2)	7(17.9)	0.614
Limbs paralysis (N (%))	29(53.7)	15(38.5)	0.146
Bowel and bladder dysfunction (N (%))	9(16.7)	5(12.8)	0.609
Brainstem damage symptom (N (%))	3(5.6)	2(5.1)	1.000
Laboratory investigation outcome			
CSF WBC (median (IQR), $x10^6$/L)	47(73)	30(89)	0.326
CSF Protein (median (IQR), g/L)	0.37(0.25)	0.34(0.27)	0.564
MOG antibody titer (median (IQR))	32(90)	100(79)	0.009
Duration of persistent MOG antibody positive (median (IQR), months)	3(3)	6(3)	0.010
Anti-NMDAR antibody (Positive, N (%))	8(14.8)	3(7.7)	0.384
Lesions in MRI			
Cortical gray matter (N (%))	21(38.9)	17(43.6)	0.649
Subcortical WM (N (%))	24(44.4)	18(46.2)	0.870
Deep WM (N (%))	15(27.8)	12(30.8)	0.754
Thalamus (N (%))	17(31.5)	5(12.8)	0.037
Basal ganglia (N (%))	23(42.6)	19(48.7)	0.558
Brainstem (N (%))	18(33.3)	11(28.2)	0.598
Optic nerve (N (%))	8(14.8)	10(25.6)	0.192
Spinal cord (N (%))	11(20.4)	9(23.1)	0.754
Lesion size (>2cm, N (%))	38(70.4)	29(74.4)	0.672
Gadolinium enhancement (N (%))	22(40.7)	15(38.5)	0.852
Acute treatment and outcome			
EDSS at onset (median (IQR))	6.5(3.5)	6(3)	0.778
EDSS after acute treatment (median (IQR))	1(2)	2(1)	<0.001
Follow-up			
EDSS at last follow-up (median (IQR))	0(0)	1(1)	<0.001
Relapse (N (%))	8(14.8)	15(38.5)	0.009

ADEM, acute disseminated encephalomyelitis; CRP, C-reactive protein; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; IQR, interquartile range; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance image; NMDAR, N-methyl-D-aspartate receptor; NMOSD, neuromyelitis optica spectrum disorders; OCB, oligoclonal bands; ON, optic neuritis; WBC, white blood cell; WM, white matter.

study, we focused on pediatric patients, while pediatric and adult patients were involved in Zhou et al.'s study. Viral illnesses are prevalent among patients and healthy children at the age of MOGAD onset. Whether these infections are occasionally presented in MOGAD or play a role in the pathogenesis of pediatric MOGAD needs further investigation.

We found the top three neurological symptoms initially and during the whole course were seizure, headache, and limb paralysis.

Seizure, headache, and limb paralysis are common symptoms of ADEM and encephalitis. Consistent with the distribution of clinical phenotypes, the most frequent phenotype was ADEM (58.1%). The phenotype distribution in our study was similar to other pediatric MOGAD studies (6, 13, 29, 30). However, in contrast to the adult MOGAD, where ON and NMOSD were the common phenotypes, ADEM was less seen (7, 19). In our study, the visual deficit which was the core feature of ON initially and during the whole course was seen in 15.1% and 31.2%, respectively.

The radiological features of MOGAD spontaneously separated from MS but overlapped with AQP4 antibody disease (25). We found basal ganglia was commonly involved and corpus callosum was frequently involved, and the lesions of a majority of patients (72.0%) had unclear boundaries. However, corpus callosum involvement was commonly seen in MS, and basal ganglia and unclear boundaries lesions were uncommonly seen in MS (25). Furthermore, Jurycnzyk et al. found that T1 hypointense lesions, Dawson's fingers, and ovoid lesions adjacent to the body of lateral ventricles helped discriminate MS from MOGAD (25). The typical lesion locations of MOGAD, including subcortical white matter, cortical gray matter, cerebellum, brainstem, and deep white matter in our study and previous studies, were also common to see in AQP4 disease, except for basal ganglia and thalamus, which was less common in AQP4 disease (13, 25). In orbital MRI, we found bilateral optic nerve involvement was more common than unilateral (61.1% VS 38.9%), and the orbital and intracanalicular segments were frequently involved, similar to previous studies (3, 13, 31–34). In the spinal cord MRI, 21.5% (20/93) of patients were abnormal, with LETM (80.0%) commonly seen and the cervical segment the most frequently involved. LETM was commonly seen in MOGAD, similar to the AQP4 disease but different from MS, in which SM was more common (7, 13, 35–37). Both the thoracic and cervical spinal cord were frequently involved in MOGAD (7, 13, 38, 39). Conus involvement was also more commonly seen in MOGAD (reported in 11%-41%) than in AQP4 disease and MS (39). In our study, 10% of patients had conus involvement. Analyzing MRI recovery at the last follow-up, we found lesions completely absorbed or mostly absorbed in more than 80%, similar to previous studies, showed that resolution of lesions in MRI was more commonly seen in MOGAD, which was not typically seen in AQP4 disease (25, 39, 40). Moreover, we found that the MRI lesion recovery varied in different clinical phenotypes. Lesions in patients with ON/NMOSD or encephalitis were more likely to be completely absorbed. In contrast, lesions in patients with ADEM were more likely to be partially absorbed with residual neuron necrosis regarding the onset attack phenotype.

In our study, the relapse rate was 24.7%, with 34 episodes in total. The relapse rate of MOGAD in previous studies varied from 17.0% to about 95.1% (6, 13, 19, 20, 41–43). Though nearly one-quarter of relapsed patients experience their first relapse within 12 months after onset, the median interval from onset to the first onset varies from 5 to 36 months, and the longest interval even can be longer than ten years (43). Therefore, the follow-up duration must be considered when referring to the relapse rate. In our relapsed patients, 26.5% of episodes occurred during the steroid less than 5 mg/d or within 3 months after steroid withdrawal. Previous studies also found that more than 30% to 40% of patients experienced relapses during steroids on a low dose or withdrawal (33, 40, 41). Moreover, we found that relapsed patients had a longer interval from onset to diagnosis, higher MOG antibody titer at onset, longer duration of persisting MOG positive, and most relapsed attacks occurred with persistent MOG antibody positive. Previous studies also found high MOG antibody titers at onset were associated with increased relapse risk. Furthermore, patients who became MOG antibody negative were less likely to develop relapses than those who remained seropositive (6, 44, 45). Besides, Juryńczyk et al. found persistence of MOG antibodies in children with ADEM phenotype appears to predict further relapses (30). A high titer of species-specific MOG antibodies may be critical for demyelinating effects in mouse and rat animal models (28, 46). These suggest that the MOG antibody might play a pathogenic role in MOGAD. Therefore, it is recommended to tailing to a low dose of oral prednisolone for six months after the initial attack, especially in MOG antibody-positive patients (30).

The treatment of MOGAD is adopted mainly from the AQP4 antibody NMOSD, and much remains unclear (30). IVMP, IVIG, or plasma exchange comprise the first-line immunotherapy for MOGAD. All patients in our study received IVMP and IVIG treatment. Most patients (73.1%, 68/93) achieved remission after only one IVMP and IVIG treatment course. We also found that another 21 patients who received more courses of IVMP or IVIG also achieved remission. Additional IVMP or IVIG treatment courses improve remission, similar to anti-NMDAR encephalitis patients (47). One patient responded poorly to IVIG, and IVMP achieved remission after RTX treatment. In Armangue et al.'s study, three patients also received RTX treatment at disease onset (6). Regarding the recovery from the onset attack, we found that patients with ON/NMOSD or ADEM were more likely to achieve complete recovery. In contrast, patients with uncategorized MOGAD were more likely to be absent from recovery. Furthermore, EDSS at onset and after acute treatment in patients with ON/NMOSD or ADEM tended to be lower than in patients with uncategorized MOGAD. It suggested that the difference in treatment response between the patients with ON/NMOSD or ADEM and uncategorized MOGAD might be caused by the difference in disease severity at the onset.

MMF, monthly IVIG, and maintenance of a low dose of oral prednisone were used as maintenance immunotherapy for relapsed patients in our study. About half of them became relapse-free with only one immunotherapy, and another half became relapse-free after combining with another immunotherapy. Similar to the previous study, MMF, monthly IVIG, and maintenance of a low dose of oral prednisone can decrease the relapse frequency in most patients with MOGAD (6, 34, 48, 49).

Our study found that 41.9% of patients had neurological sequelae with a movement disorder and mild visual impairment. Pediatric MOGAD patients had a better prognosis than adult patients (7). Moreover, visual impairment was common sequelae in pediatric and adult patients but more common in adult patients (7). Furthermore, we found that compared with patients without sequelae, patients with sequelae had higher MOG antibody titer at onset, longer duration of persisting MOG antibody positive, and higher relapse rate. As

mentioned above, relapsed patients also had higher MOG antibody titer at onset and longer duration of persisting MOG antibody-positive than relapse-free patients. Jurynczyk et al. found that tailing steroids to a low dose and maintenance helped reduce relapse and improve the prognosis for patients with a severe attack at onset or relapse (30). However, it was unknown whether it could be beneficial for patients with high MOG antibody titer at onset, and the longer duration of persisting MOG antibody.

In summary, our study of 93 pediatric MOGAD patients had a relatively large sample size, with the largest sample size among Chinese pediatric MOGAD studies (7, 13, 20). The demographical features, neurological symptoms, and radiological features were similar to previous pediatric MOGAD studies (3, 6, 13, 18–22, 29–34). However, the ratio of patients who had prodromal events within one month before onset was obviously higher than previous study (28), among which more than 90% were acute respiratory infection and vaccination. Moreover, we found that MRI lesion recovery and recovery from the onset attack varied in different MOGAD clinical phenotypes. In addition, we found that additional IVMP or IVIG treatment courses could improve remission, similar to the anti-NMDAR encephalitis patients (47). The relapse rate was relatively high, and we found that relapsed patients had a longer interval from onset to diagnosis, higher MOG antibody titer at onset, longer duration of persisting MOG positive, and most relapsed attacks occurred with persistent MOG antibody positive. Furthermore, we found that compared with patients without sequelae, patients with sequelae also had higher MOG antibody titer at onset, longer duration of persisting MOG antibody positive, and higher relapse rate. Therefore, it is recommended to tailing to a low dose of oral prednisolone for six months after the initial attack, especially in MOG antibody-positive patients (30). However, it was unknown whether the above-said strategy could benefit those patients with high MOG antibody titer at onset, the longer duration of persisting MOG antibody, or both. Further work is required to identify the optimal therapeutic strategies to reduce relapse and minimize disability in MOGAD patients.

4 Conclusions

Of pediatric MOGAD in southern China: the median onset age was 6 years, with no obvious sex distribution difference; seizure or limb paralysis, respectively, being the most common onset or course symptom; the lesions of basal ganglia, subcortical white matter, the orbital segment of the optic nerve, and cervical segment were commonly involved in the central nerve system MRI; ADEM was the most common clinical phenotypes; most had a good response to immunotherapy; the relapse rate was relatively high maybe relation to delay diagnosis and MOG antibody titer status; MMF, monthly IVIG and maintaining a low dose of oral prednisone is effective in reducing relapse; neurological sequelae were not less seen and associated with MOG antibody status, as well as disease relapse.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Guangzhou Women and Children Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XL, WLW, CH and YRZ devised the study concept, handled the acquisition of data, and drafted the manuscript. WXW, LC and YTL aided in the acquisition of data. HZ, YT, BP, KZ, KS and YL analyzed and interpreted the data. YG, YNZ and HL interpreted of data. W-XC helped with study concept, study design, and critical revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Investigating the association between neoplasms and MOG antibody-associated disease

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Introduction: The association of myelin oligodendrocyte glycoprotein (MOG) antibody associated disease (MOGAD) and tumors has seldom been reported. We aim to investigate the occurrence of tumors in a cohort of patients with MOGAD and to describe their clinical features, in addition to previously reported cases.

Methods: We retrospectively identified patients with MOGAD (i.e., compatible clinical phenotype and positive MOG antibodies analysed with a live cell-based assay) from 1/1/2015 to 1/1/2023 who had a neoplasm diagnosed within 2 years from MOGAD onset. Furthermore, we performed systematic review of literature to identify previously reported cases. Clinical, paraclinical and oncological findings were collected and reported as median (range) or number (percentage).

Results: Two of 150 MOGAD patients (1%) had a concomitant neoplasm in our cohort. Fifteen additional cases were retrieved from literature. Median age was 39 (16–73) years-old, 12 patients were female. ADEM (*n* =4;23.5%), encephalomyelitis (*n* =3;17.6%), and monolateral optic neuritis (*n* =2;11.8%) were the most frequent phenotypes. Median number of treatments was 1 (range 1–4), improvement was reported in 14/17 cases (82.4%). Oncological accompaniments were teratoma (*n* =4), CNS (*n* =3), melanoma (*n* =2), lung (*n* =2), hematological (*n* =2), ovary (*n* =1), breast (*n* =1), gastrointestinal (*n* =1), and thymic (*n* =1) neoplasms. Median time from tumor diagnosis to MOGAD onset was 0 (range−60 to 20) months. MOG expression in neoplastic tissue was reported in 2/4 patients. Median PNS-CARE score was 3 (range 0–7): 11 patients were classified as "non-PNS," 5 as "possible PNS," and 1 as "probable PNS."

Discussion: Our study confirms that MOG is a low-risk antibody for paraneoplastic neurological syndromes and that the clinical presentation and oncological accompaniments are extremely variable. Most of these patients were classified as non-PNS, whereas only a minority was diagnosed with possible/probable PNS, frequently in association with ovarian teratoma. These findings support the notion that MOGAD is not a paraneoplastic disease.

KEYWORDS

myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), paraneoplastic neurological syndrome, tumor, cancer, immune checkpoint inhibitors

Introduction

Paraneoplastic neurological syndromes (PNS) are defined by the presence of specific clinical features in association with cancer and specific autoantibodies (1). Among these autoantibodies, those targeting aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) are associated with a low risk of cancer, even though MOG or AQP4 expression may be detected on cancer tissue, supporting a paraneoplastic origin in those few reported cases. While the association between neoplasms and AQP4-seropositive neuromyelitis optica spectrum disorder (NMOSD) has been investigated in previous studies (2–4), data on patients affected by MOG antibody-associated disease (MOGAD) (5) are still lacking and limited on few case reports (6). Aim of this study is to report the association between neoplasms and MOGAD in a single-center cohort and, additionally, to provide a systematic evaluation of previously reported cases.

Materials and methods

We retrospectively identified patients with MOGAD [i.e with a compatible phenotype and positive MOG-Abs analysed with a live cell-based assay as previously described (7)] and a neoplasm diagnosed within 2 years from disease onset. Clinical, paraclinical, and oncological data were collected and are herein reported. As cancer screening is currently not required in patients with MOGAD, paraneoplastic analyses were performed by treating physicians on an individualized basis according to physical examination or routine laboratory screening. In addition, to identify previously reported cases of paraneoplastic MOGAD, a systematic literature review based on PubMed/Medline database was performed (March 7th, 2023) using the following research queries: ("myelin oligodendrocyte glycoprotein" OR "MOG"OR "MOG-EM" OR "MOGAD") AND ("cancer" OR "paraneoplastic" OR "tumor" OR "teratoma") including studies on individual cases. Furthermore, all articles included after abstract screening were cross-referenced. Relevant reported clinical, paraclinical, and oncological findings were collected in an electronic database. PNS Care score was evaluated in each case at clinical presentation, as previously described (1).

A descriptive statistical analysis was performed using median (range) and number (%), as appropriate (IBM SPSS 26) including both data obtained from the retrospective study and the systematic review. For estimating the percentage of cancer occurring within 2 years in patients with MOGAD, we included only cases identified in our cohort excluding those obtained from the systematic review. Finally, patients classified as non-PNS were compared to patients fulfilling the criteria of Probable/Possible/Definite PNS (Fisher's and U-Mann Whitney tests). Patients gave their informed consent for being included in this study.

Results

Retrospective cohort study

Of 185 patients diagnosed with MOGAD from 1/1/2015 to 1/1/2023, two patients out of 150 with available clinical information had a neoplasm within 2 years from MOGAD onset (~1%). These two cases are reported below. Both reported cases resulted negative for additional autoantibodies analysed with commercial and on in-house tissue-based assay (8).

Case #1

A 59-year-old man presented with acute onset of fever, imbalance, dysarthria, and hallucinations. Brain MRI was unremarkable, while on CSF analysis pleocytosis (645 cells/mm^3 N.V. <5) and increased protein levels (477 mg/dL N.V. <45 mg/dL) were observed. Although an extensive infectious and autoimmune screening including antibodies to neuronal and cell surface antigens were negative, the clinical suspicion of brainstem encephalitis led to start treatment with steroids, with complete recovery. Respectively two and 9 months after onset, generalized tonic–clonic seizures occurred and antiepileptic drugs (AED) were commenced. A repeated brain MRI showed multiple T2/FLAIR hyperintense lesions in the supratentorial and infratentorial white matter, with pons contrast enhancement. 4 months later, the patient developed a severe paraparesis with sensory level and sphincter dysfunction. Total body computed tomography (CT) scan was unremarkable while spinal cord MRI revealed multiple T2/FLAIR hyperintensities (at C7-D1, D8-D10, and D11 level) suggestive of mixed short and longitudinally extensive transverse myelitis (LETM). A repeated CSF analysis showed slightly increased cell count (7/mm^3), normal protein values (41.8 mg/dL), and negative oligoclonal bands (mirror pattern). An expanded autoimmune screening with live cell-based assay revealed the presence of serum MOG-Abs (titre 1:320). The patient was diagnosed with MOGAD and treated with high dose intravenous steroids followed by slow tapering. Since only a partial response was observed, treatment with Rituximab was commenced. 20 months later, the appearance of a unilateral axillary lymphadenopathy led to a diagnosis of a non-Hogdkin lymphoma and the patient was treated with chemotherapy.

Case #2

A 64-year-old man while admitted for pneumonia and acute kidney failure developed subacute consciousness impairment requiring orotracheal intubation. On neurological examination he was comatose and unresponsive to pain stimulus with right-sided pyramidal signs. Brain MRI showed diffuse T2/FLAIR hyperintense lesions in the supratentorial and infratentorial white matter involving the brainstem (Figure 1A). EEG revealed generalized theta and delta slowing without epileptic abnormalities. CSF analysis demonstrated mild pleocytosis (10 cells/mm^3). An extensive screening for CNS infections, autoimmune/paraneoplastic encephalitis, metabolic encephalopathy, and uremic hemolytic syndrome yielded negative results except for the detection of serum MOG-Abs (titer 1:320) using a live cell-based assay. The patient was diagnosed with MOGAD-related encephalitis and treatment with high dose intravenous steroids followed by oral tapering led to significant neurological improvement. Clinical inspection revealed a skin lesion localized in the right hemithorax suggestive for malignancy. Thus, a biopsy was performed and histological analysis confirmed a locally invasive melanoma (stage pT1b). Total body CT as well as sentinel lymph node biopsy excluded systemic localization. 4 month later the patient was asymptomatic with a normal neurological evalution, MOG-Abs titers were decreased (1:160), and a control MRI showed almost complete resolution of pre-existent lesions (Figure 1B).

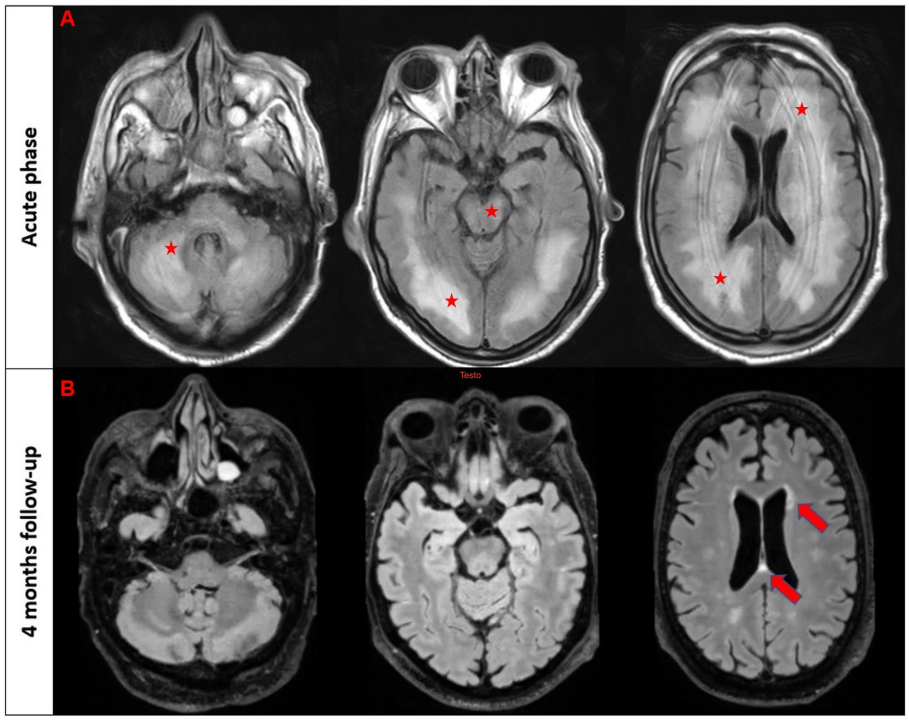

FIGURE 1
T2/FLAIR imaging in the acute phase (first raw) and follow-up brain MRI after 4 months in patient #2. The first three images from the acute phase reveal a diffuse T2/FLAIR hyperintensity involving bilateral white matter, brainstem, and cerebellum (marked with stars). The follow-up scans demonstrate a nearly complete resolution of these abnormalities with few scattered white matter hyperintensities in the periventricular regions (marked with an arrow).

Systematic review

Of 616 results, 10 studies underwent to full-text evaluation and 8 were included in the final analysis. Furthermore, 7 studies were included through cross-referencing of relevant articles. A total number of 15 studies with 15 cases were included in the final synthesis [(9–23). The PRISMA flow chart is reported in the Supplementary materials.

Clinical features of the pooled cohort

In the pooled cohort analysis 17 cases were included (Table 1). Median age at onset was 39 years (range 16–73) and 12 patients were female (70.5%).Clinical phenotypes were consistent with: ADEM (n = 4, 23.5%), encephalomyelitis (n = 2, 11.8%), monolateral optic neuritis (n = 2, 11.8%) and one (5.9%) of each of bilateral optic neuritis, encephalitis, encephalomyeloradiculitis, isolated myelitis, myelitis and bilateral optic neuritis, myelitis and bilateral optic neuritis with brainstem involvement, optic neuritis and brainstem syndrome, optic neuritis and meningoencephalitis, brainstem syndrome, encephalitis and myelitis. One patient was also positive for anti-GFAP and anti ITPR−1 antibodies and presented with combined CNS and PNS involvement, which has been previously reported in MOGAD (24, 25). Patients received a median of 1 acute treatment (range 1–4): steroids were administered in 16 cases, intravenous immunoglobulins in 3, plasma exchange in 3, and rituximab in 3. Clinical improvement after immunotherapy was reported in 14 patients (82.4%), whereas no improvement was observed in 3 cases (17.6%). Regarding the oncological accompaniments, associated neoplasms were teratoma (n = 4, in one case with also ganglioneuroma), CNS tumors (n = 3, pituitary macroadenoma, meningioma, and astrocytoma), melanoma (n = 2), lung cancer (n = 2, both adenocarcinoma), hematological malignancies (n = 2, non-Hodgkin lymphoma and cutaneous T cell lymphoma), borderline tumor of the ovary (n = 1), ductal breast carcinoma (n = 1), colon adenocarcinoma (n = 1), and thymic hyperplasia (n = 1). MOG protein expression in the excised tumoral tissue was reported in 2/4 patients (50%). Median time from tumor diagnosis to MOGAD onset was 0 months (range from −60 to +20, with negative values indicating that tumor preceded the onset of the neurological syndrome). Oncological treatment included surgery in 11 cases, chemotherapy in 4, radiotherapy in 1, other treatments in 3 (including hormonal therapy, pembrolizumab, and anti EGFR-TKI). Three patients did not receive any treatment. Median PNS-CARE score was 3 (range 0–7). In particular, 11 patients were classified as "non-PNS," 5 patients as "possible PNS," and 1 patient as "probable PNS." The comparison between patients with non-PNS and with possible and probable PNS did not yield any significant difference, with the exception for a trend favoring the association with ovarian teratoma (p = 0.063), Table 2.

Discussion

Our study supports the weak association between MOGAD and tumors, since: (a) the prevalence of neoplasms in a cohort of patients with MOGAD is low, (b) oncological accompaniments are extremely variable and MOG is usually not expressed in neoplastic tissue, (c) most of reported cases do not fulfill the criteria of PNS; (d) there are

TABLE 1 Demographic, clinical, and oncological features of the included cohort.

Study	Sex/ age	Neurological manifestation	Tumor association	MOGAD onset in relation to tumor	Neurological treatments	Tumor treatment	Neurological outcome	MOG expression on tumor	PNS-CARE score/ final diagnosis	Other antibodies
Herein presented case (nr. 1)	M/59	Brainstem syndrome, followed by supratentorial encephalitis, myelitis	Non-Hodgkin lymphoma	20 months prior	Steroids, RTX	CHT	Improvement	N.A.	(2 + 0 + 1) 3/non-PNS	No
Herein presented case (nr. 2)	M/64	Encephalitis	Melanoma	Concomitant	Steroids	Surgery	Improvement	N.A.	3 (2 + 0 + 1)/non-PNS	No
Li et al.	F/49	Myelitis, bilateral optic neuritis, and brainstem syndrome	Lung adenocarcinoma	1 month after	Steroids	Surgery, anti EGFR-TKI	Improvement	N.A.	1 (0 + 0 + 1)/non-PNS	No
Cherian et al.	F/37	Myelitis	Ductal breast carcinoma	12 months after	Steroids	Surgery, CHT, Hormones	Improvement	N.A.	3 (2 + 0 + 1)/non-PNS	No
Rodenbeck et al.	F/64	ADEM	Lung carcinoma	Concomitant	Steroids, PLEX	N.A.	No improvement	N.A.	(0 + 0 + 1)/non-PNS	No
Jarius et al.	F/18	ADEM	Teratoma+Ganglioneuroma	2 months after	Steroids, PLEX, IvIg	Surgery	Improvement	N.A.	4 (0 + 0 + 4)/possible-PNS	No
Kwon et al.	M/38	Myelitis and bilateral optic neuritis	Cutaneous T-cell lymphoma	6 months prior	Steroids	CHT	Improvement	Negative	1 (0 + 0 + 1)/non-PNS	No
Cohen et al.	F/52	ADEM	Colon adenocarcinoma with lung metastases	5 years after adenocarcinoma	Steroids	N.A.	No improvement	N.A.	0 (0 + 0 + 0)/non-PNS	No
Wildemann et al.	F/26	Optic neuritis	Teratoma	11 months after	Steroids	Surgery	Improvement	Positive	4 (0 + 0 + 4) /possible-PNS	No
Cirkel et al.	F/44	Encephalomyeloradiculitis	Borderline tumor of the ovary	Concomitant	Steroids, IvIg, RTX, PLEX	Surgery	No improvement	Negative	(3 + 0 + 1)4/possible-PNS	GFAP, ITPR-1
Ajam et al.	M/25	Optic neuritis	Meningioma	3 months after	Steroids	Surgery	Improvement	N.A.	1 (0 + 0 + 1)/non-PNS	No
Delgado et al.	F/37	Bilateral optic neuritis	Pituitary macroadenoma	Concomitant	Steroids	None	Improvement	N.A.	1 (0 + 0 + 1)/non PNS	No
Zhang et al.	F/61	Encephalomyelitis	Teratoma	Concomitant	Steroids	Surgery	Improvement	Positive	7 (3 + 0 + 4)/probable-PNS	No
Cobo-Calvo et al.	F/16	ADEM	Teratoma	Concomitant	IvIg	Surgery	Improvement	N.A.	4 (0 + 0 + 4)possible-PNS	No
Liu et al.	M/39	Encephalomyelitis	Melanoma	6 months after	Steroids	Surgery+pembrolizumab	Improvement	N.A.	4 (3 + 0 + 1)/possible-PNS	No
Zhong et al.	F/49	Optic neuritis and brainstem syndrome	Astrocytoma	4 years after	Steroids	Surgery+RT	Improvement	N.A.	0 (0 + 0 + 0)/non-PNS	No
Hurtubise et al.	F/18	Optic neuritis and meningoencephalitis	Thymic hyperplasia	3 months prior	Steroids, RTX	None	Improvement	N.A.	1 (0 + 0 + 1)/non-PNS	No

M, male; F, female; ADEM, acute disseminated encephalomyelitis; RTX, rituximab; PLEX, plasma exchange; IvIg, intravenous immunoglobulins; PNS, paraneoplastic neurological syndrome; CHT, chemotherapy; RT, radiotherapy; GFAP, glial fibrillart acid protein; ITPR-1, inositol trisphosphate receptor-1.

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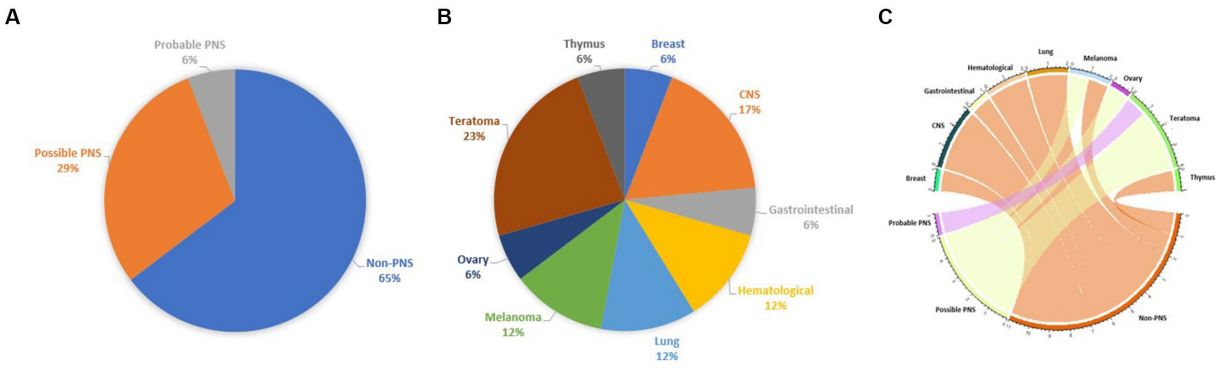

FIGURE 2
Chart representing the percentage of each tumor in the pooled cohort analysis **(A)**, the fulfillment of PNS diagnostic criteria **(B)**, and a circos plot represents the association between neoplasms and fulfillment of PNS diagnostic criteria **(C)**.

TABLE 2 Comparison of patients according to the PNS-CARE classification.

	Non-PNS (*n* =11)	Possible/probable PNS (*n* =6)	value of *p*
Age (years)	49 (18–64)	32.5 (16–61)	0.256
Sex (female)	7 (63.6%)	5 (83.5%)	0.365
Clinical phenotype	ADEM 2 (18.2%) Bilateral optic neuritis 1 (9.1%) Encephalomyelitis 1 (9.1%) Myelitis 1 (9.1%) Myelitis and bilateral optic neuritis 1 (9.1%) Myelitis, bilateral optic neuritis, and brainstem syndrome 1 (9.1%) Monolateral optic neuritis 1 (9.1%) Optic neuritis + meningoencephalitis 1 (9.1%) Optic neuritis and brainstem syndrome 1 (9.1%)	ADEM 2 (33.3%) Encephalomyelitis 2 (33.3%) Encephalomyeloradiculitis 1 (16.7%) Monolateral optic neuritis 1 (16.7%)	0.676
Associated tumor	CNS 3 (27.3%) Hematological 2 (18.2%) Lung 2 (18.2%) Gastrointestinal 1 (9.1%) Breast 1 (9.1%) Melanoma 1 (9.1%) Thymus 1 (9.1%)	Teratoma 4 (66.7%) Ovary 1 (16.7%) Melanoma (16.7%)	*0.063*
Time from MOGAD to tumor diagnosis	0 (−60–20)	-1 (−11–0)	0.733
Number of treatments	1 (1–2)	1 (1–4)	0.660
Neurological outcome (improvement)	9 (81.8%)	5 (83.3%)	0.728

ADEM, acute disseminated encephalomyelitis; PNS, paraneoplastic neurological syndrome; CNS, central nervous system; MOGAD, myelin oligodendrocyte antibody-associated disorder.

no striking features that could distinguish cases with possible/probable PNS from those with non-PNS, with the notable exception for a trend favoring the presence of ovarian teratoma in the first group (Figure 2).

In comparison with a previous study (14) reporting 11.3% of patients with a history of cancer within 12 months from MOGAD onset, with higher rates of prevalence in elderly patients, we observed a significant lower number (1%) of MOGAD cases associated with tumors. In addition, we found a significant lower number of patients with concomitant neoplasms and MOGAD (6.5% vs. 35%). These discrepancies may be explained by the differences in terms of population groups and inclusion criteria.

In support of the absence of a strict association between MOGAD and tumors by systematically reviewing the published literature we observed that neoplasms associated with MOGAD are extremely variable and include even some non-malignant tumors, which mostly fell in the non-PNS group. Even though we did not find an association between MOGAD and a specific cancer, the presence of ovarian teratoma seems to be particularly relevant, as both tumors that

expressed MOG protein were teratomas (17, 18), and these data may support a paraneoplastic origin. Furthermore, the presence of teratomas has been associated with different antibody-mediated CNS disorders including AQP4 positive NMOSD (26) and anti-NMDAR encephalitis (27). Consistently, even though no patients were diagnosed with definite PNS, those who had a diagnosis of probable/possible PNS had a statistical trend favoring the presence of an underlying teratoma when compared to non-PNS patients. Consistently, PNS-CARE score was mostly driven by the presence of an underlying teratoma which, alone, would give a score of 4, leading to a diagnosis of possible PNS regardless of the clinical phenotype. This finding could suggest that PNS-CARE scoring system may present some limitations in the setting of a condition characterized by heterogeneous clinical presentations and very specific oncological accompaniments. Of note, one patient without an ovarian teratoma who fulfilled the criteria of possible PNS was receiving treatment with the immune checkpoint inhibitor pembrolizumab, which probably triggered MOGAD. Accordingly, iatrogenic demyelination as an immune-related adverse event of cancer immunotherapy is rare but should not be overlooked.

Finally, we did not find any specific clinical phenotype or demographic feature which may suggest a paraneoplastic trigger and thus should prompt an oncological screening. Furthermore, most of patients improved with immunotherapy only, regardless of neoplasm removal, which is atypical for PNS (28). We previously suggested to perform a paraneoplastic screening regardless of clinical presentation in AQP4 positive NMOSD despite the lack of specific clinical features in suspected paraneoplastic NMOSD, since several cases of paraneoplastic NMOSD have been reported and AQP4 tumor expression can occur even in patients with atypical oncological accompaniments (as non-adenocarcinomas) (2). On the contrary, we do not support tumor screening in MOGAD, since the lack of cancer expression beyond ovarian teratoma and the lack of other suggestive features do not support this extensive screening.

Our study presents several limitations including (a) the small sample size, the absence of a control group, and the unavailability of a systematic and uniform screening of neoplasms in our cohort, (b) the lack of evaluation of MOG expression in many studies, including our cases, and (c) the potential reporting bias favoring the overreporting of patients presenting with MOGAD and neoplasms.

Despite these limitations, our study confirms that MOG is a low-risk antibody for paraneoplastic neurological syndromes and that the clinical presentation and oncological accompaniments are extremely variable. These findings support the notion that MOGAD is not a paraneoplastic disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Verona University Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MT and AD equally contributed and collected data, and wrote the first draft of the manuscript. GM and SM shared the senior co-authorship. All the authors performed a revision to the manuscript, gave the critical intellectual content, contributed to the article, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1193211/full#supplementary-material

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Transverse myelitis in myelin oligodendrocyte glycoprotein antibody-associated disease

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Transverse myelitis (TM) is the second most common presentation of myelin oligodendrocyte antibody-associated disease (MOGAD), occurring in approximately 26% of affected patients. The diagnosis may be complicated by the lack of diagnostic specificity of low titers of MOG antibody in serum, fluctuation in seropositivity overtime, including initially normal MRI in up to 10% of patients, and in many instances complete resolution of radiological abnormalities when MRI is done in a significantly delayed fashion. The use of preventive disease modifying treatments is limited by the uncertainty whether the disease process will remain monophasic or become relapsing, as well as by the lack FDA approved treatments. In this review, we discuss clinical, radiological and cerebrospinal fluid (CSF) characteristics, including the significance of MOG titers and changes in the seropositivity status for the diagnosis of MOGAD-associated TM, its radiological features and management options, highlighting the data on the risk of relapses associated with TM at presentation and the need for further randomized clinical trials to empower effective treatment algorithms.

KEYWORDS

transverse myelitis, MOG myelitis, myelin oligodendrocyte glycoprotein associated disease, MOG antibody positive myelitis, MOGAD myelitis

Introduction

Transverse myelitis (TM) is the second most common presentation of myelin oligodendrocyte antibody-associated disease (MOGAD), occurring in approximately 26% of MOGAD (1). TM can occur in isolation, simultaneously with optic neuritis (less than 10% of patients) or as part of acute disseminated encephalomyelitis (ADEM) (2–4). Clinical presentation in children and adults may vary. TM in MOGAD can occur shortly after an infectious illness (1). It is therefore not surprising that rare cases of MOGAD TM have been reported both after SARS-CoV2 vaccination (ChAdOx1 nCoV-19) and after the infection itself (5, 6). The severity of the attack varies, typically moderate to severe with EDSS scores >4 in about half of patients (7) with up to one third being nonambulatory at the nadir of acute myelitis attack (8), and many requiring bladder catheterization (9). In a prospective UK cohort, transverse myelitis as part of MOGAD was found to be less common in children as compared to adults, and relapsing TM was only observed in adults (3). Optic neuritis is the most common relapsing phenotype of MOGAD, and patients with TM at onset have less risk of relapse as compared to those with other MOGAD phenotypes (3).

Clinical features of MOGAD-associated TM

The clinical manifestations of MOGAD myelitis include sensory, motor or bowel-bladder symptoms, erectile dysfunction, typically with acute to subacute onset of paraparesis or quadriplegia (10). Motor and sensory symptoms are usually bilateral, and sphincter dysfunction is more common than in aquaporin 4 antibody (AQP 4 antibody) positive NMOSD (4). Patients may also present with acute flaccid myelitis (AFM) and may be initially thought to have post-viral or viral-induced AFM (8, 11). Tonic spasms and severe neuropathic pain are less common with MOGAD as compared to AQP4 positive NMOSD (12). Prognosis is generally good, with excellent motor recovery, but residual neurogenic bladder and sexual dysfunction can occur (2).

Diagnosis of MOGAD myelitis

MOGAD myelitis is diagnosed when a patient has neurological deficits and tempo of symptomatic development compatible with myelitis, a clear positive serum MOG-IgG test, and supportive of diagnosis MRI features (2). The latest international expert consensus advocates towards the use of live cell-based assays to increase diagnostic specificity. If not available, fixed cell-based assays can be used, with a clear positive result being a titer >1:100 (2). Titers lower than 1:100 have a lower predictive value (number of true-positive results/total positive results) for MOGAD and may lead to misdiagnosis. For example, a titer of MOG of 1:20 to 1:40 carry a positive predictive value of 51%, meaning that nearly 50% of patients with this titer may have a different etiology of their clinical presentation (13). Serological testing should ideally occur before administration of corticosteroids, intravenous immunoglobulins, or plasma exchange, as these interventions can increase the risk of false negative result. In cases of a high clinical suspicion but a negative test, if done after initiation of immune therapies, testing should be repeated about 3 months or later. Screening for the presence of serum MOG-IgG routinely in patients with clear features of multiple sclerosis is not recommended, as false positives can occur, decreasing the positive predictive value of the test and leading to misdiagnosis (2, 10).

In addition, titers of MOG antibody can fluctuate with intermittent seroconversion to negativity and can become undetectable over time (14); this, and the fact that the MRI abnormalities can disappear (up to 72% of the brain lesions; 79% of spinal cord lesions) (13, 15, 16), make a retrospective diagnosis of MOGAD impossible in some scenarios, which warrants a continuity of high degree of suspicion if new neurological symptoms arise (17).

Cerebrospinal fluid (CSF) analysis typically demonstrates lymphocytic pleocytosis, with >50 WBC/mm^3 seen in about 30% of patients (9). Oligoclonal bands are frequently absent, with positivity rates being less than 10%–15% (4, 18). MOG-IgG antibody concentrations in CSF are typically low, however in some cases MOG-IgG can be positive in CSF and not in serum. Intrathecal antibody production occurs more frequently in MOGAD than in AQP4-positive NMOSD (19). Caution is advised in interpretation of the MOG-IgG positivity when clinical features are atypical of MOGAD, as false positives can occur. Testing both CSF and serum is not recommended for routine evaluations (2). However, if the serum MOG antibody is negative in a patient presenting with clinical, radiological and CSF findings typical of MOGAD, CSF testing for MOG antibody may be considered, as well as re-testing serum several months later.

Current diagnostic criteria for MOGAD require exclusion of an alternative diagnosis. Differential diagnostic considerations include multiple sclerosis, neuromyelitis optica spectrum disorder, CRMP-5 antibody positive paraneoplastic myelopathy, GFAP antibody positive encephalomyelitis, neurosarcoidosis, SLE associated TM, ischemic myelopathy, metabolic myelopathy, infections and neoplastic causes. Specific findings pointing to other inflammatory diagnoses are summarized in Table 1.

Radiological features of MOGAD myelitis

Acute myelitis due to MOGAD is typically longitudinally extensive involving 3 or more vertebral segments in length (Figure 1). Short lesions can occur in about 7% of patients, more commonly in those patients that are approximately 40 years of age (3). Multifocal spinal cord lesions can occur (2, 18). Spinal cord necrosis is typically not seen (20). Some T2 signal abnormalities may be initially subtle and contrast the severity of clinical presentation. In fact, in some cases linear T2 signal abnormalities may be difficult to distinguish from a prominent central canal. In these instances, carefully evaluating axial images may be helpful, as well as repeating the MRI at a later time to evaluate for the evolution of the lesion. MRI of the brain may also show MOGAD-associated lesions and should be considered in TM evaluation. Some patients with MOGAD TM may also have clinically silent spinal cord lesions (20). Although current data are limited by the retrospective nature, one study found silent spinal cord MRI lesions occurred in none of the patients during remission and in up to 7.3% of those during acute attack (21). Another study confirmed that finding new or enlarging spinal cord lesions inter-attack is rare and occurs in <1% of patients (22). Initial MRI of the spinal cord may be normal in up to 10% of patients, and repeat MRI within days would be warranted (13–15).

A negative MRI in a patient presenting acutely with clinical features of myelitis should not deter from testing for MOG antibody. The spinal cord lesions are typically located in the central cord, can involve both the gray and white matter, affect more than 50% of the axial section or can be restricted to the grey matter in about 50% of patients, which on axial imaging can be seen as the "H sign" (2, 23). T2 signal abnormality confined to gray matter (sagittal line and axial H sign) as well as lack of enhancement favor diagnosis of MOGAD over NMOSD or MS (8).

A straight T2 hyperintense line with surrounding hyperintense signal in the anterior and posterior gray matter horns on sagittal view can also be seen in MOGAD myelitis and is known as pseudo dilation of the central canal (23). The conus medullaris can be affected in about 26% of patients with MOGAD (24), which is a valuable radiographic clue, as the conus medullaris is less frequently affected in other demyelinating conditions, such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), with rates of involvement as low as 1.3 and 6%, respectively, (8, 24–26). Gadolinium enhancement can occur in about half of patients with MOGAD myelitis and can be heterogeneous giving a cloud-like appearance (2,

TABLE 1 Differential diagnosis of MOGAD associated-TM.

Disorder	Multiple sclerosis	MOGAD	Aquaporin 4 positive NMOSD	Neurosarcoidosis	NeuroBehcet's	Anti-GFAP astrocytopathy	Anti-CRMP-5
Onset	Acute/subacute	Acute/ subacute	Acute	Subacute/chronic	Acute/subacute	Acute/ subacute	Subacute
Evolution	Relapsing/ progressive	Monophasic/ relapsing	Relapsing	Progressive	Progressive	Progressive	Progressive
Clinical cues	Sensory symptoms predominantly.	Bladder/bowel symptoms.	Area postrema syndrome Other autoimmune comorbidities. (Ex SLE, Sjogren's)	Evidence of systemic involvement. (Ex: Lymphadenopathy)	History of recurrent oral or genital ulcers.	Associated with AQP4 ab and NMDA ab. Concomitant ovarian teratoma.	History or increased risk for cancer. Constitutional symptoms.
Laboratory							
Biomarkers	n/a	Anti-MOG ab in serum >>CSF	Aquaporin-4 ab in serum	n/a	N/A	Anti-GFAP ab in CSF > serum	Anti-CRPM5 ab in serum and CSF
CSF cells	Pleocytosis <50cells/μL (mainly lymphocytes)	Pleocytosis (mainly lymphocytes, neutrophils present in over 40%)	Pleocytosis (neutrophils predominant early on)	Pleocytosis (mainly lymphocytes)	Pleocytosis (neutrophils predominant)	Pleocytosis >50cells/ μL (lymphocytes, monocytes)	Pleocytosis
O-bands unique to CSF	>80%	<10%	<20%	<20%	Rare	50%	Can be present
Neuroimaging							
Extension	Short/long if confluent lesions	LETM, short lesions may be present, conus medullaris involvement	LETM, up to 15% with short segment lesions	Short/LETM	Short/LETM	LETM	LETM
Number of lesions	Single/ multifocal	Single or multifocal	Single	Single/multifocal	Single/multifocal	Single	Single
Location	Dorsal/lateral column	Central (30% only gray matter) H sign	Central (gray and white matter)	Central / subpial/ leptomeningeal involvement	Central or anterior horn cells	Diffuse	Tract specific (lateral columns)
Enhancing	Nearly always in the acute setting	Enhancing in 50% cases acutely	Yes (most commonly in optic neuritis and transverse myelitis) Variable incidence of brain enhancing lesions	Yes, usually persistent for months.	Yes	Often faint enhancement	Variable
Enhancing pattern	Ringlike or homogeneous	Faint; dorsal nerve root enhancement, cauda equina and pial enhancement may occur	Ringlike or patchy "cloud-like" Pencil-thin linear enhancement of the ependymal surface of lateral ventricles	Dorsal subpial (trident sign)	Ringlike or non-specific (bagel sign)	Patchy, punctate and pia	Tract specific

NA, not applicable; MOG, Myelin oligodendrocyte glycoprotein; MOGAD, Myelin oligodendrocyte glycoprotein antibody disease (MOGAD); ab, antibody; NMOSD, Neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus; CSF, cerebrospinal fluid; GFAP, Glial fibrillary acidic protein; anti-CRPM-5, collapsin response-mediator protein-5; NMDA, N-methyl-D-aspartate; LETM, Longitudinal extensive transverse myelitis; O-bands, oligoclonal bands.

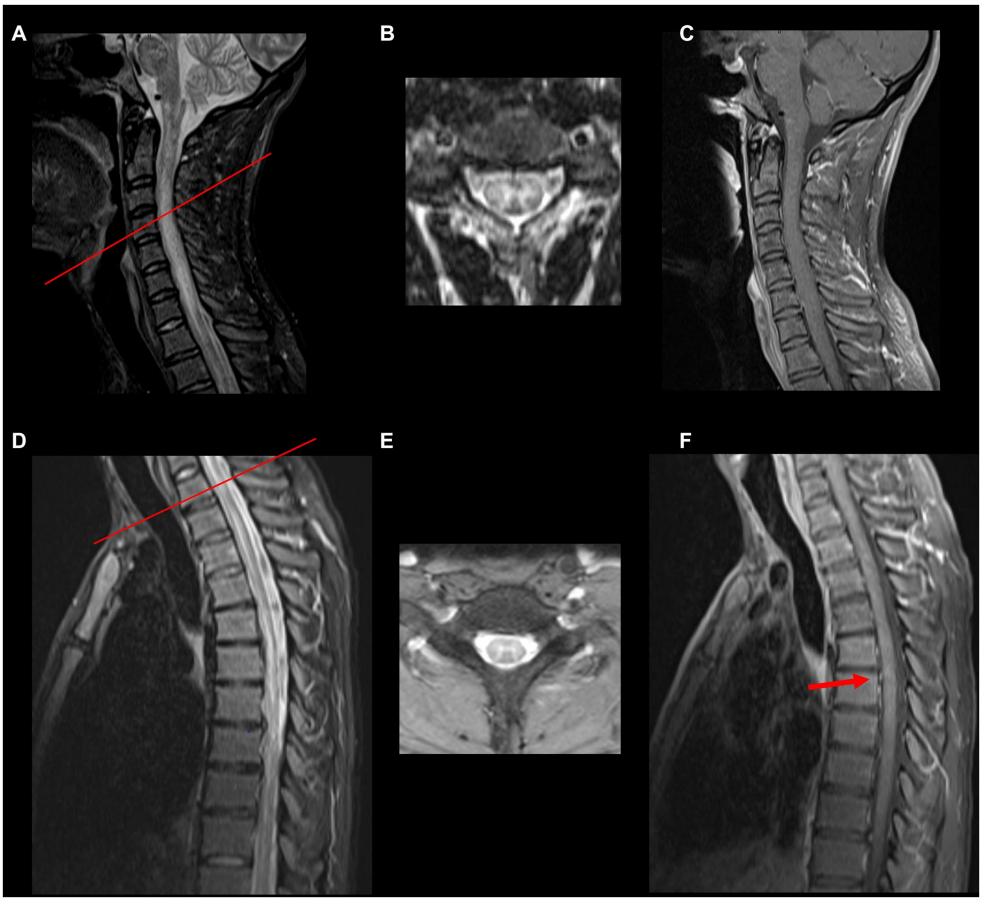

FIGURE 1
Spinal cord MRI in MOGAD myelitis. **(A,D)** Abnormal hyperintense T2/FLAIR signal abnormality with cord expansion from the cervicomedullary junction extending to the thoracic spinal cord. **(B,E)** Show axial T2 images (red bar indicates the spinal cord of the axial section) resembling H sign (grey matter involvement). **(C,F)** Show post gadolinium T1 sequences, respectively. No enhancement is noted in the cervical spinal cord, but a small focus of enhancement is noted at T9 and T10 (red arrow).

9, 23). Interestingly, dorsal nerve root enhancement, cauda equina and pial enhancement can also occur (2).

Clinically silent new lesions on MRI are rare and occur in only 3% of patients with MOGAD (21, 27). Upon follow up and resolution of acute myelitis, complete resolution of spinal cord lesions can be seen in up to 79% of MOGAD cases (4). Spinal cord atrophy can be seen in severe cases, but this is rare (2).

Acute management of MOGAD transverse myelitis

In the acute setting, patients presenting with TM receive intravenous corticosteroids. For those with incomplete recovery or severe clinical picture overall, plasma exchange is typically used next (9, 28). Intravenous immunoglobulins (IVIG) can also be used following the plasma exchange completion, given that intravenous immunoglobulins can also serve as an effective preventive therapy for those patients who elect long-term preventive therapy option (29). Steroids are typically tapered slowly over at least a month or longer, with some data pointing to a lower risk of relapse in those with steroid use >1 month (16).

Chronic management of MOGAD

Disease modifying treatments

In about 40%–50% of cases, MOGAD appears to be monophasic long-term; however, 50%–60% patients presenting with their first attack of MOGAD will go on to develop the relapsing type of the disease. While the disappearance of MOG antibody serologically cannot be used as a definitive sign of the disease being monophasic (17), some data show that pediatric patients who seroconvert to negativity may have a somewhat lower risk of relapse (30). In the UK cohort, the final status of MOG antibody was not found to be associated with the relapsing disease overall, but the longitudinal analysis showed a reduction of 4–5% in monthly relapse risk in those who seroconverted negative for MOG IgG. Same study showed that the patients presenting with TM may have lower rates of relapsing disease: TM as the first attack was associated with a lower risk of relapse (OR, 0.03; 95% CI, 0.004–0.23; $p = 0.001$) and a longer time to first relapse (HR, 0.42; 95% CI, 0.22–0.82; $p = 0.011$) (16). In another study, TM at presentation alone or in combination with another syndrome (ON, ADEM, brainstem) was likewise associated with lower risk of relapse (HR, 0.41; 95% CI, 0.20–0.88; $p = 0.01$) (3).

A discussion whether a long-term disease modifying treatment needs to be started after the first attack or only after the disease course proves itself to be relapsing, risks versus benefits of both approaches should be carefully explored with every patient. Some clinicians may offer preventive disease modifying treatments as early as after the first attack, if the attack was severe with poor recovery leading to significant residual disability, thus if the second attack were to occur, it would be detrimental to the patient's quality of life and independence.

Treatments commonly used in the prevention of MOGAD relapses are rituximab, azathioprine, mycophenolate mofetil, tocilizumab, and intravenous immunoglobulins. A recent meta-analysis of 41 studies (3 prospective, 1 ambispective, 37 retrospective) evaluating efficacy of MOGAD-associated treatments found that the proportions of patients free of relapse were 65% [95% confidence interval (CI): 49%–82%] on azathioprine, 73% (95% CI: 62%–84%) on mycophenolate mofetil, 66% (95% CI: 55%–77%) on rituximab, 79% (95% CI: 66%–91%) on IVIG, and 93% (95% CI: 54%–100%) on tocilizumab (31).

Symptomatic management

Patients with MOGAD transverse myelitis can go on to develop chronic neuropathic pain, weakness, and bladder dysfunction. Addressing these symptoms effectively and in a timely manner is critical to the patient's quality of life. Medications utilized for the treatment of neuropathic pain such as gabapentin, pregabalin, and in some instances addition of duloxetine can be utilized. Physical and occupational therapy during recovery period and periodically in those without complete recovery are recommended. Bladder symptoms are best addressed and managed by a knowledgeable urologist or a neuro-urologist. Neuropsychiatric consultation may be warranted in patients with adjustment disorder, anxiety or depressive symptoms secondary to the medical condition.

MOGAD TM outcomes

Neurological outcomes of patients with TM due to MOGAD are typically more favorable than of those with anti-aquaporin4 antibody positive NMOSD. A recent study evaluating long-term outcomes of patients with TM due to MOGAD ($n = 32$) vs. NMOSD ($n = 57$) found that MOGAD TM patients on average had a lower EDSS score than patients with AQP4-Ab TM (1.8 [1.0–8.0] vs. 3.0 [1.0–8.0]), reflecting better outcomes. Due to higher predilection of MOG positive TM to conus localization, persistent bladder dysfunction was more common in patients with MOGAD (59% with MOGAD and 48% with AQP-4 positive NMOSD), with up to 23% requiring long-term catheterization in both groups. In addition, neuropathic pain was less common in patients with MOGAD TM vs. NMOSD TM (29% vs. 13%) (32).

Discussion

Transverse myelitis is the second most common presentation of MOGAD, with a substantial number of patients presenting with para- or quadriplegia at nadir of the attack. Although generally purporting better outcomes than AQP 4 antibody positive NMOSD, some patients are left with persistent bladder dysfunction, erectile problems, and weakness. The diagnosis is often complicated by the lack of diagnostic specificity of low titers of MOG antibody in the serum, its serologic fluctuation from positive to negative and back to positive, disappearance in some cases when diagnostic workup is delayed by months, including initially normal MRI in up to 10% patients, and resolution of radiological abnormalities when MRI is done in a significantly delayed fashion. Moreover, many patients with low titer of MOG antibody in serum such as 1:20 or 1:40 are initially misdiagnosed with MOGAD and may go one to develop other conditions such as MS or NMOSD, among others. Long-term management of MOGAD-associated TM is complicated by the uncertainty as to whether the disease process will remain monophasic or become relapsing. Because MOG antibody titers can fluctuate and go from positive to negative to positive again, basing the risk of relapse purely on a decrease in titer or seroconversion to negativity does not appear to guarantee monophasic course of the disease. Recent data suggest that male gender and TM at onset may overall have a lower risk of relapse; however, small patient numbers, and the length of follow up continue to be important limiting factors. Because at least 40%–50% cases will remain monophasic, most clinicians will start preventive disease modifying treatment only if the disease proves to be of relapsing phenotype; others may choose to start disease modifying treatments after the first attack in those with poor response to initial treatment and significant residual disability, in fear that the second attack might be devastating to what may already be a significant neurological disability with poor quality of life and reduced independence. Currently there are no FDA approved drugs specifically targeting MOGAD. Despite several off label management options discussed above, some patients may relapse through multiple disease modifying therapies. Randomized controlled clinical trials are crucially needed to create an evidence-based treatment algorithm for those affected by MOGAD.

Author contributions

GP-G and EG made a substantial, direct, and intellectual contribution to the work. NC provided MRI imaging Figure 1 and Table 1 with legends. All authors approved the submitted version.

Conflict of interest

EG has served on advisory boards and received honoraria from Horizon Therapeutics, Alexion, Genentech, Prevail Therapeutics and has received research support from NIH and Genentech.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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High level of agreement in a fixed vs. live cell-based assay for antibodies to myelin oligodendrocyte glycoprotein in a real-world clinical laboratory setting

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Introduction: As recognition of myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease becomes more widespread, the importance of appropriately ordering and interpreting diagnostic testing for this antibody increases. Several assays are commercially available for MOG testing, and based on a few small studies with very few discrepant results, some have suggested that live cell-based assays (CBA) are superior to fixed CBA for clinical MOG antibody testing. We aimed to determine the real-world agreement between a fixed and live CBA for MOG using two of the most commonly available commercial testing platforms.

Methods: We compared paired clinical samples tested at two national clinical reference laboratories and determined the real-world agreement between the fixed CBA and live CBA.

Results: Of 322 paired samples tested on both platforms, 53 were positive and 246 were negative by both methodologies (agreement 92.9%, Cohen's kappa 0.78, [0.69-0.86]). Spearman correlation coefficient was 0.80 ($p < 0.0001$). Of the discrepant results, only 1 of 14 results positive by the live CBA had a titer greater than 1:100, and only 1 of 9 results positive by the fixed CBA had a titer of greater than 1:80. Lower titers on the fixed CBA correlate to higher titers on the live CBA.

Conclusion: Overall, there is excellent agreement between fixed and live CBA for MOG antibody testing in a real-world clinical laboratory setting. Clinicians should be aware of which method they use to assess any given patient, as titers are comparable, but not identical between the assays.

KEYWORDS

myelin oligodendrocyte glycoprotein (MOG), cell-based assay (CBA), MOG testing, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), demyelinating disease, fixed CBA, live CBA

Introduction

Clinical testing for antibodies to myelin oligodendrocyte glycoprotein (MOG) is increasingly done in the workup of suspected immune-mediated inflammatory demyelinating disorders of the central nervous system, given the phenotypic overlap of MOG antibody-associated disease (MOGAD) with neuromyelitis optica (NMO) spectrum disorders and multiple sclerosis (MS). In adults, MOGAD most often presents with optic neuritis, myelitis, or a combination of the two (1). In pediatric patients, the initial presentation is most commonly acute disseminated encephalomyelitis (ADEM) or optic neuritis (2–4). When compared to those who are positive for antibodies to aquaporin-4 (AQP4), MOGAD patients tend to be younger, with equal numbers of males and females affected, and are more likely to have a monophasic disease course (5–10). The recognition that MOGAD represents a unique clinical syndrome with distinct epidemiology, relapse rates, and treatment responses has led to guidelines for diagnosis and antibody testing (11, 12).

As antibody testing for MOG becomes more widespread, it is critical that clinicians understand the differences between the various assays. Early studies of serum MOG antibodies used western blot or enzyme-linked immunosorbent assay (ELISA) to detect the presence of autoantibodies; these assays showed that up to 38% of MS patients and 53% of patients with other inflammatory neurologic diseases (viral or bacterial encephalitis) have detectable MOG IgG, compared to 3% in patients with noninflammatory neurologic diseases (13). However, when cell-based assays (CBAs) using cell lines expressing native proteins were subsequently developed to detect anti-MOG antibodies, they were able to more clearly distinguish MS patients (negative for MOG-IgG with nearly 100% specificity) from MOGAD patients (14, 15). The technical differences between assays which use peptide antigens or denatured proteins (e.g., western blot, ELISA) and those using native full-length proteins (e.g., CBAs) are important to consider when interpreting test results; currently, CBAs are recommended for the diagnosis of MOGAD (12, 16, 17).

When CBAs are used for detection of MOG-IgG, laboratories may use live CBAs with detection via immunofluorescence (CBA-IF) or flow cytometry (CBA-FC) or fixed CBAs with detection via IF (fCBA-IF). Fixed CBAs are widely used in diagnostic laboratories because they allow for the purchase of validated, prepared slides from commercial sources. Live CBAs require maintenance and validation of the cell line within the individual laboratory, a technical hurdle, which limits their utility outside of specialized laboratory settings. Studies comparing these CBAs at multiple institutions using sera from patients with clinically defined syndromes or previously defined seropositive or seronegative samples have led to the dogma that live CBA are superior to fixed CBA (18–20). In this study, we sought to determine the real-world agreement between live CBA-FC and fCBA-IF performed at two major clinical reference laboratories in the United States using samples sent in for routine clinical testing.

Materials and methods

Standard protocol approvals, registrations, and patient consents

This study was approved by the University of Utah IRB (IRB_0082990 for the retrospective analysis and IRB_00068933 for the validation and prospective testing); participant consent was waived, as data were extracted using a limited dataset and all testing was performed on residual clinical samples. Patient sera were identified by retrospective analysis of results from samples received from United States medical centers and tested for MOG antibodies between February 2019 and November 2022 at both ARUP Laboratories and Mayo Clinic Laboratories (MCL). Patients were included if they had MOG antibody testing performed at both ARUP and MCL using serum collected within 30 days of one another (to limit the possible impact of treatment on antibody titer). If multiple serum pairs from a given patient were available, the earliest submitted samples were prioritized, followed by the samples with the smallest time difference between them, for analysis. Patients were excluded if they had a MOG antibody result from only one of the laboratories, or multiple results from the same patient using sera collected more than 30 days apart. In addition to the retrospective analysis, prospective testing was performed on residual serum available at ARUP from patients tested for MOG antibodies at MCL. Specimens tested prospectively were obtained in one of three ways: as split aliquots prior to being sent to the MCL, as additional samples collected at the same time as the MCL sample, or as additional samples collected within 30 days of the original sample. These residual specimens were stored at −20°C until the time of testing. Each case was crosschecked with the retrospective analysis by the patient identification number and date of birth to avoid duplication of results in the final analysis. Additional samples from a validation cohort tested between October 2017 and February 2019 at MCL and used in validating the ARUP assay were included.

ARUP laboratories MOG assay

Testing for antibodies to MOG using fCBA-IF was performed at ARUP Laboratories as recommended by the manufacturer (EUROIMMUN, FA 1156-1010-50 Anti-Myelin Oligodendrocyte Glycoprotein IIFT). Briefly, patient sera were screened at a 1:10 dilution on a substrate of fixed HEK293 cells transiently transfected to express a full-length human MOG protein. Slides were washed and incubated with FITC-conjugated anti-human IgG and examined for positivity by visual observation using a fluorescence microscope. If positive fluorescence was observed at the 1:10 dilution, additional testing was performed at serial 1:2 dilutions, and the highest dilution demonstrating positive fluorescence was reported as the end-point titer.

Mayo clinical laboratory MOG assay

Testing for antibodies to MOG using live CBA-FC was performed at MCL as previously described (14). According to Mayo Clinical Laboratories reported protocols, patient sera are routinely screened at a 1:20 dilution on a substrate of live HEK293 cells expressing full-length MOG protein. Cells are washed and incubated with anti-human IgG1. Cells are washed again prior to evaluation by flow cytometry. Positivity is determined based on the ratio of mean fluorescence intensity (MFI) of transfected cells to MFI of non-transfected cells. A ratio of 2.5 or greater is considered positive. If samples screen positive at 1:20, additional testing is performed at 1:40, 1:100, and subsequent 10-fold dilutions (1,100, 1:10,000, etc.) until MFI ratio drops below 2.5.

Statistical analysis

Correlation of parameters was analyzed with Spearman's rank correlation coefficient. Cohen's kappa statistic was used to assess the agreement between assays. All statistical analyses were performed using R Statistical Software (v4.1.2; R Core Team 2022) (21).

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

In total, 322 serum samples were tested at both ARUP and MCL during the study period (Supplementary Figure 1). Of the 76 samples positive by either methodology, 53 were concordant between both assays, nine were positive by the ARUP fCBA-IF assay only, and 14 were positive by the MCL live CBA-FC assay only. 246 samples were negative by both assays. Overall, percent agreement between the two assays was 92.9 (Cohen's kappa 0.78, [0.69–0.86]). Spearman correlation coefficient was 0.80 ($p < 0.0001$; Figure 1).

Of the 14 samples positive by live CBA-FC and negative by fCBA-IF, 8/14 (57%) had an antibody titer of ≤1:40, and 13/14 (93%) had an antibody titer of ≤1:100. Of the nine samples positive by fCBA-IF and negative by live CBA-FC, 7/9 (78%) had an antibody titer of ≤1:40 and 8/9 (89%) had an antibody titer of ≤1:80. Antibody titers are not identical between the live CBA-FC and fCBA-IF; of the 53 samples positive by both assays, 45/53 (85%) had a higher titer by live CBA-FC than by fCBA-IF.

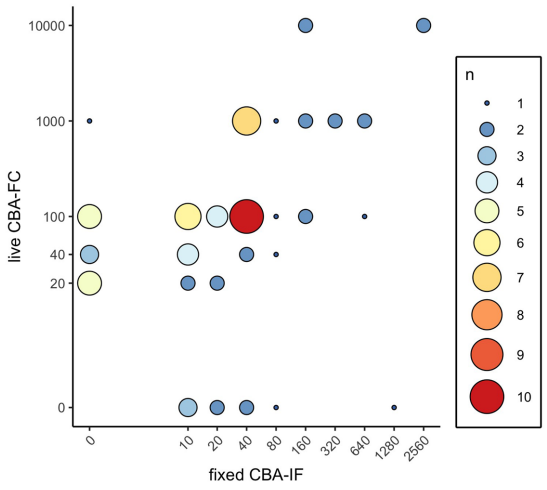

FIGURE 1
Distribution of MOG-IgG results by titer and frequency. Antibody titers of the live CBA-FC and fixed CBA-IF were plotted for all positive values. Size and color of plotted points represents the number of samples with the corresponding antibody titers.

Discussion

In a set of 322 serum samples analyzed for MOG-IgG by both live CBA-FC and fCBA-IF at two different clinical reference labs, we found an overall agreement of 92.9%, with a strong Spearman correlation coefficient (0.80). Previous studies have compared live and fixed CBA using samples from clinically or serologically defined subsets of patients (18, 19). Specifically, Waters et al. performed a comparison between live CBA-FC, live CBA-IF, and fCBA-IF in a clinically defined group of patients with ADEM, seronegative NMO, optic neuritis, or longitudinally extensive transverse myelitis ($n = 91$) and found that of 25 samples positive by any of these methodologies, 21 were concordant on all three assays. The live CBA-IF detected 25 positives, the fCBA-IF detected 23 positives and the live CBA-FC detected 21 positives. In the control group of 244 MS patients, one false positive (FP) was identified by both the live CBA-FC and the fCBA-IF, and four additional FPs were identified by the fCBA-IF (18). Based on these results, the three assays have similar negative predictive values (ranging from 78.8 to 79.8) but diverging positive predictive value (100% for live CBA-IF, 95.5% for live CBA-FC, and 82.1% for fCBA-IF). While these statistics are valid, it is important to consider that this analysis includes a small number of discordant samples overall. Concluding that these data "emphasize the superiority of live CBA testing," as some have suggested, is an oversimplification (22).

Reindl et al. (19) conducted an international study to compare 11 different assays for MOG antibodies at five different testing centers, using a strategy whereby a predefined set of positive or negative serum samples were tested across all platforms. Of note, predefined samples were determined based on testing via live CBA at four different institutions. Cell based assays tested in the study included seven live CBAs (four CBA-IF, three CBA-FC) and one fCBA-IF. Of the 39 clear positive samples tested, 32/39 were positive in all eight CBAs, and 36/39 were positive in all seven of the live CBAs. Of the 40 samples tested as clear negatives, 39/40 were negative in all eight CBAs, and 40/40 were negative in all seven live CBAs. Overall, there was 90% concordance between all the CBA (similar to the 92.9% seen in our study) and 96% concordance across the live CBAs. In a second phase of the same study, low positive and borderline negative samples were compared between the assay platforms; there was 77% agreement between all eight of the CBA platforms tested, without a clear distinction between live or fixed CBA being superior (19). The inclusion of these borderline negative and low positive samples highlights the limitations of all of these assays when evaluating borderline results, and the key role treating clinicians play in interpreting the results of these assays within the clinical context of each patient.

Positive cutoffs vary from assay to assay. The live CBA-FC reported here is the same one used in a study looking at the positive predictive value (PPV) of MOG testing at various assay cutoffs (23). In that paper, two neurologists reviewed the charts of 92 positive MOG-IgG1 assays and found 26/92 (28%) were designated as FP by both raters. When the end-titer of the assay for MOG was 1:20–40, the PPV was 51%; this increased to 82% at an end titer of 1:100 and 100% when the end-titer of ≥1:1,000 was used (23). To better understand the correlation between positive antibody titers in different assays, we plotted the assay titers for the live CBA-FC against the fCBA-IF in our study. Most of the samples that were negative by fCBA-IF yet

positive by live CBA-FC had titers below 1:1,000 (Figure 1). This figure also illustrates that lower titers on fCBA-IF correspond to higher titers by live CBA-FC. As these assays have different methodologies, the titers are not directly comparable. This is important to consider based on the recently published International MOGAD Panel proposed diagnostic criteria, which recommends a cutoff of ≥1:100 for both of the assays described here to be considered a "clear positive," with lower titers needing additional supporting clinical or MRI criteria to be considered consistent with MOGAD (12). Future studies applying these diagnostic criteria to patients tested by both live CBA-FC and fCBA-IF are needed to better understand the ideal cutoff for each individual assay to optimize sensitivity and specificity.

As a reference laboratory receiving samples from around the country, we did not have access to patient information in the discrepant cases to determine whether these incongruities represented false positives or false negatives in these assays. The absence of patient information in regard to the core clinical demyelinating event, supporting clinical or MRI features, and the temporal association of the tested sample with attack, relapse, or immunotherapy represents a clear limitation of this study. It is noteworthy that both the live CBA-FC and fCBA-IF identified some positives that the other assay did not, and that these discrepancies tended to occur at lower assay titers (see Figure 1). The preponderance of discrepancies at low titers reinforces the importance of applying clinical criteria in addition to antibody testing when making a diagnosis of MOGAD. Recognizing that different CBA testing methodologies will not give identical titers, and that higher titers by live CBA-FC generally correspond to lower titers by fCBA-IF is an important idiosyncrasy to be aware of when interpreting these results. Of the results positive by both assays in our comparison, 45/53 (85%) had a higher titer when measured by live CBA-FC than when tested by fCBA-IF.

Our study demonstrates that in a real-world reference laboratory setting, there is a high degree of agreement between fCBA-IF and live CBA-FC. This, along with data from prior studies comparing CBAs in clinically and serologically defined populations, confirms that both fixed and live CBA are a reasonable option for clinicians who suspect MOGAD in their patients and seek serologic confirmation. False positives and false negatives are a reality of all clinical laboratory testing; in the case of MOG, false positives may lead to treatment with an inappropriate immunosuppressive medication or delayed diagnosis of a different clinical entity. Avoiding indiscriminate testing for antineural antibodies and selecting tests based on clear clinical criteria is important to improve the positive predictive value of these assays. Clinicians need to consider testing availability, turnaround time, cost at their institution, and reliability when ordering any test. Future studies need to focus on improving testing reliability and determining markers of monophasic vs. relapsing disease to further inform treatment decisions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

TS, TH, SC, and LP contributed to the conception and design of the study. TS, TH, and LZ organized the data. TS and LZ performed statistical analysis. KL assisted with data collection. TS wrote the first draft of the manuscript. TH, LZ, and LP wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

TS, TH, LZ, KL, and LP are affiliated with the ARUP Institute for Clinical and Experimental Pathology, which performs the fCBA-IF reported herein. They receive no royalties from the sale of myelin oligodendrocyte glycoprotein antibody testing; however, ARUP Laboratories receives revenue from conducting such tests.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1192644/full#supplementary-material

SUPPLEMENTARY FIGURE S1

Flow chart showing consecutive steps for inclusion of sera in the study. **(A)** retrospective cohort strategy **(B)** prospective cohort strategy **(C)** validation cohort strategy.

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Two case reports and a systematic review of the literature on adult cerebral cortical encephalitis with anti-myelin oligodendrocyte glycoprotein antibody

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Background and purpose: Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) has gained recognition in recent years as an immune-mediated inflammatory demyelinating disease of the central nervous system. The clinical features and prognosis of MOGAD adult cerebral cortical encephalitis (adult CCE) have not been fully elucidated. This study aims to further characterize the clinical symptoms, magnetic resonance imaging (MRI) findings, and prognosis of CCE with anti-MOG antibody.

Methods: We present two adult cases of CCE with anti-MOG antibody and summarize the clinical symptoms, magnetic resonance imaging (MRI) findings, and prognosis of this phenotype as per a completed systematic review of the literature.

Results: We found a total of 39 cases of MOGAD adult CCE (36% females; average age of onset of 29 years). Among them, 85% had seizure, 82% had headache, 64% had cortical symptoms, 64% had fever, 54% had changes of consciousness, and 38% had ocular symptoms. All cases demonstrated cerebral cortical T2 fluid-attenuated inversion recovery (FLAIR) lesions on MRI. Of the 25 patients (with seizure or not) who had EEG reports, 76% of patients showed abnormal EEG. Cerebrospinal fluid (CSF) white blood cell count of 90% of patients and CSF total protein of 67% of patients were elevated. In 16 patients with available CSF cytology data, 11 (69%) had abnormal cytology findings with monocytic predominance. In the 15 cases for which MOG antibody IgG was tested in both serum and CSF, 14 (93%) demonstrated a higher positive MOG IgG titer in serum than CSF. The majority of patients were treated with immunosuppressive therapy (97% corticosteroids, 15% mycophenolate mofetil, 13% IVIg, 5% azathioprine, and 5% other). The majority of patients had a favorable prognosis after treatment, as exemplified by improved clinical symptoms and imaging. Two patients relapsed.

Conclusions: The clinical presentation and prognosis of adult CCE remain less understood in comparison to more common MOGAD phenotypes. It is important to consider MOGAD as an underlying etiology for adult CCE, as early detection and immunotherapy may improve outcomes.

KEYWORDS

adult, cerebral cortical encephalitis, myelin oligodendrocyte glycoprotein antibody, myelin oligodendrocyte glycoprotein antibody-associated disease, MRI

Introduction

MOGAD is a recognized immune-mediated central nervous system inflammatory demyelinating disease. It is an independent spectrum of disease distinct from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). In 2017, Ogawa et al. (2017) proposed a unique clinical type: benign unilateral cortical encephalitis, which presented with epileptic seizures in the context of positive MOG antibodies (1). Since this initial description, further case reports and cohort studies describing CCE in MOGAD have been published (2–6). A systematic review of the literature of published cases revealed that clinical manifestations of CCE with anti-MOG antibody are diverse. The recognized diversity of the clinical presentation of MOGAD adult CCE highlights a need to differentiate this process from alternative diagnoses such as MS, NMOSD, leukodystrophies, and others. Herein, we report two cases of adult CCE with anti-MOG antibody positivity in conjunction with a systematic review of pertinent literature.

Case 1

A 24-year-old man (no past neurologic history) presented with persistent neck stiffness and occipital pain without known cause. Approximately one week later, he was admitted to a local hospital for management of status epilepticus. He required endotracheal intubation and there was no significant improvement in seizure control despite pharmacologic sedation. CSF examination showed pleocysis (310×10^6/L, normal range $0\sim8\times10^6$/L), normal protein (38 mg/dl), and elevated glucose (5.0 mmol/L). The autoimmune encephalitis antibodies (including anti N-methyl-D-aspartate receptor antibody, anti-contactin-associated-protein-like 2 antibody, anti-leucine-rich gliomain activated 1 antibody, anti-a-amino-3-hydroxy-5-methyl-isoxazo-lepropionic acid receptor antibody, anti-γ-aminobutyric acid-B receptor antibody, anti-IgLON5 antibody, anti-D2R antibody, and anti-DPPX antibody) in serum and CSF and virus antibodies (including HSV-I-IgG, HSV-I-IgM, HSV-II-IgG, HSV-II-IgM, TOX-IgG, TOX-IgM, CMVIgG, CMV-IgM, RVIgG, RVIgM, EBV capsid antigen antibody IgG, IgM and IgA, EBV early antigen antibody IgG, IgM, and IgA) in CSF were all negative. Serum leukocytosis was present (white blood cell count 22×10^9/L, normal range $3.5\sim9.5\times10^9$/L). T2 FLAIR brain MRI revealed hyperintense lesions involving the brainstem, left frontal, parietal, and temporal cortex, see Figures 1A, B; there was no contrast enhancement. A second lumbar puncture was then performed in order to observe changes in CSF, revealing persistent yet increasing leukocytosis (26×10^6/L) and normal protein (32 mg/dl). Empiric treatment for viral encephalitis was initiated with penciclovir, sodium valproate, dexamethasone, dehydrant, and symptomatic supportive treatment. After discharge, clinically significant diaphoresis and subjective concerns regarding fever remained, prompting re-admission; he was then transferred to our hospital with a temperature of 38.4°C. A repeat CSF examination revealed lymphocytic pleocytosis (293×10^6/L, 77% lymph) and elevated protein (76 mg/dL). The following day, recurrent status epilepticus ensued. Brain MRI showed FLAIR hyperintense lesions in the left frontal cortex and bilateral temporo-parietal cortex, see Figures 1C, D. A fourth CSF examination three days later revealed leukocytosis (436×10^6/L) and elevated protein (116 mg/dl), and cytological classification showed 35% lymphocytes, 55% neutrophils, and 10% monocytes. Central nervous system demyelinating autoantibodies (including anti-AQP4, anti-MOG, and anti-MBP) testing was performed. Serum and CSF anti-MOG antibodies were positive at titers of 1:100 and 1:10 (CBA), respectively. Anti-AQP4 was negative in the serum and CSF. The autoimmune encephalitis antibodies (including anti-N-methyl-D-aspartate receptor antibody, anti-contactin-associated-protein-like 2 antibody, anti-Leucine-rich glioma inactivated 1 antibody, anti-a-amino-3-hydroxy-5-methyl-isoxazo-lepropionic acid receptor antibody, and anti-$_\gamma$-aminobutyric acid-B receptor antibody), paraneoplastic syndrome antibodies (including anti-Hu, anti-Yo, anti-Ri, anti-$CV2_{(CRMP5)}$, anti-Amphiphysin, anti-Ma1, anti-Ma2, anti-SOX1, anti-$Tr_{(DNER)}$, anti-Zic4, anti-GAD65, anti-PKCγ, anti-Recoverin, and anti-$Titin_{(MGT30)}$), and anti-ganglioside antibodies of serum (including anti-Sulfatide, anti-GM1, anti-GM2, anti-GM3, anti-GM4, anti-GD1a, anti-GD1b, anti-GD2, anti-GD3, anti- GT1a, anti-GT1b, and anti- GQ1b) were all negative. A diagnosis of MOGAD was concluded. Treatment was initiated with intravenous immunoglobulin 0.4 g/kg for 5 days and IV methylprednisolone (IVMP) 1 g/d for 3 days and the dose halved every 3 days. Oral prednisone tablets (1 mg/kg/d) were administered following the IVMP course. Two weeks later, repeat

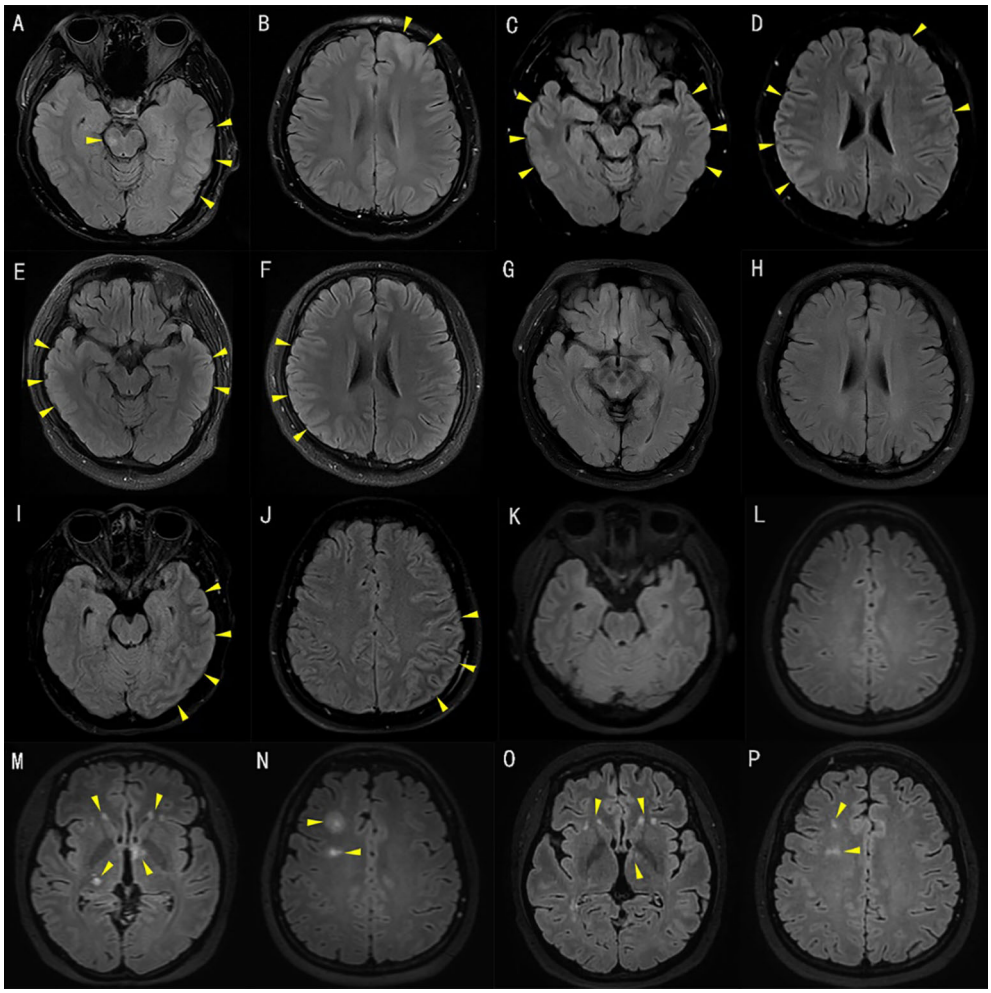

FIGURE 1
T2 fluid-attenuated inversion recovery (FLAIR) of brain magnetic resonance imaging (MRI). [A–H patient 1, I–P patient 2]. T2 FLAIR brain MRI of patient 1 at initial presentation demonstrated hyperintensities involving the brainstem, left frontal, parietal, and temporal cortex **(A, B)**. T2 FLAIR brain MRI after admission to our hospital and suffering from status epilepticus demonstrated hyperintensities involving the left frontal cortex and bilateral temporo-parietal cortex **(C, D)**. Repeat T2 FLAIR brain MRI three weeks after immunotherapy initiation showed improvement in the bilateral temporo-parietal cortex **(E, F)**. There were no obvious lesions on images seven months after the initial treatment **(G, H)**. Axial T2 FLAIR brain MRI of patient 2 at initial presentation demonstrated hyperintensities involving the left temporal, parietal, and occipital cortex **(I, J)**. T2 FLAIR brain MRI ten days after immunotherapy initiation was normal **(K, L)**. T2 FLAIR brain MRI after disease relapse demonstrated multiple hyperintensities, in keeping with acute disseminated encephalomyelitis involving the bilateral thalamus, basal ganglia, and right centrum semiovale **(M, N)**. At re-assessment four months after second discharge, the patient was clinically asymptomatic with improving FLAIR lesions on repeat T2 FLAIR brain MRI **(O, P)**.

testing showed a decrease in MOG serum and CSF titers to 1:10 and 1:1, respectively. Electroencephalogram (EEG) demonstrated interictal, irregular sharp waves in the left temporal and right frontal regions. Repeat brain MRI three weeks from immunotherapy initiation showed improvement in FLAIR hyperintensity, see Figures 1E, F; there was no contrast enhancement. The visual evoked potential (VEP) and MoCA scale were normal. He was discharged with oral prednisone tablets (1 mg/kg/d, reduced by 1 tablet every two weeks), with ongoing clinical improvement. There were no obvious lesions on images seven months after the initial treatment, see Figures 1G, H, and the MOG antibody titer decreased (serum and CSF at titers of 1:1 and 1:1, respectively). After completion of a course of steroid tablets, he remains clinically improved without relapse and MOG antibody negative eleven months after the start of treatment.

Case 2

A 31-year-old woman (no past neurologic history) suffered from sudden headache without obvious cause. She was admitted to the local hospital with fever, nausea, and vomiting a week later, and empiric antibiotics were prescribed for concern regarding a bacterial infection. Three days later, she returned due to worsened headache. CSF analysis revealed elevated opening pressure (225 mmH_2O), leukocytosis ($465x10^6$/L, normal range $0\sim8\times10^6$/L), elevated protein (92 mg/dL), and normal glucose. Serum leukocytosis was also present ($16x10^9$/L, normal range $3.5\sim9.5\times10^9$/L). Empiric antivirals were initiated for presumed viral meningitis. Rapid clinical deterioration to unconsciousness ensued over a few hours. Repeat lumbar puncture revealed worsened opening pressure elevation ($400mmH_20$), persistent

pleocytosis (208 cells/uL), and persistent elevated protein (72 mg/dL). On the third day of admission, she was aware after supportive treatment and physical examination showed positive Kernig sign. This patient did not have papilledema. Brain MRI showed FLAIR hyperintensity in the left temporal, parietal, and occipital cortex and there was no contrast enhancement, see Figures 1I, J. The MOG antibody titer in the serum was positive at a titer of 1:10 (CBA). She was diagnosed with unilateral cortical encephalitis with anti-MOG antibody. Empiric IVMP (1 g/d for 3 days, dose halved every 3 days) was initiated with subsequent clinical improvement. On the 13th day of admission, the repeated LP pressure was 243 mmH_2O, and CSF examination revealed elevated leukocytes (24×10^6/L) and protein (31 mg/dL). Repeated brain MRI showed no obvious lesions, see Figures 1K, L. She was discharged on oral prednisone tablets (1 mg/kg/d, reduced by 1 tablet every two weeks). The patient self-discontinued oral prednisone due to side effects and in this setting had disease relapse manifesting as paresthesias, blurry vision, and ataxia approximately 2 months later. Brain MRI showed multiple FLAIR hyperintensity, in keeping with acute disseminated encephalomyelitis involving the bilateral thalamus, basal ganglia, and right centrum semiovale, see Figures 1M, N. The MOG antibody titer in the serum was 1:10. IVMP again resulted in clinical improvement, and she was discharged with oral prednisone tablets (1 mg/kg/d, reduced by 1 tablet every two weeks) and mycophenolate mofetil (three tables each time, taken two times daily). At re-assessment four months after discharge, she was clinically asymptomatic with improving FLAIR lesions on repeat brain MRI, see Figures 1O, P. The prednisone course was completed after three months of therapy, and she remains on mycophenolate mofetil monotherapy. A repeat serum MOG titer three months after completion of the steroid course was 1:32.

Methods

We searched PubMed for '[encephalitis] AND [MOG]' and '[cortical] AND [MOG]' to review the literature for cases of adult cortical encephalitis with anti-MOG antibody. All relevant published articles from 2017 through 2022 were reviewed for potential study inclusion. Cases were included if they (a) had predominantly cortical T2-FLAIR hyperintense lesions, (b) MOG-IgG antibodies were positive by CBA in serum and/or CSF, (c) were older than 18 years, and (d) excluded other infectious/autoimmune cases. Cases were excluded if available data were not sufficiently reported in the publication. Discrepancies between authors regarding the inclusion of cases were resolved by discussion. Information on the selected cases and our cases are presented in Table 1.

Results

A systematic literature review yielded 37 total cases meeting the inclusion criteria for our study of MOGAD adult CCE, supplemented by the 2 unique cases from our institution. Among these 39 cases, there was a slight male predominance (25M:14F), with an average age at clinical presentation of 29 years. Prominent clinical features were seizure (85%), headache (82%), focal neurologic deficits (64%), fever (64%), altered mentation (54%), and ocular symptoms ranging from eye pain or photophobia to vision changes (38%). All cases demonstrated abnormal radiographic findings on brain MRI. Among these, T2 FLAIR hyperintense lesions were more commonly unilateral (79%), although bilateral hemispheric lesions were present in others (21%), with less common brainstem or corpus callosal involvement. Of the 25 patients (with seizure or not) who had EEG reports, 76% of patients showed continuous EEG monitoring abnormal in the seizure phase, 12/20 showed slow waves, 6/20 showed epileptic waves, and 2/20 showed decreased amplitude and brain function. The CSF white blood cell count of 90% of patients and CSF total protein of 67% of patients were elevated. In 16 patients with available cytological data, 11/16 showed elevated CSF cytology with monocytes as the dominant cell and 5/16 had polykaryocytes as the dominant cell. In 15/39 patients whose data were available for both serum and CSF MOG antibody IgG, 14/15 serum antibody titers were higher than those of CSF. A total of 38/39 patients received IVIg, IVMP, or oral prednisone therapy, while one case only received supportive treatment, and 10/39 received immunosuppressants such as azathioprine, mycophenolate mofetil, rituximab, and adalimumab. Of the 39 reported cases, 2 cases (5%) relapsed, presenting with dizziness, memory impairment, slow responsiveness, paresthesia, blurry vision, ataxia optic neuritis, etc. Two patients relapsed and there was nothing unique about them. The relapse of case 2 was related to rapid discontinuation of oral prednisone, with a repeated MOG antibody titer in the serum of 1:10 (CBA), while, unfortunately, another patient who also relapsed after completion of appropriate oral prednisone tablets did not agree to undergo a MOG antibody titer assay again.

Discussion

MOGAD is a CNS demyelinating disorder with a variable spectrum of clinical disease, in part understood by the various anatomical regions where myelin oligodendrocyte glycoprotein is present within the nervous system. It is exclusively expressed on the outer surface of the myelin sheath and plasma membrane of oligodendrocytes in the CNS. MOG can participate in microtubule stability as a regulator, can regulate immune responses as an activator of complement, and may have a significant role in cellular adhesion (33). The experimental autoimmune encephalomyelitis (EAE) model by Spadaro et al. (2018) (34) showed that the pathogenic mechanisms of MOG antibody were complicated. On the one hand, it can induce blood-brain barrier damage and the activation of macrophages as a result of its synergy with MBP-specific T cells and antibodies, eventually leading to demyelinating changes *via* cytotoxicity and complement activation. On the other hand, it can interact with MOG-specific T cells to enhance the infiltration and activation of T cells, thereby enhancing the inflammatory response. A brain biopsy performed before glucocorticord therapy in the case of Ikeda et al. (8) showed mild inflammatory changes in the cortex and subcortex, without distinct demyelination. In the case of Patterson et al.

TABLE 1 Summary of the characteristics of 39 cases of MOGAD adult cerebral cortical encephalitis.

Case (Reference)	Age/ Sex	Clinical Manifestations						Imaging	EEG	CSF WBC cell (mono:poly)	Protein (mg/ dL) (CSF)	MOG (serum)	MOG (CSF)	Treatment	Relapse
		Headache	Fever	Seizure	ND	CD	VS								
1 (1)	M/38	—	—	+	+	+	+	Unilateral	Slow waves	29(80:20)	35	1:512	1:32	IVMP, oral prednisone	No
2 (1)	M/36	—	—	+	+	+	+	Unilateral	Normal	63(98:2)	38	1:2048	1:4	IVMP, oral prednisone	No
3 (1)	M/23	+	—	+	—	+	—	Unilateral	Slow waves	101(51:49)	86	1:256	1:16	DEX, oral prednisone	No
4 (1)	M/38	+	—	+	+	+	—	Unilateral	—	311(41:59)	53	1:1024	—	IVMP	No
5 (3)	M/23	+	+	+	+	—	—	Unilateral	Slow waves	85	Elevated	Positive	Positive	IVMP, oral prednisone	No
6 (7)	M/24	+	+	+	+	+	—	Bilateral	Focal discharge	436	116	1:100	1:10	IVIg, IVMP, oral prednisone	No
7 (7)	M/25	+	+	+	+	—	—	Unilateral	—	219	68	1:100	1:10	IVIg, IVMP, oral prednisone	No
8 (8)	F/29	—	+	+	+	+	+	Bilateral	Delta waves	73(mono)	—	1:512	—	IVMP, oral prednisone	No
9 (9)	F/29	+	+	+	—	—	—	Unilateral	—	349	74	—	Positive	IVMP, oral prednisone	No
10 (10)	F/19	+	+	+	+	+	—	Unilateral	High-voltage slow waves	200(72:28)	56	1:256	1:128	IVMP, oral prednisone	No
11 (11)	M/27	+	+	+	+	+	—	Bilateral	Left amplitude is lower	205(mono 67%)	84	1:1024	—	IVMP, oral prednisone	No
12 (12)	F/39	+	+	—	+	+	+	Unilateral	—	64	49	—	1:8	IVMP, oral prednisone	No
13 (13)	F/31	+	—	+	—	—	—	Unilateral	Epileptiform abnormalities	Normal	46	1:10	—	IVMP, oral prednisone, MM	No
14 (14)	M/19	+	+	+	—	—	+	Unilateral	—	120	49	1:32	—	IVMP, oral prednisone, MM	No
15 (14)	M/23	+	—	+	+	+	—	Unilateral	—	Elevated	77	1:32	1:1	IVMP, oral prednisone, MM	No
16 (15)	F/31	+	+	+	—	+	—	Bilateral	Cerebral dysfunction	Normal	Normal	Positive	—	IVMP, oral prednisone, azathioprine	No
17 (16)	F/18	—	—	+	+	+	+	Unilateral	Slow waves	132	—	1:2560	1:64	IVMP, oral prednisone, rituximab	No

(Continued)

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TABLE 1 Continued

Case (Reference)	Age/ Sex	Clinical Manifestations						Imaging	EEG	CSF WBC cell (mono:poly)	Protein (mg/ dL) (CSF)	MOG (serum)	MOG (CSF)	Treatment	Relapse
		Headache	Fever	Seizure	ND	CD	VS								
18 (17)	M/23	+	+	+	+	+	—	Unilateral	Delta activity	57(15:85)	36	1:100	—	IVMP, oral prednisone	No
19 (18)	F/19	+	+	+	—	—	+	Unilateral	Normal	46(mono)	54	1:512	—	IVMP, oral prednisone	—
20 (19)	F/36	+	—	+	+	—	—	Unilateral	Slow waves	25lymp (lymp)	—	Positive	—	IVMP, oral prednisone, adalimumab	No
21 (20)	M/37	+	+	—	+	+	+	Unilateral	Slow waves	164 (34:66)	83.3	1:2048	1:64	IVMP, oral prednisone	No
22 (21)	M/34	+	—	+	+	—	+	Unilateral	—	411 (lymp 62%)	Elevated	Positive	Positive	IVMP, oral prednisone	No
23 (22)	M/20	+	+	+	+	+	—	Bilateral	Normal	80	48	1:10	—	IVMP, oral prednisone, MM	No
24 (22)	M/20	—	—	+	—	—	—	Unilateral	Sharp-slow waves	31	Normal	1:100	—	IVMP, oral prednisone, MM	No
25 (23)	M/30	+	+	+	+	+	—	Unilateral	Slow waves	324 (mono 83%)	108	Positive	—	IVMP, oral prednisone	No
26 (24)	M/23	+	—	+	+	—	+	Unilateral	Epileptic wave	32 (lymp69%)	54	1:1000	—	IVMP, oral prednisone	No
27 (25)	F/29	+	—	—	+	—	—	Unilateral	Normal	37 (27%poly)	61	Positive	—	IVMP	—
28 (26)	M/32	+	+	+	—	—	—	Bilateral	—	46	Normal	1:10	Negative	IVMP, oral prednisone, MM	No
29 (26)	M/28	+	+	+	—	+	+	Unilateral	—	105	Normal	1:10	—	IVMP	No
30 (27)	F/22	+	+	+	—	—	+	Unilateral	Normal	92 (mono 47%)	55.7	1:1024	—	Supportive treatment	No
31 (28)	M/31	+	—	—	—	—	—	Unilateral	Slow wave	114 (90:10)	48.5	1:1024	1:128	IVMP, oral prednisone	No
32 (18)	F/19	+	+	+	—	—	+	Unilateral	Normal	46 (mono)	54	1:512	—	IVMP, oral prednisone	—
33 (29)	M/44	—	+	+	+	—	—	Unilateral	—	43	58.2	Positive	—	IVMP, oral prednisone	No
34 (29)	F/52	+	—	+	+	+	—	Unilateral	—	12	26.9	Positive	—	IVMP, oral prednisone, azathioprine	No

(Continued)

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TABLE 1 Continued

Case (Reference)	Age/ Sex	Clinical Manifestations						Imaging	EEG	CSF WBC cell (mono:poly)	Protein (mg/dL) (CSF)	MOG (serum)	MOG (CSF)	Treatment	Relapse
		Headache	Fever	Seizure	ND	CD	VS								
35 (30)	M/39	+	+	+	+	—	+	Bilateral	—	—	—	Positive	—	IVIg, IVMP	No
36 (31)	M/55	+	+	—	+	+	+	Unilateral	Slow, Epileptic waves	2	48	1:80	1:40	IVIg, IVMP, oral prednisone	Yes
37 (32)	M/26	+	+	+	—	—	—	Unilateral	—	692	151	1:512	1:32	IVMP, oral prednisone	No
38 (Case 1)	M/24	—	+	+	+	+	—	Bilateral	Sharp or sharp slow waves	720 (polycyte)	38	1:100	1:10	IVIg, IVMP, oral prednisone	No
39 (Case 2)	F/31	+	+	—	—	+	—	Unilateral	—	465 (lymp 65%)	92	1:10	1:10	IVMP, oral prednisone	Yes

ND, neurological deficits; CD, consciousness or dysphrenia; VS, visual symptoms; MM, mycophenolate mofetil; "—"indicates negative in clinical manifestations and no clinical data in other items.

(12), a brain biopsy of the left parietal lobe and dura showed interstitial and perivascular lymphocytic infiltrates, with marked involvement of the vessel wall. These two brain biopsy cases did not present any evidence of demyelination. These pathological characteristics differed from the EAE model and those in previous reports on NMOSD, ADEM, and atypical MS. As mentioned by van der Valk et al. (35), in the process of myelin breakdown in MS, MOG is rapidly degraded, whereas the process for myelin basic protein (MBP) may take more time. The case reported by Ikeda et al. (8), demonstrating limited loss of MOG immunoreactivity, might suggest 'pre-active' lesions of demyelination. Fujimori's case did not exhibit the loss of MOG, probably because biopsy was performed after steroid therapy, and the treatment may modify the pathology. Further studies are still needed to elucidate the pathogenesis of this phenotype.

The clinical manifestations of cerebral cortical encephalitis with anti-MOG antibody are not typical. Many cases were delayed or even misdiagnosed due to various reasons, such as the neglect of clinical symptoms, self-medication, lack of doctors' theoretical knowledge, and so on. Our cases had clinical characteristics similar to infectious encephalitis; therefore, they were easily misdiagnosed initially without detection of anti-MOG antibody. A total of 9/39 patients were initially diagnosed with infectious encephalitis and were given antiviral or antibiotic treatment; however, the disease progressed during the treatment. In addition, a case (12) was misdiagnosed as central nervous system vasculitis, whose routine blood and cerebral imaging examination were normal, with cerebral biopsy showing lymphocyte infiltration in the small blood vessels and no obvious demyelinating lesions. The CSF MOG antibody was positive after retrospective analysis and the biopsy specimen showed no fibrinoid necrosis; the clinical diagnosis was then corrected. Therefore, it is of great significance to improve the detection of various examinations and tests, including head MRI and antibody, as soon as possible for early diagnosis of this disease. The rapid deterioration of our case 1 and the case by Hang Shu et al. (7) emphasizes the importance and necessity of early diagnosis and treatment.

In terms of imaging manifestations, it is necessary to distinguish whether MRI abnormalities are brain damage caused by epilepsy or MOG. In general, cortical damage caused by epilepsy is characterized by hyperintensity on diffusion-weighted MR images (DWI). Transient focal hyperintensity on DWI with corresponding reduction of the apparent diffusion coefficient (ADC) indicates cytotoxic edema, which is an increasingly recognized phenomenon in the phase of epileptic seizures (36), while CCE of MOGAD usually presents with cerebral cortical hyperintensity on FLAIR. Unilateral cerebral cortical lesions on FLAIR of MRI are more frequent, and cortical lesions may be accompanied by corresponding leptomeningeal enhancement (4). According to a literature review, CSF cytology of MOGAD-related CCE may be characterized by an inflammatory response dominated by neutrophils (37). Cerebrospinal fluid inflammation is easily confused with infectious diseases of the nervous system, and early diagnosis is difficult. Adequate etiological examination is needed to exclude infection. Since MOG-IgG is produced in the peripheral blood, serum is the preferred test sample, and CSF testing only provides supplementary information (37). The serum MOG-IgG titer was correlated with

disease activity, and the titer was higher in the acute stage than in the remission stage. In addition, serum MOG-IgG titers were associated with treatment status and decreased after immunosuppression or plasmapheresis (38). In 15 available datasets for both serum and CSF MOG antibody IgG, the serum antibody titer was higher than that of CSF. Some studies have reported that the higher the antibody titer at the time of onset and the longer the duration of antibody positivity, the greater the likelihood of relapse (7). In addition, as a relapse biomarker, the expression of TNFAIP3 was downregulated during relapse as compared to remission in MOGAD patients (39).

The treatment response varies in cerebral cortical encephalitis with anti-MOG antibody. The first-line treatment of patients includes HIMP and IVIg in the acute stage, and significant improvements in clinical symptoms and imaging can usually be observed after steroid treatment. However, some patients relapse after withdrawal therapy, and therefore, patients may be treated with prolonged steroid tablets or immunosuppressive therapy, such as mycophenolate mofetil (MM), rituximad (RTX), and cyclophosphamide, to prevent relapse.

At present, a recommendation of diagnostic criteria for MOG encephalomyelitis (MOG-EM) has been proposed (38); however, there are no unified diagnostic criteria for CCE with anti-MOG antibody. There were a few cases of adult MOGAD with CCE reported internationally. We conducted a systematic review of the literature for a better understanding of this unique clinical phenotype. In general, clinical diagnosis must be made based on symptoms, signs, and auxiliary examinations. In particular, a diagnosis of adult CCE with anti-MOG antibody should be considered when young patients present with fever, headache, epilepsy, or unilateral (or bilateral) cortical or sulcus FLAIR hyperintensity. Timely detection of MOG antibody in serum is helpful for accurate diagnosis of this phenotype, avoiding misdiagnosis and unnecessary treatment.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

M-hX and YL collected the clinical data and reviewed the literature. M-hX and CM wrote the manuscript. C-jG and S-mY improve the quality of all the images. XW and MD critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Pathology of myelin oligodendrocyte glycoprotein antibody-associated disease: a comparison with multiple sclerosis and aquaporin 4 antibody-positive neuromyelitis optica spectrum disorders

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Myelin oligodendrocyte glycoprotein (MOG) is expressed on the outermost layer of the myelin sheath in the central nervous system. Recently, the clinical concept of MOG antibody-associated disease (MOGAD) was established based on the results of human MOG-transfected cell-based assays which can detect conformation-sensitive antibodies against MOG. In this review, we summarized the pathological findings of MOGAD and discussed the issues that remain unresolved. MOGAD pathology is principally inflammatory demyelination without astrocyte destruction, characterized by perivenous demyelination previously reported in acute disseminated encephalomyelitis and by its fusion pattern localized in both the white and gray matter, but not by radially expanding confluent demyelination typically seen in multiple sclerosis (MS). Some of demyelinating lesions in MOGAD show severe loss of MOG staining compared with those of other myelin proteins, suggesting a MOG-targeted pathology in the disease. Perivascular cuffings mainly consist of macrophages and T cells with CD4-dominancy, which is also different from CD8+ T-cell-dominant inflammation in MS. Compared to aquaporin 4 (AQP4) antibody-positive neuromyelitis optica spectrum disorders (NMOSD), perivenous complement deposition is less common, but can be seen on myelinated fibers and on myelin degradation products within macrophages, resembling MS Pattern II pathology. Thus, the pathogenetic contribution of complements in MOGAD is still debatable. Together, these pathological features in MOGAD are clearly different from those of MS and AQP4 antibody-positive NMOSD, suggesting that MOGAD is an independent autoimmune demyelinating disease entity. Further research is needed to clarify the exact pathomechanisms of demyelination and how the pathophysiology relates to the clinical phenotype and symptoms leading to disability in MOGAD patients.

KEYWORDS

myelin oligodendrocyte glycoprotein, antibody, acute disseminated encephalomyelitis, perivenous demyelination, confluent demyelination, multiple sclerosis lesion pattern-II

1. Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein (consisting of 218 amino acids) expressed in oligodendrocytes and is characterized by its distribution in the outermost layer of the myelin sheath (1). MOG is composed of multiple splicing variants (2, 3), all of which have extracellular immunoglobulin variable domains and thus belong to the immunoglobulin superfamily (4). Because of these structural features, MOG has a long history of research as an autoantigen that can induce inflammatory demyelinating pathology in the central nervous system (CNS) (5–9), and is one of the best-studied antigens in experimental autoimmune encephalomyelitis (EAE) (10–12). Therefore, autoantibodies against MOG have long been considered a potential cause of human inflammatory demyelinating diseases, particularly multiple sclerosis (MS). However, the discovery of clinically relevant MOG antibodies in human disease has not been successful until recently. Previous results on the detection of MOG antibodies by enzyme-linked immunosorbent assay (ELISA) or Western blot were confusing due to the low specificity (13). This is because the antigen is linear in ELISA or denatured in Western blot such that the three-dimensional structure of native MOG was lost; the issue was resolved when the conformation-sensitive MOG antibody became detectable by human MOG-transfected cell-based assays (CBAs) (14–16). As a result, MOG antibodies have been found in patients with optic neuritis, acute myelitis, neuromyelitis optica spectrum disorders (NMOSD) without aquaporin 4 (AQP4) antibodies (17, 18), acute disseminated encephalomyelitis (ADEM) (19, 20), and brainstem (21–23) and cerebral cortical encephalitis (24–26). In contrast, typical MS patients are essentially negative for MOG antibodies (27, 28). Consequently, patients with MOG antibodies came to be recognized as belonging to a group with inflammatory demyelinating conditions distinct from MS, and the international diagnostic criteria of MOG antibody-associated disease (MOGAD) were recently published (29).

In this review, we summarized the histopathological findings of MOGAD in published studies. In particular, we outlined the pathologies typically found in MOGAD and the issues that remain unresolved because of inconsistent results in previous studies. We also discussed the unique pathogenesis of MOGAD by comparing it with MS and AQP4 antibody-positive NMOSD (AQP4 + NMOSD).

2. Histopathological features of MOGAD

2.1. Patterns of demyelination

The pattern of demyelination seen in well-known inflammatory demyelinating diseases can be classified into "confluent demyelination" in MS, "perivenous demyelination" in ADEM and "concentric demyelination" in Balo's disease (Figure 1) (30, 31). "Confluent demyelination" is characterized by fusion and enlargement of perivascular demyelinating lesions with well-defined borders, resulting in the formation of large plaques, and the lesions may occasionally exhibit a map-like morphology (Figure 1A). On the other hand, "perivenous demyelination" is the one with indistinct borders around a single small vessel with inflammatory cell infiltration, and often multifocal (Figure 1B). Perivenous demyelination is considered useful in the pathological differentiation of ADEM from MS (32). However, it should be noted that we may miss "perivenous demyelination" because it can be very small, and the activity of myelin phagocytosis by macrophages is sometimes scarce, requiring careful observation (Figure 2).

The pathology of MOGAD is characterized by a mixture of perivenous and confluent demyelinating lesions (Figure 1D) (33, 34), and their proportions may depend on the timing of tissue sampling and disease severity (Tables 1, 2) (24, 33–47). The median time to tissue sampling in our study (one month) (33) was shorter than that in Höftberger et al. (seven months) (34) (Table 1), and the demyelination patterns in the two studies were different (90% of the lesions in our cases had perivenous demyelination, while 50% of the lesions in Höftberger's study had a transitional pattern [a combination of perivenous and confluent demyelinations]). However, it is important to mention that among confluent demyelinating lesions, slowly expanding lesions (SELs) typically seen in the subacute to chronic stage of MS (Figure 3) (48) are rarely observed in MOGAD patients (34) or AQP4 + NMOSD patients (49). SELs are characterized by the accumulation of activated macrophages/microglia at the lesion edge with iron deposition (50), which is thought to be involved in the progression of MS (51–53). In other words, demyelinating lesion formation in MOGAD patients is characterized by simultaneous development of multiple perivascular inflammatory demyelination and its fusion to form confluent demyelination, which is different from radial expansion of the lesions in MS.

2.2. Distribution of demyelinating lesions

Demyelinating lesions in MOGAD patients are found mainly in the white matter but also in the subpial cortex to cortico-medullary junction and deep gray matter (Figure 4) (33, 34, 47). Within these lesions, CD68-positive macrophages/microglia widely infiltrate the cortex (Figure 4). The frequency of cortical demyelination is reported to be higher in MOGAD patients with cerebral involvement than in MS patients (34), which is compatible with the high incidence of cortical involvement in MOGAD patients, evidenced by conditions such as ADEM and cerebral cortical encephalitis (29). In addition, inflammatory cells infiltrate around meningeal vessels adjacent to subpial demyelinating lesions (33, 34, 45, 47). In cerebral cortical encephalitis of MOGAD patients, brain MRI scans often show contrast enhancing effects in the meninges which may reflect such inflammation around the meningeal vessels (47).

2.3. Preferential loss of specific myelin component(s)

When evaluating demyelinating lesions, it is important to identify primarily damaged myelin component(s) by immunohistochemistry to assess the type and stage of the disease (48, 54). Our study and several previous case reports indicated that some demyelinating lesions found in patients with MOGAD showed MOG-dominant myelin loss especially in the early-stage (Figure 5) (33, 37, 42, 46), and some myelin-laden macrophages localized at the perivascular space showed MOG-dominant phagocytosis (33). In addition,

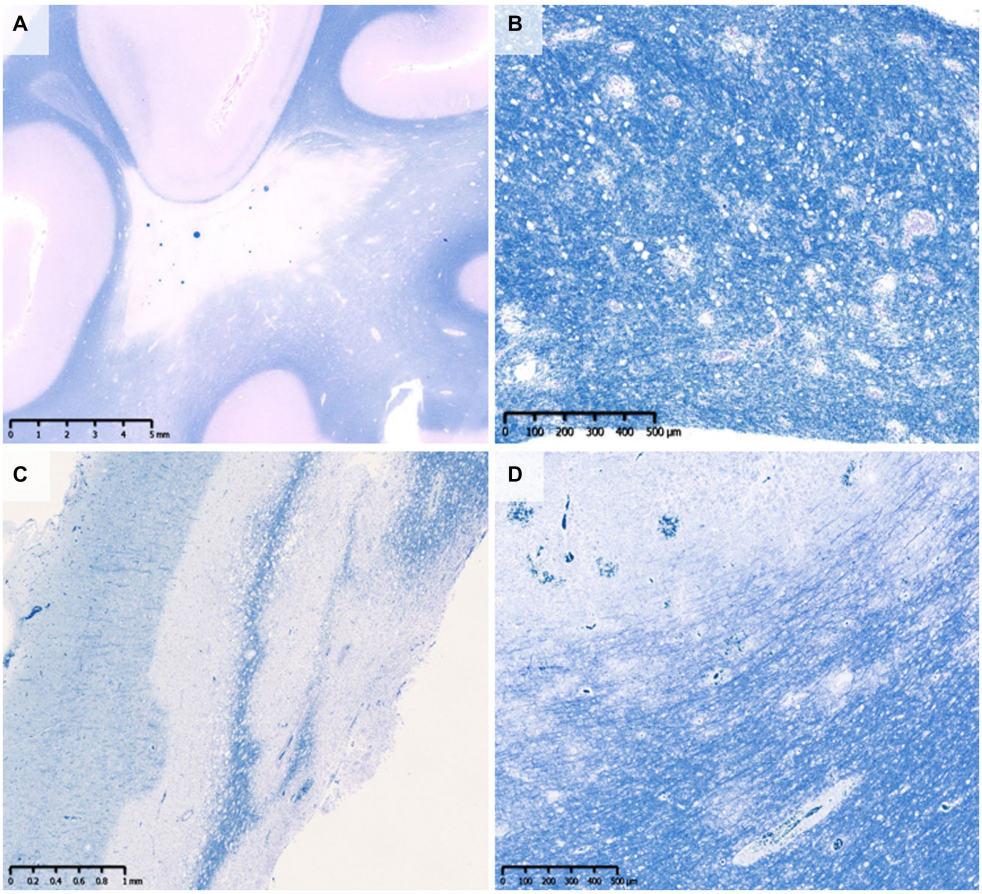

FIGURE 1
Various types of demyelination. **(A)** Confluent demyelination (SPMS). **(B)** Perivenous demyelination (ADEM). **(C)** Concentric demyelination (Balo's disease). **(D)** Mixed pathology of confluent and perivenous demyelination (MOGAD). **(A–D)** Klüver-Barrera staining. ADEM, acute disseminated encephalomyelitis; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; SPMS, secondary progressive multiple sclerosis.

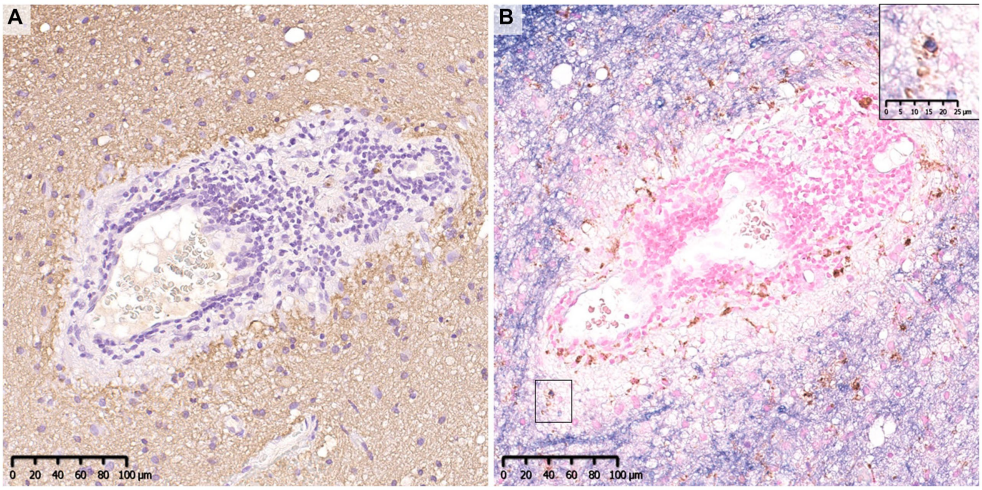

FIGURE 2
Perivenous demyelination in MOGAD. A demyelinating lesion was seen around small vessels with inflammatory cell infiltration. There were a small number of macrophages that phagocytosed myelin debris (insert in **B**). **(A)** MBP, **(B)** MOG (blue)/CD68 (brown). MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG antibody-associated disease.

TABLE 1 Comparison of clinical findings and pathology of MOGAD in two studies of more than 10 patients.

Reference		Takai et al. (33)	Höftberger et al. (34)
Clinical findings	Patients, *n*	11	24 (Autopsy 2)
	Age (year)	29 (9–64)*	10 (1–66)*
	Female/Male (female %)	6/11, 55%	13/22, 59%
	Diagnosis	ADEM-like: 6/11 LE: 3/11 CCE: 2/11	ADEM-like: 11/18 NMOSD: 1/18 Myelitis: 2/18 ON: 2/18 CCE: 1/18 BS: 1/18
	Time from attack to biopsy (month)	1 (0.5–96)*	7 (0–516)*
	Total follow up period (month)	33 (12–180)*	43 (3–516)*
Pathology	Demyelination pattern		
	Perivenous (ADEM-like)	91%	21%
	Confluent (MS-like)	2%	29%
	Transitional (perivenous + confluent)	7%	50%
	MOG-dominant myelin loss	37%	0%
	Astrocytopathy	0/11 (0%)	0/17 (0%)
	CD4-dominant T-cell infiltration	10/11 (91%)	+
	Complement deposition	2/11 (18%)	8/8 (100%)

*Median (range). ADEM, acute demyelinating encephalomyelitis; BS, brain stem lesion; CCE, cortical encephalitis; LE, leukoencephalopathy; NMOSD, neuromyelitis optica spectrum disorders; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG antibody-associated disease; MS, multiple sclerosis; ON, optic neuritis.

oligodendrocytes are relatively preserved in MOGAD demyelinating lesions (33, 37, 38, 44). These findings support that MOGAD actually targets MOG and that its demyelination process may initially occur on the surface of the myelin sheath. However, Höftberger et al. reported no MOG dominant myelin loss in their study (34), and it remains to be clarified what this difference originated from. On the other hand, some reports indicated that preferential loss of myelin associated glycoprotein (MAG) could occur in MOGAD patients although the incidence was very low (34, 40). Since MAG is expressed in the innermost layer of the myelin sheath and is most distant from the oligodendrocyte cell body, preferential loss of MAG is thought to reflect oligodendrocyte damage (distal oligodendrogliopathy) (55). This finding is seen in patients with MS pattern III lesions (56); Balo's disease (57); AQP4 + NMOSD (58); and ischemic tissue damage such as cerebral infarction (59). Since MOG is also expressed at the surface of oligodendrocytes, depending on the concentration or characteristics of MOG antibodies, some oligodendrocytes may be damaged by MOG antibodies.

2.4. Characteristics of inflammatory cell infiltration

The cellular infiltrate in inflammatory demyelinating lesions is composed mainly of myelin phagocytosing macrophages at the sites of demyelination and T-cell clusters in the perivascular space (perivascular cuffing). Infiltrating cells in the lesions of MOGAD are essentially similar (Tables 1, 2), but a characteristic feature of MOGAD is CD4+ T-cell-dominant infiltration in the demyelinating lesions (33, 34), which is different from the dominance of CD8+ T-cell infiltrates in MS lesions (60, 61). Some of those CD4+ T cells in MOGAD might be reactive to MOG epitopes. However, it should be noted that the timing of the sampling of specimens should be considered. In AQP4 + NMOSD, the main subpopulation of T cells infiltrated in the lesions changes from CD4 in the acute phase to CD8 in the chronic phase of the disease (49). Most of the CNS tissue specimens of MOGAD patients examined in the published studies were obtained in the acute phase, and the pathological findings in the chronic phase have not been examined. Therefore, the characteristics of T cells infiltrating the lesion may reflect differences in the stage of the disease rather than pathogenesis, and further detailed verification is required in the future. However, it is known that the levels of T helper 17 (Th17)-related cytokines are markedly elevated in the cerebrospinal fluid (CSF) of patients during the acute phase of MOGAD and AQP4 + NMOSD when compared with those of MS patients and control subjects (62). Thus, in the acute phase, T-cell subpopulations infiltrating the lesions are different between MOGAD and MS patients.

B cells are seen in small numbers in the perivascular space, but are less frequent than T cells (33, 34). Additionally, ectopic lymphoid follicles, as reported in MS (63, 64), have not been detected in MOGAD patients. However, occasionally B-cell aggregates may be seen in the leptomeninges (47). In MOGAD patients, intrathecal production of MOG antibodies seems to occur more frequently than in AQP4 + NMOSD patients (65–68), suggesting that B cells infiltrating the CNS produce MOG antibodies and contribute to the pathogenesis of the disease. In addition, CXCR4 is upregulated in B cells in patients with MOGAD (69), and its ligand, CXCL12, is known to be elevated in the CSF (70). Thus, CXCL12/CXCR4 may contribute

TABLE 2 Summary of the clinical and pathological findings of MOGAD in case reports.

A					
Clinical findings					Reference
Case	Age	Sex	Clinical phenotype	Antibody other than MOG	Author
1	49	F	Rel.TDL (open ring)	nr	Konig et al. (35)
2	71	M	Blt.ON, MY, multiple brain lesions	AQP4	Di Pauli et al. (36)
3	66	F	Rel.myelitis + TDL (open ring)	-	Spadaro et al. (37)
4	63	F	CIS	-	Jarius et al. (38)
5	67	F	Rel.LETM + TDL (multiple)	-	Wang et al. (39)
6	49	M	ADEM (MY + multiple brain lesion)	nr	Körtvélyessy et al. (40)
7	34	M	ADEM (MY + multiple brain lesion)	nr	
8	28	F	Blt.ON + TDL (infiltrative)	-	Zhou et al. (41)
9	25	F	ADEM + ON	-	
10	29	F	CCE + Blt.ON	-	Ikeda et al. (42)
11	46	M	CCE + ON	-	Fujimori et al. (24)
12	47	M	ADEM (diffuse)	-	Komatsu et al. (43)
13	45	M	TDL (infiltrative)	-	Shu et al. (44)
14	6	F	TDL (infiltrative)	-	
15	37	F	CCE + MY	-	Papathanasiou et al. (45)
16	40	M	CCE + multiple brain/brain stem lesion	P/C-ANCA	
17	52	F	TDL (lymphoma)	-	Uzura et al. (46)
18	17	M	CCE + ON + MY	-	Valencia-Sanchez et al. (47)
19	35	F	CCE	-	

B											
Pathological findings											
Case	Material	Demyelination pattern	Oligodendrocyte	Damaged myelin component	Astrocytopathy		Site of complement deposition			IgG deposition	Infiltrating inflammatory cells
					Astrocyte morphology	AQP4-loss	Myelin	Inside macrophage	Perivascular		
1	Biopsy (Brain)	Nr	Nr	Nr	Nr	Nr	Nr	+	Nr	Nr	M, T
2	Autopsy	Confluent	Preoligodendrocyte	MOG = MBP > CNPase	Loss	+	Nr	Nr	+	Nr	CD3, CD8, low B,
3	Biopsy (Brain)	Confluent	Preserved	MOG > PLP	Reactive	–	+	+	–	Diffuse with fiber	M, T (CD8)

(Continued)

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TABLE 2 (Continued)

B											
Pathological findings											
Case	Material	Demyelination pattern	Oligodendrocyte	Damaged myelin component	Astrocytopathy		Site of complement deposition			IgG deposition	Infiltrating inflammatory cells
					Astrocyte morphology	AQP4-loss	Myelin	Inside macrophage	Perivascular		
4	Biopsy (Brain)	Nr	Preserved	Even	Reactive	–	Nr	+	Nr	Macrophage	CD4 = CD8, B
5	Biopsy (Brain)	Confluent	Nr	Nr	Reactive	Nr	Nr	Nr	Nr	Nr	M, T, low B
6	Biopsy (Brain)	Confluent	Apoptosis	MAG > MOG	Nr	Nr	+	+	Nr	+	M,T (CD8), B
7	Biopsy (Brain)	Confluent	Preserved	Even	Nr	Nr	Nr	Nr	+	Nr	M (rim), T dominant, CD8
8	Biopsy (Brain)	Confluent	Nr	Nr	Reactive	–	Nr	Nr	Nr	Nr	M, T (CD4), low B
9	Biopsy (Brain)										
10	Biopsy (Brain)	Perivenous, subpial	Preserved	MOG > MAG, MBP	Reactive	–	–	–	–	–	M, T (CD4 > CD8), low B
11	Biopsy (Brain)	No demyelination	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	M, T, B
12	Biopsy (Brain)	Perivenous, confluent	Preserved	MOG > MAG, MBP	Reactive	–	+	+	–	Diffuse	M, T (CD4 > CD8), low B
13	Biopsy (Brain)	Confluent	Preoligodendrocyte	Nr	Reactive	Decrease	–	Minor	–	Nr	M, T (CD4 > CD8), low B
14	Biopsy (Brain)	Confluent	Preoligodendrocyte	Nr	Reactive	Decrease	–	Minor	–	Nr	M, T (CD4 > CD8), low B
15	Biopsy (Brain)	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	M, T, B
16	Biopsy (Brain)	Perivenous, confluent	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	T, B
17	Biopsy (Brain)	Perivenous, confluent	Preserved	MOG > MAG, MBP	Reactive	–	–	–	–	Perivenous	M, T, low B
18	Biopsy (Brain)	Perivenous, subpial	Nr	even	Nr	Nr	–	–	–	Nr	M, T (CD4 > 8)
19	Biopsy (Brain)	Subpial	Nr	Nr	Nr	Nr	Nr	Nr	Nr	Nr	M, T (CD4 = 8), B*

(A) ADEM, acute disseminated encephalomyelitis; ANCA, anti-neutrophil cytoplasmic antibody; AQP4, aquaporin 4; Blt., bilateral; CCE, cerebral cortical encephalitis; CIS, clinically isolated syndrome; F, female; LETM, longitudinally extensive transvers myelitis; M, male; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MY, myelitis; ON, optic neuritis; P/C, perinuclear/cytoplasmic; Rel., relapsing; TDL, tumefactive demyelinating lesion. *, **Same patient in case11* and case7** in reference (33). (B) Nr, not reported; MAG, myelin associated glycoprotein; MOG, myelin oligodendrocyte glycoprotein; MBP, myelin basic protein; CNP, 2′,3′-Cyclic-nucleotide 3′-phosphodiesterase; PLP, Proteolipid protein; M, macrophage; T, T cells; B, B cells. +, present; –, absent. *Focal meningeal B-cell agglutination without features of ectopic B-cell follicles.

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to the chemotaxis of B cells and other inflammatory cells in MOGAD patients (71).

2.5. Deposition of humoral immunity and complement activity

Since MOG antibodies are mainly composed of those in the IgG1 subclass (27, 72), complement-mediated cytotoxicity (CDC) has been considered to contribute to the pathogenesis of MOGAD. In fact, both *in vitro* and *in vivo*, it has been reported that MOG antibody-induced cytotoxicity and demyelination can occur in a complement-mediated manner (72–74). Indeed, some previous case reports on biopsied brain lesions in MOGAD patients showed the deposition of complement components on myelin fibers and myelin debris phagocytosed by macrophages, and the authors concluded that the lesions were probably caused by humoral immune-mediated demyelination, such as MS pattern II lesions (37, 38, 40, 56). This type of MS lesion is histologically characterized by extensive confluent demyelination with tissue deposition of humoral immune factors such as complements and immunoglobulins (22). However, the histopathological findings of complements in MOGAD patients remain debatable, as the reported results have been inconsistent (33, 34). In our study, only 2 of 11 MOGAD patients showed tissue deposition of complement, which was much less frequent and dense than in AQP4 + NMOSD patients with perivascular deposition of activated complements (C9neo) in all acute lesions (33). However, Höftberger et al. concluded that active complement deposition was observed in all 8 patients they evaluated (34) (Table 2). This difference may be due to the clinical severity, timing of tissue sampling or inter-individual variability in the severity of MOG-IgG-related cytotoxicity other than complement activation, such as antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC) (75, 76). However, a recent *in vitro* study demonstrated that MOG antibodies elicited much less complement activation than AQP4 antibodies (77). AQP4 has two isoforms, M1 and M23, that differ in their transcription start sites (78). AQP4-M1 and M23 are coexpressed in the CNS, and M23 is known to form large well-ordered assemblies called orthogonal arrays of particles (OAPs) (78) and is reported to be more highly expressed in the optic nerve and spinal cord, where NMOSD lesions are more likely to occur (79).

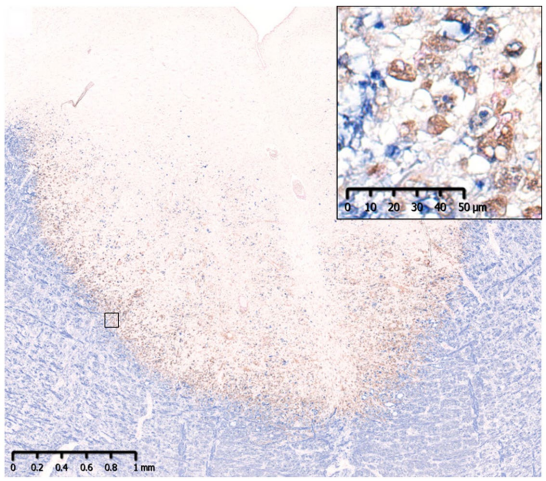

FIGURE 3
Slowly expanding lesion in SPMS. A large well-demarcated demyelinating lesion was seen with peripheral infiltration of myelin phagocytosed macrophages (insert). MBP (blue)/CD68 (brown). MBP, myelin basic protein; SPMS, secondary progressive multiple sclerosis.

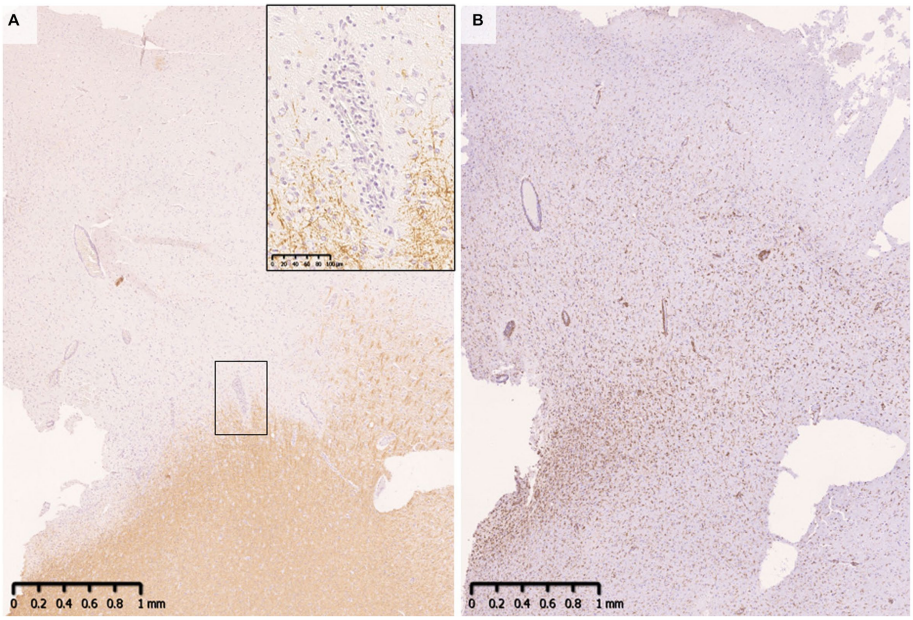

FIGURE 4
Subpial demyelination in MOGAD. **(A)** Myelin fibers were widely lost in the subpial cortex. Perivenous demyelination was observed at the cortical-medullary junction. **(B)** CD68 positive macrophages/microglia were diffusely infiltrated the demyelinated cortex. **(A)** MBP, **(B)** CD68. MBP, myelin basic protein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease.

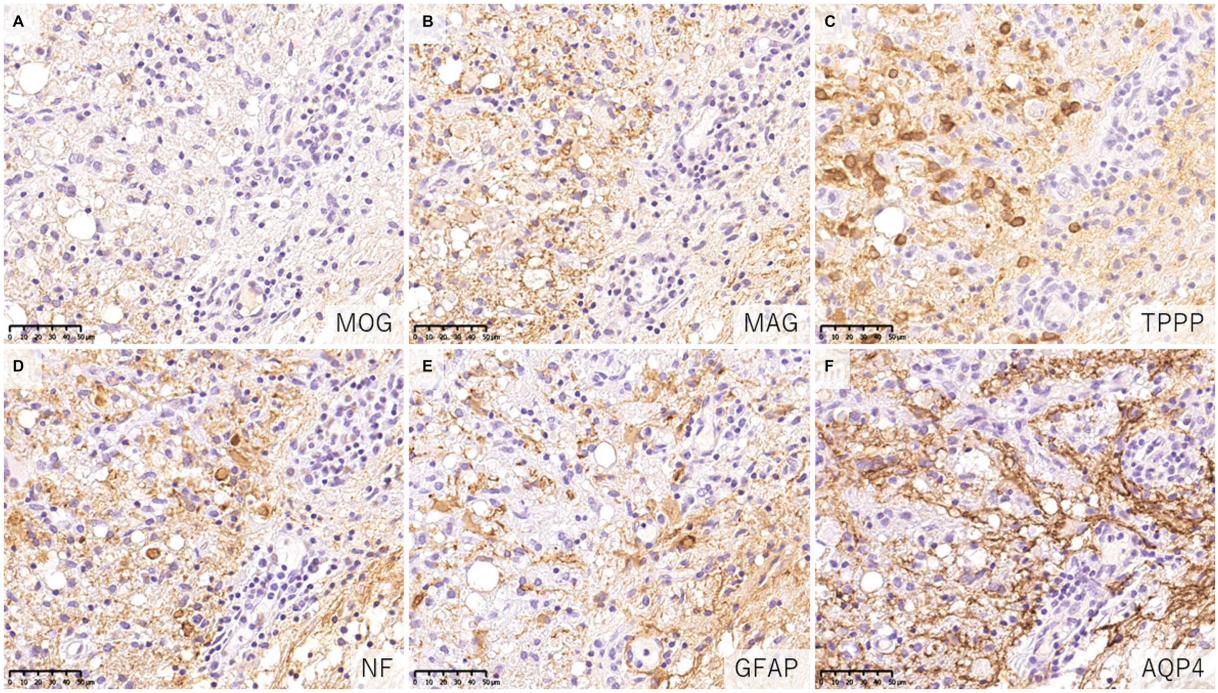

FIGURE 5
Characteristics of demyelinating lesions in MOGAD. **(A,B)** Loss of MOG staining was more evident than MAG staining. **(C)** Oligodendrocytes were well preserved in the demyelinating lesion. **(D)** Axonal enlargement was present, suggesting neuroaxonal alteration but axonal staining was relatively preserved compared to demyelination. **(E,F)** Activated astrocytes with dense AQP4 staining were observed. **(A)** MOG, **(B)** MAG, **(C)** TPPP, **(D)** NF, **(E)** GFAP, **(F)** AQP4. AQP4, aquaporin 4; GFAP, glial fibrillary acidic protein; MAG, myelin associated glycoprotein; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG antibody-associated disease; NF, neurofilament; TPPP, tubulin polymerization promoting proteins.

The formation of OAPs allows AQP4 to be densely expressed on the cell surface, facilitating AQP4 antibody clustering on the cell membrane. The classical complement activation pathway is initiated by the binding of C1q to the Fc portion of IgG, but requires bivalent or multivalent binding (80). Thus, complement components are more likely to be activated when IgG is densely bound on the plasma membrane, and in fact, the presence of OAPs significantly enhanced complement-mediated cytotoxicity by the presence of AQP4 antibodies (81). On the other hand, MOG constitutes a quantitatively minor component (0·05%) of the myelin sheath (1), and MOG antibodies require bivalent binding when binding to MOG, making it difficult for them to assemble on the cell membrane, and resulting in low C1q binding ability (82). It is necessary to study in detail whether the amount and characteristics of MOG antibodies affect the degree of complement activation following binding to AQP4.

3. Comparison between MOGAD and MS

The dominant pattern of demyelinating lesions (perivenous demyelination) in MOGAD is similar to that of ADEM rather than MS. The characteristics of infiltrating T cells also differ in MOGAD and MS, as noted above (Table 3). However, we cannot rule out the possibility that some patients with MOGAD may have a pathology similar to MS since previous studies on MOG-EAE have demonstrated that the ratios of myelin antigen-specific lymphocytes and autoantibodies to myelin could influence the dominance of perivenous or confluent demyelination (8, 85). Additionally, there is a report that MOG antibodies purified from two MOGAD patients (whose MOG antibodies were capable of binding to rodent MOG) and administered intrathecally to EAE subjects induced by MOG-specific T cells did not produce demyelinating lesions with deposition of activated complement, but in the presence of MBP-specific T cells, demyelinating lesions similar to MS pattern II developed (86). These findings suggested that T cells in some cases of MOGAD may recognize myelin protein(s) other than MOG and activate complements. Thus, further investigations are needed to confirm whether this is the case in the human pathology of MOGAD. However, it should be noted that MS Pattern II is a pathological classification proposed before the discovery of conformation-sensitive MOG antibodies and includes many brain biopsy samples from cases with atypical or fulminant cerebral lesions for MS (56). Jarius et al. found that only one of the 13 cases with MS Pattern II pathology was positive for MOG antibodies and suggested its limited involvement (38). Therefore, it may include other inflammatory demyelinating pathologies than MS and MOGAD and require further verification.

4. Comparison between MOGAD and AQP4+NMOSD

The fundamental difference in the pathologies of the two diseases is that the main target of immune attack is myelin in MOGAD but is

TABLE 3 Comparison of the major pathological findings of acute lesions in MOGAD, MS, and AQP4+NMOSD.

Disease	MOGAD	MS	AQP4+NMOSD
Primary target	Myelin > Oligodendrocyte	Myelin, Oligodendrocyte	Astrocyte
Histopathology			
Lesion distribution	Mainly in WM, the cerebral cortex and deep GM can also be involved	Mainly in periventricular and juxtacortical WM, (cerebral cortex in the progressive phase)	Both WM and GM, mainly in the spinal cord and optic nerves
Pattern of demyelination	Perivenous > Confluent or Transitional*	Confluent (SEL in the progressive phase)	Secondary in the astrocyte lytic lesions, Distal oligodendrogliopathy
Lesion edge	Ill-defined ~ sharply defined	Sharply defined	Sharply defined
Damaged myelin proteins	MOG > or = others	MAG > others (in Pattern III) or Even (in the other patterns)	MAG > others
Oligodendrocyte	Relatively preserved	Partially loss ~ regenerate	Loss
Astrocyte	Reactive	Reactive	Loss
AQP4-loss	None ~ Mild	None ~ Mild	Severe
Axon	Preserved	Relatively preserved, (degenerated in the progressive phase)	Damaged in various degrees
Site of complement deposition	Myelin, inside macrophage	Myelin, inside macrophage (in MS Pattern II)	Vasculocentric (rim/rosette pattern)
Cellular infiltration			
Macrophage	Most conspicuous in the PVS and parenchyma	Most conspicuous in parenchyma, especially at the lesion edge	Most conspicuous in the PVS and parenchyma
T cells	CD4 dominant in the PVS	CD8 dominant in the PVS	CD4 dominant in the PVS (CD8 dominant in the chronic phase)
B cells	A small number in the PVS, occasional aggregates in the leptomeninges	A small number in the PVS (Ectopic lymphoid follicles in the progressive phase)	A small number in the PVS
Neutrophil/Eosinophil	Mild ~ Moderate	Rare	Mild ~ Marked
Fluid pathology			
Cell damage marker	MBP elevated, GFAP not elevated	MBP elevated, GFAP not elevated (elevated in the progressive phase) (83, 84)	MBP elevated, GFAP remarkably elevated
Cytokine profile	Marked elevation of Th17-related cytokines relative to MS		Marked elevation of Th17-related cytokines relative to MS

AQP4, aquaporin 4; GFAP, glial fibrillary acidic protein; GM, gray matter; MAG, myelin associated glycoprotein; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG antibody-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; PVS, perivascular space; SEL, slowly expanding lesion; WM, white matter. *Perivenous + Confluent.

astrocytes in AQP4 + NMOSD (62). In previous pathological studies of MOGAD, there has been no astrocytic damage except in patient doubly positive for AQP4 and MOG antibodies (36). In the demyelinating lesions in MOGAD, astrocytes are essentially activated and AQP4 is also strongly stained on immunohistochemistry images (Figure 5), although two cases of partially decreased AQP4 expression in MOGAD with tumefactive brain lesions have been reported (Table 2) (44). The pathological process starts in the perivascular regions in both MOGAD and AQP4 + NMOSD, but they show distinct features of demyelinating lesions: in MOGAD, MOG is predominantly lost with relatively preserved oligodendrocytes, whereas in AQP4 + NMOSD, MAG is preferentially damaged, and oligodendrocytes are lost, but MOG is relatively preserved (Figure 6). The immunohistochemical staining pattern of activated complement deposition also differs: a rosette-like staining around blood vessels is seen in AQP4 + NMOSD (49, 87, 88), while in MOGAD, perivascular complement deposition is much less (Figure 7) but stained on myelinated fibers and in myelin degradation products within macrophages (Figure 7; Tables 2, 3) (37, 38, 40). Despite these different patterns of demyelination, MOGAD and AQP4 + NMOSD share some clinical features, such as optic neuritis and longitudinally extensive myelitis (18, 89), and cytokine profiles (upregulation of Th17-related cytokines) in the CSF (62) as autoantibody-associated CNS diseases.

5. Conclusion

Recently, the international diagnostic criteria for MOGAD have been proposed (29), and certain pathological features of the disease have been clarified (29), indicating that MOGAD is a disease entity distinct from MS and AQP4 + NMOSD. In fact, published articles on MOGAD have been rapidly increasing in recent years, and a few international clinical trials for relapsing MOGAD have already begun.

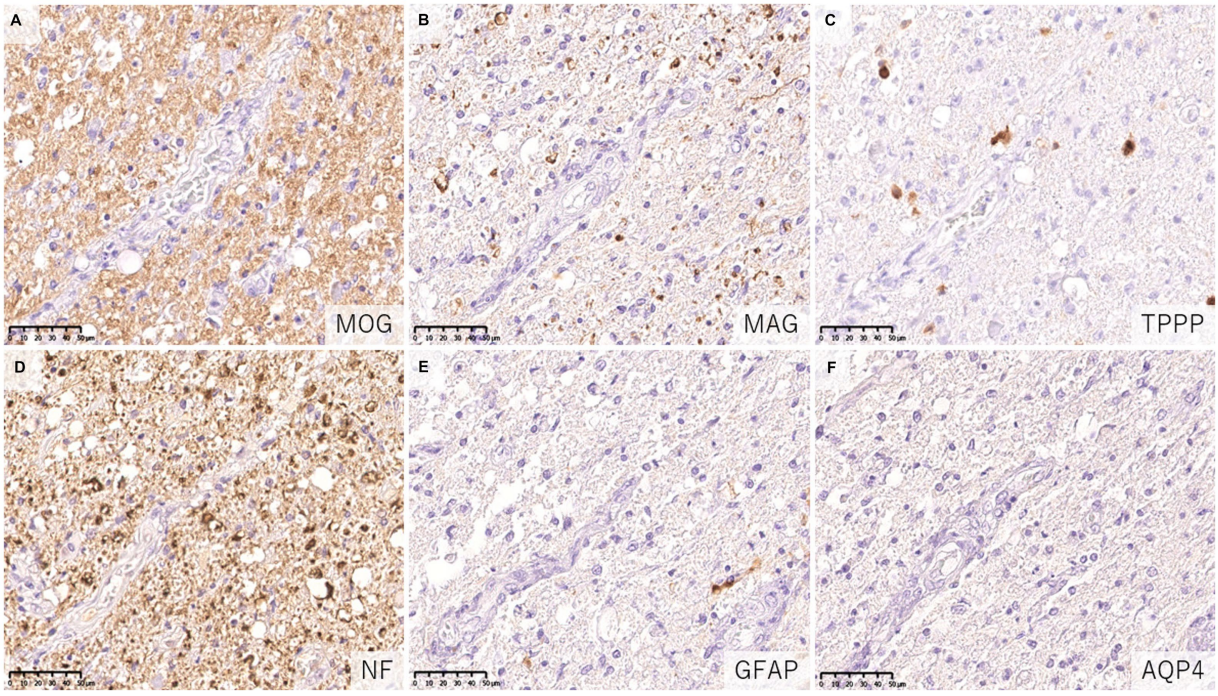

FIGURE 6
Characteristics of astrocytopathic lesions in AQP4+NMOSD. **(A,B)** Loss of MAG staining was more evident than MOG staining. **(C)** Numerous oligodendrocytes were lost in the lesion. **(D)** Axonal enlargement was present, suggesting neuroaxonal alteration, but axonal staining was relatively preserved compared to demyelination and astrocyte loss. **(D–F)** Astrocytes were almost completely lost in the lesion. **(A)** MOG, **(B)** MAG, **(C)** TPPP, **(D)** NF, **(E)** GFAP, **(F)** AQP4. AQP4: aquaporin 4, GFAP, glial fibrillary acidic protein; MAG, myelin associated glycoprotein; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG antibody-associated disease; NF, neurofilament; NMOSD, neuromyelitis optica spectrum disorders; TPPP, tubulin polymerization promoting proteins.

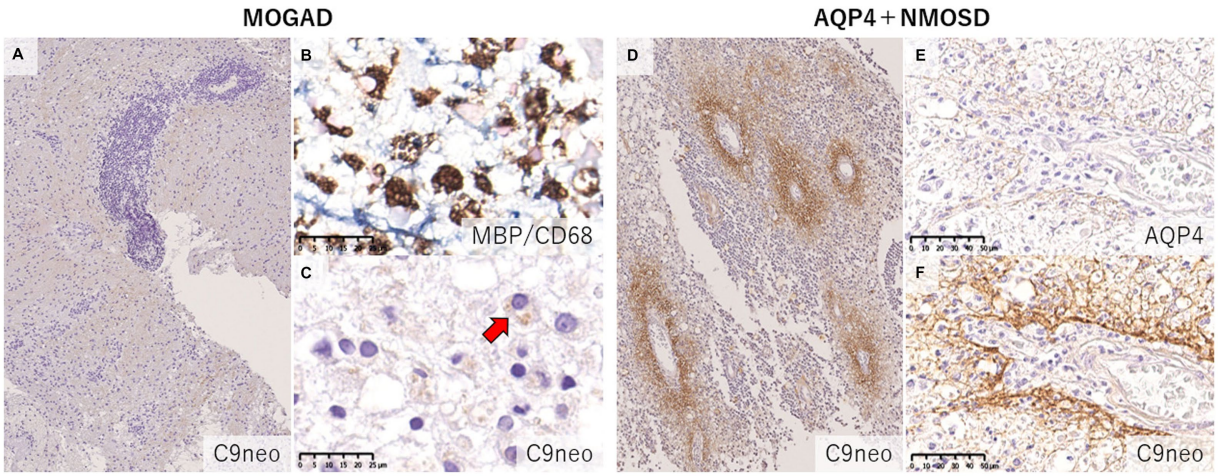

FIGURE 7
Comparison of the deposition pattern of activated complements in MOGAD and AQP4+NMOSD. **(A)** Only mild perivascular depositions of complements were seen in MOGAD even in the active lesion where perivascular cuffing was evident. **(B,C)** In active demyelinating lesions, complement staining was detected on myelin debris phagocytosed by macrophages (red arrow). **(D)** Multiple rosette-like stainings of complement deposition were seen in the NMOSD lesion. **(D–F)** Perivascular complement depositions were seen within AQP4-loss lesions. **(A,C,D,F)** C9neo. **(B)** MBP/CD68, **(E)** AQP4. AQP4, aquaporin 4; MBP, myelin basic protein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorders.

Considering the currently available data of the histopathological studies of MOGAD and some basic research with MOG antibodies, the immunopathological process in MOGAD may be summarized as follows. Initially, the breakdown of immune tolerance leads to the generation of MOG-reactive T cells that stimulate the production of MOG antibodies from B cells in the periphery. Triggered by infection,

vaccination, or other stimuli, these MOG-reactive T cells are activated and penetrate the blood–brain barrier (BBB) into the CNS and aggregate at the perivascular space of the meninges and parenchyma (perivascular cuffing). MOG antigens in the CNS further activate these cells which are primarily CD4-positive T cells and promote a Th17-dominant cytokine milieu in the CNS and the BBB disruption. As a result, more MOG antibodies enter the CNS. Then the autoantibodies target myelins, especially MOG, to demyelinate the nerve fibers from the surface of myelin sheath via CDC (noted as deposition of activated complements), ADCC (in cooperation with infiltrating granulocytes), ADCP (seen as myelin phagocytosed macrophages), and other mechanisms. A fraction of the demyelinating lesions may exhibit MOG-dominant loss, suggesting a MOG-targeted pathology, and some oligodendrocytes may also be damaged. But compared to the remarkable CDC to cause astrocytolysis in AQP4 + NMOSD, the pathological role of CDC for demyelination may be less in some cases of MOGAD. These events probably occur simultaneously around multiple blood vessels (perivenous demyelination) in the white and gray matters. Subsequently, broken MOG and other myelin components are phagocytosed by macrophages (myelin-laden macrophages in the parenchyma and perivascular space), further enhancing antigen presentation and activating MOG-reactive CD4-positive T cells that induce the activation and infiltration of cytotoxic effector T cells against myelins and B cells that produce MOG antibodies intrathecally. These cellular and humoral immune responses are augmented through the interaction with proinflammatory cytokines/chemokines, which further exacerbates the disease state resulting in fusion of the lesions to form extensive demyelination (confluent demyelination). This confluent demyelination in MOGAD may develop by a different mechanism from that of the radial expansion of MS lesions.

However, we should investigate further details of the pathophysiology of MOGAD by means of various technologies including molecular immunology, omics, advanced imaging, neurophysiological tests, therapeutic response and artificial intelligence as well as conventional histopathological analyses. Furthermore, the histopathological studies in MOGAD to date have been derived from brain biopsies, and we should clarify whether the lesion characteristics are similar in other CNS regions, such as the optic nerve and spinal cord. Studies on how differences in the histopathologic findings may affect the severity and clinical phenotype in patients with MOGAD are also needed. These studies are expected to contribute to a better understanding and management of MOGAD.

Author contributions

YT, KF, and MA contributed to conception and design of the study. YT and TM organized the database. YT wrote the first draft of the manuscript, tables, and figures. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Basic CSF parameters and MRZ reaction help in differentiating MOG antibody-associated autoimmune disease versus multiple sclerosis

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Background: Myelin oligodendrocyte glycoprotein antibody-associated autoimmune disease (MOGAD) is a rare monophasic or relapsing inflammatory demyelinating disease of the central nervous system (CNS) and can mimic multiple sclerosis (MS). The variable availability of live cell-based MOG-antibody assays and difficulties in interpreting low-positive antibody titers can complicate diagnosis. Literature on cerebrospinal fluid (CSF) profiles in MOGAD versus MS, one of the most common differential diagnoses, is scarce. We here analyzed the value of basic CSF parameters to i) distinguish different clinical MOGAD manifestations and ii) differentiate MOGAD from MS.

Methods: This is retrospective, single-center analysis of clinical and laboratory data of 30 adult MOGAD patients and 189 adult patients with relapsing-remitting multiple sclerosis. Basic CSF parameters included CSF white cell count (WCC) and differentiation, CSF/serum albumin ratio (Q_{Alb}), intrathecal production of immunoglobulins, CSF-restricted oligoclonal bands (OCB) and MRZ reaction, defined as intrathecal production of IgG reactive against at least 2 of the 3 viruses measles (M), rubella (R) and varicella zoster virus (Z).

Results: MOGAD patients with myelitis were more likely to have a pleocytosis, a Q_{Alb} elevation and a higher WCC than those with optic neuritis, and, after review and combined analysis of our and published cases, they also showed a higher frequency of intrathecal IgM synthesis. Compared to MS, MOGAD patients had significantly more frequently neutrophils in CSF and WCC>30/µl, $Q_{Alb}>10\times10^{-3}$, as well as higher mean Q_{Alb} values, but significantly less frequently CSF plasma cells and CSF-restricted OCB. A positive MRZ reaction was present in 35.4% of MS patients but absent in all MOGAD patients. Despite these associations, the only CSF parameters with relevant positive likelihood ratios (PLR) indicating MOGAD were $Q_{Alb}>10\times10^{-3}$ (PLR 12.60) and absence of CSF-restricted OCB

(PLR 14.32), whereas the only relevant negative likelihood ratio (NLR) was absence of positive MRZ reaction (NLR 0.00).

Conclusion: Basic CSF parameters vary considerably in different clinical phenotypes of MOGAD, but Q_{Alb}>10×10^{-3} and absence of CSF-restricted OCB are highly useful to differentiate MOGAD from MS. A positive MRZ reaction is confirmed as the strongest CSF rule-out parameter in MOGAD and could be useful to complement the recently proposed diagnostic criteria.

KEYWORDS

MOGAD, multiple sclerosis, cerebrospinal fluid, MRZ reaction, oligoclonal bands, CSF/serum albumin ratio

1 Introduction

Myelin oligodendrocyte glycoprotein antibody-associated autoimmune disease (MOGAD) is a rare inflammatory demyelinating disease of the central nervous system (CNS), which causes a broad spectrum of atypical, partly multiple sclerosis (MS)-mimicking demyelinating CNS syndromes including (recurrent) optic neuritis (ON), myelitis, aquaporin-4 (AQP4)-seronegative neuromyelitis optica (NMO)-like disease, (brainstem) encephalitis and others (1). It is considered a disease entity separate from MS and AQP4-seropositive NMO because of different immunological, histopathological, serological, clinical and paraclinical features, as well as distinct therapy responses and prognosis (2–5). The prevalence in Europe amounts to approximately 2/100.000 (6, 7), which makes its occurrence significantly rarer than MS (approximately 190/100.000) (8), but slightly more frequent than NMO (approximately 1/100.000) (9). While the ability to diagnose MOGAD has increased in recent years, distinguishing MOGAD from MS remains a challenge, as there are different live cell-based assays for detecting MOG-specific antibodies in serum (and to some extent in CSF) that appear to offer much higher specificity compared with commercial assays that use fixed cells expressing full-length MOG (10). Especially, low titers of MOG-specific antibodies are difficult to interpret correctly and may lead to false-positive or false-negative findings (11, 12). In contrast to MS, MOGAD can present with either monophasic or relapsing disease course (13, 14), but predicting which disease course is most likely to develop after the first relapse is not possible based on the current state of knowledge (15). Additionally, CSF parameters from routine clinical work up can differ considerably between the two entities and can already provide decisive clues for differentiating between both diseases (16), but concrete laboratory constellations and patterns of CSF findings for this purpose have been insufficiently described and validated to date. We aimed to analyze differences in demographic, clinical and CSF findings between MOGAD and MS on mono-center level, including the MRZ reaction (MRZR), which is defined as a polyspecific intrathecal production of IgG against ≥2 of 3 antigens, i.e. measles (M), rubella (R), and zoster (Z) virus and represents the most specific CSF biomarker for MS to date.

2 Materials and methods

2.1 Patients

We retrospectively analyzed demographic, clinical and laboratory data from 30 patients with MOGAD. None of the MOGAD patients received disease-modifying therapy before lumbar puncture. 28 MOGAD patients received lumbar puncture in relapse, but 2 patients received lumbar puncture in remission more than 30 days after steroid treatment at a peripheral center. Basic CSF parameters in MOGAD patients with monophasic and polyphasic disease course were compared. In a second step, basic demographic and CSF data from MOGAD patients and 189 patients with untreated relapsing-remitting MS were compared for CSF white cell count (WCC) and white cell differentiation, CSF and serum albumin with calculated ratio (Q_{Alb}), CSF/serum ratios of IgG, IgA and IgM, respectively (Q_{IgG}, Q_{IgA}, Q_{IgM}), frequency of intrathecal synthesis of IgG, IgA and IgM according to Reiber (17), respectively, frequency of CSF-restricted oligoclonal bands (OCB) and OCB patterns, intrathecal production of IgG reactive to measles (M), rubella, and varicella zoster (Z) viruses, called MRZ reaction (MRZR), CSF lactate levels and CSF/serum glucose ratio. Furthermore, basic CSF data from MOGAD and MS patients with (i) absence of CSF-restricted OCB and (ii) ON as first clinical event were compared. All MOGAD patients tested negative for AQP4-specific antibodies in serum and fulfilled the diagnostic criteria for MOGAD as recently proposed by the international MOGAD panel (15), i.e. patients were diagnosed with MOGAD based on MOGAD-typical clinical events such as unilateral- or bilateral optic neuritis or myelitis (Table 1), in most cases presence of radiological findings typical of MOGAD (such as bilateral simultaneous signal changes of the optic nerves, longitudinal optic nerve involvement [> 50% length of the optic nerve], perineural optic sheath enhancement, and/or optic disc oedema,

TABLE 1 Demographic and clinical characteristics of MOGAD patients.

Disease course	
- Monophasic, n (%)	16/30 (53.3%)
- Relapsing, n (%)	14/30 (46.7%)
Follow-up time in months	
- All, median [Q1,Q3]	28.0 [10.0, 57.0]
- Monophasic disease course, median [Q1,Q3]	21.5 [7.5, 53.5]
- Relapsing disease course, median [Q1,Q3]	33.0 [15.0, 77.0]
First clinical event	
- Unilateral optic neuritis	18/30 (60.0%)
- Bilateral optic neuritis	3/30 (10.0%)
- Longitudinal extensive transverse myelitis	9/30 (30.0%)
Lumbar puncture	
- During first clinical event	28/30 (93.3%)
- after first clinical event, in remission	2/30 (6.7%)

or spinal cord signal changes compatible with longitudinally extensive myelitis extending over three or more vertebral segments, involving the conus, thoracolumbar radices and/or central cord or central grey matter as "H-sign" in axial sequences) and absence of radiological findings typical of MS as defined by Filippi et al. (18) and Wattjes et al. (19), and in all cases evidence of positive cell-based MOG antibody assay results in serum (see below). Other differential diagnoses such as MS, AQP4-seropositive neuromyelitis optica spectrum disease, neurosarcoidosis, neuro-Sjögren, CNS systemic lupus erythematosus and/or other autoimmune or infectious causes were excluded by means of clinical, radiological and/or laboratory findings.

All MS patients were diagnosed with relapsing-remitting MS and fulfilled the criteria for the diagnosis of MS according to the 2017 revised McDonald criteria (20), i.e. diagnosis of MS was based on the combination of typical clinical, radiological and CSF laboratory findings and exclusion of other differential diagnoses, including MOGAD. In most MS cases, MOGAD could be excluded by detection of MS-typical radiological findings and absence of MOGAD-typical findings. All patients with MS were untreated and had not received steroids before lumbar puncture, and lumbar puncture was in all cases performed during MS relapse. We retrospectively controlled, how many MOGAD patients fulfilled diagnostic criteria for MS, and how many MS patients fulfilled diagnostic criteria for MOGAD. Furthermore, all MOGAD and MS patients were checked for supporting MOGAD-typical radiological findings (15) and/or MS-typical radiological findings (18, 19).

Informed consent was obtained from all patients or relatives. Since data of all patients were anonymized for this study, the local Cantonal Ethics Committee stated that the research project does not fall within the scope of the Human Reseach Act (HRA) and therefore, an authorization from the ethics committee is not required (BASEC Nr. Req-2022-01134).

2.2 MOG-specific IgG testing

In case of clinical suspicion, patients were tested for MOG-specific IgG in the in-house laboratory with a commercial kit using a fixed cell-based assay ("Assay A") (Euroimmun, Kriens, Switzerland) and/or at the Neurological Routine and Research Laboratory, Clinical Department of Neurology of the Medical University of Innsbruck (M. Reindl), which used a live cell-based assay (Live CBA-IF, IgG(H+L) + Fc) quantified by immunofluorescence and end-point titration ("Assay B") (10). Cut-off titer for MOG antibody positivity was ≥1:10 in assay A and ≥1:160 in assay B, respectively. Cut-off titer for high-titer MOG antibody levels ("clear positive") was ≥1:320 in assay A and ≥1:640 in assay B, respectively (10). In the case of weakly positive titers (≤1:320) or negative results in assay A and persistent suspicion of MOGAD, the samples were tested with assay B (Supplementary Table 1).

2.3 Cytological examination and clinical chemistry

At the CSF Laboratory of the Department of Neurology, University Hospital Zurich, cytological examinations of the CSF follow a standardized protocol as part of the clinical routine. This protocol follows the recommendations of the German Society of CSF Diagnostics and Clinical Neurochemistry (DGLN e.V.) and still represents the gold standard of cytological examination of the CSF, since automated analysis of CSF cells by flow cytometry or other automated devices are not optimized for the analysis of samples comprising low cell numbers, such as the CSF (21). Briefly, CSF-infiltrating cells of all CSF samples are counted using a Fuchs Rosenthal counting chamber under the microscope within 1 hour after lumbar puncture in order to determine WCC. If pleocytosis is detected, CSF-infiltrating cells are examined microscopically to differentiate physiologic CSF cells and search for abnormalities. For this purpose, CSF is centrifuged using cytospin preparations with cytofunnels and cytoclips (Thermo Scientific, Basel, Switzerland), and cytospin probes are stained with the standard May-Grünwald-Giemsa procedure. Approximately 200 cells are differentiated by experienced CSF cytologists microscopically and classified as lymphocytes, monocytes, plasma cells, neutrophils, eosinophils, basophils, and macrophages. Bone marrow cells, mitoses, cells lining the CSF space and other cell types are described separately. CSF cell counting and CSF cell differentiation is done by four experienced CSF cytologists as part of the clinical routine, where each sample is analyzed by one CSF cytologist and validated by another CSF cytologist. All four CSF cytologists are medical technical assistants, each with more than 10 years of experience in cytological examinations of CSF, and they are trained for CSF cell differentiation according to the recommendations of the German Society of CSF Diagnostics and Clinical Neurochemistry (DGLN e.V.) (22).

A WCC>4/µl was classified as increased, representing pleocytosis. WCC was further grouped into subgroups of 0-4/µl, 4-30/µl and >30/µl as a measurement of pleocytosis severity. In a

subgroup of patients with pleocytosis, differentiation of CSF white cells into respective leukocyte subpopulations, and the frequency of plasma cells, neutrophils, eosinophils, basophils and macrophages were available from clinical routine and were used for retrospective analysis. An age-dependent cut-off was applied for CSF lactate level interpretation as described by Jarius et al. (23). CSF/blood ratio of glucose was calculated, and a ratio of <0.5 was considered pathologic.

2.4 Evaluation of blood-CSF barrier function and humoral immune response

Albumin, IgG, IgM and IgA levels in CSF and serum were quantified by immunonephelometry (Atellica NEPH 630 System, Siemens Healthineers, Switzerland) and their respective CSF/serum ratios calculated. Blood-CSF barrier function (BCSFB) was assessed using CSF/serum albumin quotient (Q_{Alb}). The upper reference limit of Q_{Alb} (Q_{lim}) was calculated as $[4+(a/15)]\times10^{-3}$ according to Reiber (24), with "a" representing the patient's age. Dysfunction of the BCSFB was defined as $Q_{Alb}>Q_{lim}$.

IgG index was calculated as Q_{IgG}/Q_{Alb}, with Q_{IgG}=CSF IgG concentration/serum IgG concentration. The relative intrathecal fraction of IgG, IgA and IgM, respectively (IgG_{IF}, IgA_{IF} and IgM_{IF}), was calculated according to Reiber (17). IgG_{IF}, IgA_{IF} and/or IgM_{IF}>0% indicated significant intrathecal synthesis of IgG, IgA and/or IgM, respectively. OCBs were detected by isoelectric focusing (IEF) on agarose gels and immunoblotting using IgG-specific antibodies and a semi-automated approach (Interlab G26, Alberta, Canada). OCB patterns were evaluated according to international consensus criteria (25): OCB pattern 1=no OCBs in CSF or Serum; OCB pattern 2=CSF-restricted OCBs; OCB pattern 3=identical bands in CSF and serum and additional CSF-restricted OCBs; OCB pattern 4=identical OCBs in CSF and serum; and OCB pattern 5=monoclonal bands in CSF and serum. Intrathecal IgG synthesis was indicated only by IEF patterns 2 and 3. OCBs were considered CSF-restricted, if ≥2 additional bands were detected in CSF compared to serum.

2.5 MRZ reaction

IgG antibodies against measles (M), rubella (R) and varicella zoster (Z) viruses were measured in paired CSF and serum samples, either with commercial ELISA kits and fully automated ELISA processing (Euroimmun Analyzer I, Euroimmun AG, Kriens, Switzerland) or ELISA kits from Virion/Serion (one point calibration) and fully automated ELISA processing (4-plate ELISA processing system DSX, Dynex Technologies, Inc./Ruwag Bettlach, Switzerland).

The virus-specific CSF/serum antibody index (CAI_{spec}) was calculated according to Reiber (17). In short, CAI_{spec} was assessed as $CAI_{spec}=Q_{spec}/Q_{IgG}$ (if Q_{Lim} (IgG)>Q_{IgG}), or $CAI_{spec=}Q_{spec}/Q_{Lim}$ (IgG), if Q_{Lim} (IgG)<Q_{IgG}). The respective parameters were calculated as follows: $Q_{spec=}$antigen-specific IgG_{CSF} [AU]/antigen-specific IgGserum [AU]; $Q_{IgG=}$total IgG_{CSF} [mg/l]/total IgG_{serum} [mg/l]; Q_{Lim} (IgG)=$0.93\times(Q_{Alb}{}^2 + 6\times10^{-6})^{0.5}-1.7\times10^{-3}$; $Q_{Alb}=Alb_{CSF}$ [mg/l]/Alb_{serum} [mg/l] (with Alb=albumin). Q_{Lim} (IgG) refers to the upper discrimination line of the hyperbolic reference range for the blood-derived IgG in CSF as zero intrathecal IgG synthesis. CAI_{spec}≥1.5 indicated intrathecal synthesis of virus-specific antibodies. MRZR was interpreted as positive according to Reiber et al. (26), if polyclonal intrathecal production of antibodies against ≥2 of the 3 antigens measles (M), rubella (R), and zoster (Z), was detectable (27).

External quality assurance covering CSF-/serum- albumin, -IgG, -IgM, -IgA and -OCB as well as MRZ reaction have been performed every 3-6 months in round robin tests organized by INSTAND e.V. (Düsseldorf, Germany) and have always been passed during the period of assessment of CSF findings.

2.6 Statistics

Differences in age and disease duration were compared with the Kruskal-Wallis test. Differences in frequency of female gender, pleocytosis, respective white cell subpopulations, elevated Q_{Alb}, intrathecal immunoglobulin synthesis according to Reiber (17), CSF-restricted OCB, elevated CSF lactate, pathologic CSF/serum glucose ratio and positive MRZR were compared with Fisher's exact test. Differences in mean values of WCC, Q_{Alb}, immunoglobulin CSF/serum ratios and intrathecal fraction of IgG were calculated using the Mann-Whitney U test after testing for normal distribution with the Shapiro-Wilk test. Sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) with 95% confidence intervals (95% CI) of CSF/serum parameters were analyzed to estimate their value in distinguishing MOGAD from MS.

3 Results

All MOGAD patients were tested for MOG antibodies, of which 3 patients were tested only with the fixed cell-based assay ("Assay A"), 17 patients were tested only with the live cell-based assay ("Assay B") and 10 patients were tested with both assays (Supplementary Table 1; Supplementary Figure 1). Retrospective data of MOG antibody results was available from 97/189 MS patients, 89 results from assay A and 23 results from assay B. 30/30 (100.0%) MOGAD patients and 1/97 (1.1%) MS patients tested positive for MOG antibodies, but 18/30 (60.0%) MOGAD patients and none of the MS patients showed a clear positive (high-titer) MOG antibody result (Supplementary Table 2). The one MS patient with a positive MOG antibody finding had a positive low-titer MOG antibody result (1:32) in assay A and tested negative in the more sensitive assay B. Since this patient showed MS-typical MRI changes and fulfilled the diagnostic criteria for MS, but not for MOGAD, this patient was diagnosed with MS. Altogether, assay A showed a sensitivity of 82.4% and specificity of 98.9% for MOGAD versus MS in our cohort, and assay B showed a sensitivity of 100.0% and specificity of 100.0% (Supplementary Table 2). All MOGAD patients, but none of the MS patients fulfilled diagnostic criteria

for MOGAD (15), and all MS patients, but none of the MOGAD patients fulfilled diagnostic criteria for MS (20) (Supplementary Table 3). 2 MOGAD patients with optic neuritis (ON) did not fulfill radiological criteria for MOGAD in first brain MRI, but fulfilled diagnostic criteria for MOGAD and showed clear positive MOG antibody titers. 3 MOGAD patients with longitudinally extensive transverse myelitis (LETM) fulfilled diagnostic criteria for MOGAD and showed MOGAD-typical radiological signs, but also fulfilled radiological, but not diagnostic, criteria for MS (inflammatory lesions with dissemination in time and space). 2 of those 3 patients showed no CSF-restricted OCB. None of the MS patients showed MOGAD-typical MRI findings (Supplementary Table 3).

First clinical events in MOGAD patients included unilateral ON (18/30, 60%), LETM (9/30, 30%) and bilateral ON (3/30, 10%) (Table 1). During the follow-up period, 53.3% showed a monophasic disease course with a median follow-up of 21.5 months (IQR 7.5-53.5), whereas 46.7% were polyphasic (median follow-up 33.0 months [IQR 15.0-77.0]) (Table 1). Basic CSF parameters did not vary between MOGAD patients with monophasic and polyphasic disease course (Supplementary Table 4). Basic CSF parameters in MOGAD patients with ON as first clinical presentation varied from those with LETM, but due to the small number of LETM patients, almost all results were not significant. The only exception was the mean WCC (9.8 [SD 20.0] vs. 55.7 [SD 60.3], p=0.004) and the frequency of WCC>100/µl (0/21 [0.0%] vs. 3/9 [33.3%], p<0.001), which was significantly higher in MOGAD patients with LETM than with ON (Supplementary Table 5). Previously, Jarius et al. (16) reported differences of basic CSF parameters between acute ON and acute myelitis of adult MOGAD patients and found significant differences for frequency of pleocytosis (18/53 [34.0%] vs. 46/54 [85.2%], p<0.001), of WCC>100/µl (1/52 [1.9%] vs. 17/54 [31.5%], p<0.001), of elevated CSF lactate (7/39 [17.9%] vs. 18/37 [48.6%], p=0.007) and of elevated Q_{Alb} (16/46 [34.8%] vs. 28/50 [56.0%], p=0.043), but not for frequency of intrathecal synthesis of IgG, IgA or IgM, respectively (Supplementary Table 5). When we combined all MOGAD patients from our cohort and the cohort described by Jarius et al. (16) and compared all parameters between ON and LETM (Supplementary Table 5), we could confirm a significantly higher frequency of pleocytosis, of WCC>100/µl, of elevated CSF lactate and of elevated Q_{Alb} in LETM, and in addition, discovered for the first time significant differences in frequency of intrathecal synthesis of IgM (combined ON 4/60 [6.7%] vs. combined LETM 12/47 [25.5%], p=0.012). Differences in intrathecal synthesis of IgG, as determined by Reiber diagram or detection of CSF-restricted OCB), or intrathecal synthesis of IgA remained non-significant in both single and combined analysis (Supplementary Table 6).

In our cohort, patients with MOGAD were significantly older at time of lumbar puncture than MS patients (median age 40.5 [IQR 28.2-55.8] vs 31.0 [IQR 27.0-38.0] years, p=0.004), but did not differ in terms of disease duration (median 0.0 [IQR 0.0-2.5] vs 0.0 [IQR 0.0-2.0] months, p=0.773). Although MS patients tended to be more often female than MOGAD patients (64.6% vs. 46.7%), this finding was not statistically significant (p=0.094, Table 2). Pleocytosis was less frequent in MOGAD than in MS patients (40.0% vs. 61.9%, p=0.028), particularly in the WCC range 5-30/µl (20.0% vs. 57.7%, p<0.001), but mean WCC (in MOGAD 36.1/µl [SD 95.2/µl], in MS 9.1/µl [SD 10.9/µl], p=0.231) did not differ significantly (Figure 1A; Supplementary Figure 2A). Notably, WCC>30/µl was more frequent in MOGAD than in MS patients (20.0% vs. 4.2%, p=0.006) and WCC>100/µl occurred in MOGAD patients only (10.0% vs. 0.0%, p=0.002) (Figure 2A). In a subgroup of patients with pleocytosis (10 patients with MOGAD, 107 patients with MS), differentiation of CSF white cells was available (Figure 2B). While MS patients showed a significantly higher frequency of plasma cells (80.4% vs. 30.0%, p=0.002), MOGAD patients showed a significantly higher frequency of neutrophils (60.0% vs. 22.4%, p=0.018). Frequency of CSF eosinophils (20.0% vs. 8.4%, p=0.238), CSF basophils (10.0% vs. 0.9%, p=0.164) and CSF macrophages (20.0% vs. 11.2%, p=0.342) tended to be higher in MOGAD patients, but neither of those results were statistically significant (Table 3).

Elevation of Q_{Alb} was more common in MOGAD than in MS (43.3% vs. 24.3%, p=0.044). An intermediate elevation of $Q_{Alb}>10\times10^{-3}$ showed an even stronger association with MOGAD (16.7% vs. 1.6%, p=0.002) and mean Q_{Alb} was significantly higher in MOGAD than in MS patients (7.3 [SD 4.6] vs. 4.9 [SD 1.8], p<0.001) (Figure 1B; Supplementary Figure 2B). Mean CSF/serum IgG ratio (4.6 [SD 4.4] vs. 4.4 [SD 2.5], p=0.817) and mean CSF/serum IgM ratio (1.3 [SD 2.5] vs. 0.8 [SD 1.4], p=0.337) showed no significant differences between both groups, but there was a significant difference in mean CSF/serum IgA ratio (2.5 [SD 2.7] vs. 1.7 [SD 1.7], p=0.024) (Supplementary Table 6). Intrathecal synthesis of IgG according to Reiber (17) was less frequent in MOGAD than in MS patients (13.3% vs. 52.9%, p<0.001), whereas there was no significant difference in intrathecal synthesis of IgA (0.0% vs. 7.9%, p=0.233) and IgM (13.3% vs. 17.5%, p=0.794) (Table 4). If intrathecal IgG synthesis according to Reiber (17)

TABLE 2 Demographic features of MOGAD and MS patients.

Parameter	Overall	MOGAD	MS	p-value
N	219	30	189	-
Female gender, n (%)	136 (62.1%)	14 (46.7%)	122 (64.6%)	0.094
Age at LP, median [Q1,Q3]	32.0 [27.0, 40.0]	40.5 [28.2, 55.8]	31.0 [27.0, 38.0]	**0.004**
Disease duration in months, median [Q1,Q3]	0.0 [0.0, 2.0]	0.0 [0.0, 2.5]	0.0 [0.0, 2.0]	0.773

Bold values indicate statistical significance (p < 0.05).

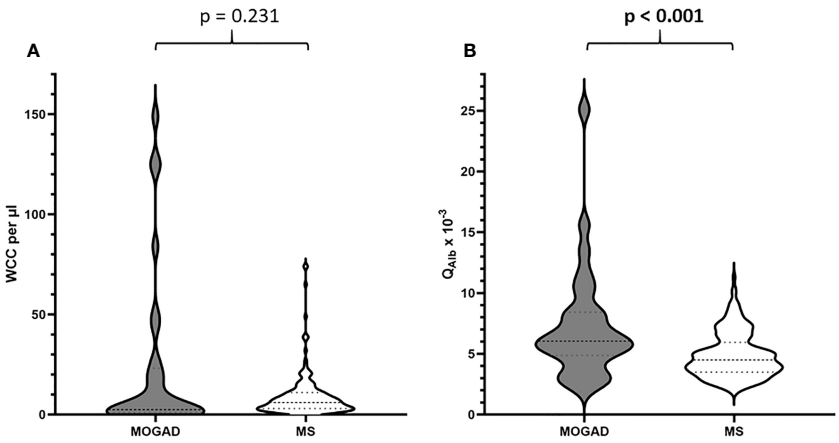

FIGURE 1
(A) Distribution of WCC per µl in patients with MOGAD vs. MS. **(B)** Distribution of Q_{Alb} x 10^{-3} in patients with MOGAD vs. MS.

was present, mean intrathecal fraction of IgG, i.e. IgG_{IF}, did not vary between MOGAD and MS patients (31.1 [SD 23.9] vs. 38.8 [SD 18.4], p=0.617) (Supplementary Table 6). CSF-restricted OCB were present in most of the MS patients (94.2%), but only in 16.7% of the MOGAD patients (p<0.001) (Figure 3). Patients with MOGAD were furthermore significantly more likely to show pathological levels of CSF lactate (10.7% vs. 1.6%, p=0.030) and pathological CSF/serum glucose ratio (14.3% vs. 0.0%, p<0.001) than MS patients (Table 4). Of particular interest, a positive MRZR was only found in MS patients and in none of MOGAD patients (35.4% vs. 0.0%, p<0.001, Table 5; Figure 3). 6/30 (20.0%) MOGAD patients had a single virus-specific antibody reactivity (Supplementary Table 7). Rubella- and zoster-specific CAI values, but not measles-specific CAI values, were significantly lower in MOGAD patients than in MS patients (Supplementary Table 8).

Our findings of increased frequency of pleocytosis and BCSFB dysfunction in MOGAD patients, as well as decreased frequency of CSF-specific OCBs are in line with the results reported in the current literature (13, 16, 23, 28–30) (Supplementary Table 9). Interestingly, until now, a positive MRZR has been reported in 0/62 samples of 48 adult MOGAD patients (16), 0/28 samples of 24 pediatric MOGAD patients (23) and 0/30 patients in our study (Supplementary Table 10), resulting in the absence of a positive MRZR as a typical finding in MOGAD.

The probable prevalence of MOG seropositivity and positive MRZR in the general population can be calculated according to the estimated population-based prevalence of the respective disease (2/100.000 for MOGAD, 190/100.000 for MS) (6–8) and the disease-specific sensitivity of the respective positive diagnostic test. With a MOG seropositivity in 100% of MOGAD patients and 35.4% of MS patients being positive MRZR in our cohort, the estimated population-based prevalence of MOG seropositivity is more than 33x less frequent than a positive MRZR (2/100.000 vs. 67.3/100.000, p<0.00001) (Supplementary Table 11). The odds ratio for a positive disease-specific test result is 33.5 (95% CI 8.2-136.8, p<0.00001), when positive MRZ reaction is compared to MOG seropositivity and all true MS and MOGAD patients are included for testing. Based on these numbers, testing MOG antibodies in patients with low probability of MOGAD, e.g. including all MS-caused ON and myelitis cases, would result in a significant number of false-positive MOG antibody results in patients with low positive MOG serotiters (Supplementary Table 12).

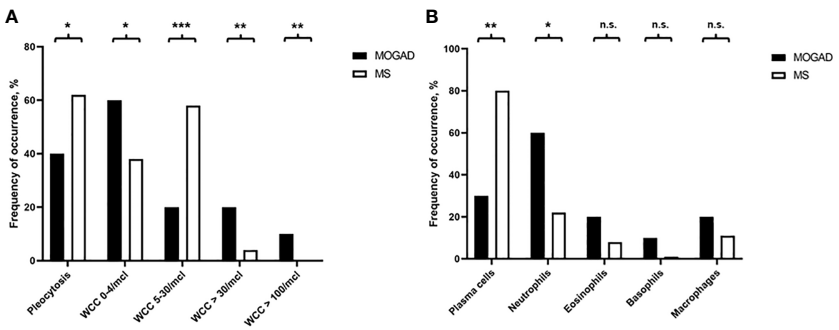

FIGURE 2
(A) Frequency of occurrence of pleocytosis, i.e. WCC 0-4/µl, WCC 5-30/µl, WCC>30/µl, or WCC>100/µl, in MOGAD and MS patients (%).
(B) Frequency of occurrence of plasma cells, neutrophils, eosinophils, basophils, or macrophages in MOGAD and MS patients (%). n.s., not significant, * p<0.05, ** p<0.001, *** p<0.001.

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TABLE 3 Comparison of A) CSF white cell counts and B) white cell differentiation in MOGAD and MS.

CSF parameter	Overall	MOGAD	MS	p-value
A) CSF WCC				
Pleocytosis, n/N (%)	129/219 (58.9%)	12/30 (40.0%)	117/189 (61.9%)	**0.028**
- WCC 0-4/µl, n/N (%)	90/219 (41.1%)	18/30 (60.0%)	72/189 (38.1%)	**0.028**
- WCC 5-30/µl, n/N (%)	115/219 (52.5%)	6/30 (20.0%)	109/189 (57.7%)	**<0.001**
- WCC>30/µl, n/N (%)	14/219 (6.4%)	6/30 (20.0%)	8/189 (4.2%)	**0.006**
- WCC>100/µl, n/N (%)	3/219 (1.4%)	3/30 (10.0%)	0/189 (0.0%)	**0.002**
CSF WCC, mean (SD)	12.8 (37.3)	36.1 (95.2)	9.1 (10.9)	0.231
B) CSF white cell differentiation*				
- Frequency of plasma cells, n/N (%)	89/117 (76.1%)	3/10 (30.0%)	86/107 (80.4%)	**0.002**
- Frequency of neutrophils, n/N (%)	30/117 (25.6%)	6/10 (60.0%)	24/107 (22.4%)	**0.018**
- Frequency of eosinophils, n/N (%)	11/117 (9.4%)	2/10 (20.0%)	9/107 (8.4%)	0.238
- Frequency of basophils, n/N (%)	2/117 (1.7%)	1/10 (10.0%)	1/107 (0.9%)	0.164
- Frequency of macrophages, n/N (%)	14/117 (12.0%)	2/10 (20.0%)	12/107 (11.2%)	0.342

*assessed in 117 patients (10 patients with MOGAD, 107 patients with MS) with WCC>4/µl.
Bold values indicate statistical significance ($p < 0.05$).

TABLE 4 Comparison of basic CSF parameters in MOGAD and MS.

CSF parameter	Overall	MOGAD	MS	p-value
Elevated Q_{Alb}, n/N (%)	59/219 (26.9%)	13/30 (43.3%)	46/189 (24.3%)	**0.044**
- $Q_{Alb}>10\times10^{-3}$	8/219 (3.7%)	5/30 (16.7%)	3/189 (1.6%)	**0.002**
- Q_{Alb}, mean (SD)	5.2 (2.5)	7.3 (4.6)	4.9 (1.8)	**<0.001**
$IgG_{IF}>0\%$, n/N (%)	104/219 (47.9%)	4/30 (13.3%)	100/189 (52.9%)	**<0.001**
$IgA_{IF}>0\%$, n/N (%)	15/219 (6.8%)	0/30 (0.0%)	15/189 (7.9%)	0.233
$IgM_{IF}>0\%$, n/N (%)	37/219 (16.9%)	4/30 (13.3%)	33/189 (17.5%)	0.794
CSF-restricted OCB, n/N (%)	183/219 (83.6%)	5/30 (16.7%)	178/189 (94.2%)	**<0.001**
Elevated CSF lactate, n/N (%)	6/215 (2.8%)	3/28 (10.7%)	3/187 (1.6%)	**0.030**
Pathologic CSF/serum glucose ratio, n/N (%)	4/215 (1.9%)	4/28 (14.3%)	0/187 (0.0%)	**<0.001**

Bold values indicate statistical significance ($p < 0.05$).

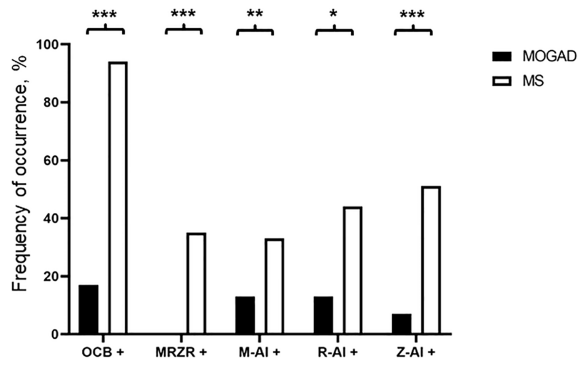

FIGURE 3
Frequency of occurrence of CSF-restricted OCB (OCB+), positive MRZR (MRZ+), positive M-CAI (M+), positive R-CAI (R+), and positive Z-CAI (Z+) in MOGAD and MS patients (%). * p<0.05, ** p<0.001, *** p<0.001.

In order to determine the value of single CSF parameters, sensitivity and specificity as well as positive and negative likelihood ratios (PLR and NLR) were calculated (Table 6). A PLR>10 and NLR<0.1 are considered useful in general practice (31, 32). Highest sensitivity for MOGAD was found in absence of intrathecal IgG synthesis (86.6% according to Reiber diagram, 83.3% according to IEF) and absence of a positive MRZR (100.0%), whereas reduced CSF/serum glucose ratio (100.0%), elevated CSF lactate (98.4%), Q_{Alb}>10×10^{-3} (98.4%), WCC>30/µl and absence of CSF-restricted OCB (94.2%) showed highest specificity for MOGAD. Highest PLRs for MOGAD were found for absence of CSF-restricted OCB (14.32) and Q_{Alb}>10×10^{-3} (12.60), while the potentially highest PLR for MOGAD, i.e. reduced CSF/serum glucose ratio, could not be calculated due to a specificity of 100.0%. The by far lowest NLR for MOGAD was found for absence of positive MRZR (0.00), followed by absence of CSF-restricted OCB (0.18) and absence of intrathecal IgG synthesis according to Reiber diagram (0.25). In addition, combined analysis of multiple parameters, i.e. i) WCC>30/µl or absence of CSF-restricted OCB, and simultaneous absence of positive MRZR, or ii) Q_{Alb}>10×10^{-3} or absence of CSF-restricted OCB, and simultaneous absence of positive MRZ reaction, showed a significant PLR (12.60) with an overall low NLR (0.14), the second lowest NLR value detected (Table 7).

Despite some clear trends, the comparison of basic CSF parameters between MOGAD patients and MS patients without CSF-restricted OCB (n=25 vs. n=11) showed no significant differences in terms of mean WCC (24.7 [SD 45.7] vs. 3.1 [SD 2.7], p=0.564), frequency of pleocytosis (36.0% vs. 18.2%, p=0.439), WCC>15/µl (28.0% vs. 0.0%, p=0.076), WCC>30/µl (20.0% vs. 0.0%, p=0.295), elevated Q_{Alb} (44.0% vs. 18.2%, p=0.259), intrathecal synthesis of IgG (0.0% vs. 0.0%), IgA (0.0% vs. 0.0%) or IgM (8.0% vs. 9.1%, p=1.000), elevated CSF lactate (17.4% vs. 9.1%, p=1.000) or pathologic CSF/serum glucose ratio (13.0% vs. 0.0%, p=0.536) (Supplementary Table 13).

When comparing MOGAD and MS patients with ON as first clinical event (n=21 vs. n=74), mild pleocytosis was less frequent in MOGAD patients (28.6% vs. 55.4%, p=0.047), but higher mean WCC (9.8 [SD 20.0] vs. 8.4 [SD 11.2], p=0.017) and moderately increased pleocytosis (WCC>30/µl) was associated with MOGAD (19.0% vs. 4.1%, p=0.041). In addition, pathologic CSF/serum glucose ratio occurred in MOGAD patients only (10.5% vs. 0.0%, p=0.041). Intrathecal synthesis of IgG, either according to Reiber diagram (14.3% vs. 55.4%, p=0.001) or through presence of CSF-restricted OCB (14.3% vs. 93.2%, p<0.001), and positive MRZR (0.0% vs. 35.1%, p<0.001) proved useful to distinguish MOGAD from MS (Table 8). There was no statistical significance in terms of Q_{Alb} elevation (28.6% vs. 24.3%, p=0.777), intrathecal synthesis of IgA (0.0% vs. 8.1%, p=0.333) or IgM (4.8% vs. 12.2%, p=0.450) and elevated CSF lactate (5.3% vs. 0.0%, p=0.369).

4 Discussion

In clinical routine, physicians find themselves daily in the situation of having to distinguish differential diagnoses in order to quickly initiate an indicated therapy. Autoimmune and inflammatory diseases of the central nervous system can clinically and radiologically present in a very similar fashion (33–36) at first manifestation, which is why a well thought-out strategy and interpretation of diagnostic findings is necessary. One of the most common differential diagnoses of multiple sclerosis, which is the

TABLE 5 Frequency of intrathecal IgG production against measles (M)-, rubella (R)- or zoster (Z) antigens and of positive MRZ reaction in MOGAD and MS.

CSF parameter	Overall	MOGAD	MS	p-value
Intrathecal measles-specific IgG production (M), n/N (%)	67/219 (30.6%)	4/30 (13.3%)	63/189 (33.3%)	**0.032**
Intrathecal rubella-specific IgG production (R), n/N (%)	88/219 (40.2%)	4/30 (13.3%)	84/189 (44.4%)	**0.001**
Intrathecal zoster-specific IgG production (Z), n/N (%)	98/219 (44.7%)	2/30 (6.7%)	96/189 (50.8%)	**<0.001**
Positive MRZ reaction[1], n/N (%)	67/219 (30.6%)	0/30 (0.0%)	67/189 (35.4%)	**<0.001**

[1]positive MRZ reaction (MRZR) was defined as intrathecal production of IgGs reactive against at least two of three antigens, measles (M), rubella (R) and varicella zoster (Z) virus antigens, i.e, M+R or M+Z or R+Z or M+R+Z.
Bold values indicate statistical significance (p < 0.05).

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TABLE 6 Sensitivity, specificity, and likelihood ratios of single basic CSF parameters to distinguish MOGAD from MS.

CSF parameters	MOGAD	MS	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)
1. Pleocytosis	12/30 (40.0%)	117/189 (62.0%)	40.0% (24.6-57.7)	38.1% (31.5-45.2)	0.65 (0.4-1.02)	1.58 (1.12-2.22)
2. WCC>30/µl	6/30 (20.0%)	8/189 (4.0%)	20.0% (9.3-37.8)	95.8% (91.7-97.9)	4.73 (1.76-12.66)	0.84 (0.70-1.00)
3. Presence of plasma cells	3/10 (30.0%)	86/107 (80.0%)	30.0% (10.6-60.8)	19.6% (13.2-28.3)	0.37 (0.14-0.97)	3.57 (2.04-6.23)
4. Presence of neutrophils	6/10 (60.0%)	24/107 (22.0%)	60.0% (31.2-83.1)	77.6% (86.76-84.5)	2.68 (1.44-4.96)	0.52 (0.24-1.11)
5. Elevated Q_{Alb}	13/30 (43.0%)	46/189 (24.3%)	43.0% (27.4-60.8)	75.7% (69.0-81.2)	1.78 (1.10-2.88)	0.75 (0.54-1.04)
6. $Q_{Alb}>10\times10^{-3}$	6/30 (20.0%)	3/189 (1.6%)	20.0% (9.3-37.8)	98.4% (95.2-99.7)	**12.60** (3.33-47.70)	0.81 (0.68-0.97)
7. Absence of $IgG_{IF}>0\%$	26/30 (86.6%)	89/189 (47.1%)	86.6% (69.5-95.2)	52.9% (45.8-59.9)	1.84 (1.50-2.26)	0.25 (0.10-0.63)
8. Absence of CSF-spec. OCB	25/30 (83.3%)	11/189 (5.8%)	83.3% (65.8-93.0)	94.2% (89.7-96.8)	**14.32** (7.89-25.97)	0.18 (0.08-0.39)
9. Absence of positive MRZR	30/30 (100.0%)	122/189 (64.6%)	100.0% (86.2-100.0)	35.4% (29.0-42.5)	1.55 (1.39-1.72)	**0.00** (-)
10. CSF lactate elevated	3/28 (10.7%)	3/187 (1.6%)	10.7% (3.0-28.2)	98.4% (95.1-99.6)	6.68 (1.42-31.47)	0.91 (0.80-1.03)
12. CSF/serum glucose ratio reduced	4/28 (14.3%)	0/187 (0.0%)	14.3% (5.2-32.3)	100.0% (97.5-100.0)	–	0.86 (0.74-1.00)

Bold values indicate statistical significance ($p < 0.05$).

most frequent chronic-inflammatory CNS disease (37), is MOGAD, for which diagnostic criteria have recently been proposed in a comprehensive consensus paper (15). In this retrospective single-center study, we demonstrate the importance of CSF routine diagnostics in clinical practice and describe the usefulness of absence of the biomarker MRZR, which is considered the most specific marker for multiple sclerosis to date (38), in distinguishing MOGAD from MS. Our results confirm the absence of a positive MRZR as a typical finding in MOGAD and add evidence to the data supporting positive MRZR as an MS-specific marker (38). Absence of positive MRZR could potentially complement the recently proposed diagnostic criteria of MOGAD (15). Since the diagnosis of MOGAD can be difficult due to, among other things, the clinical variability, the limited availability of high-sensitivity live cell-based assays (10), and the difficulty in interpreting low-titer antibody results, it is important to reliably distinguish between these two diseases and to identify patients who should be tested for MOG antibodies in the first place in order to avoid false-positive results by over-testing (39). Despite high sensitivities and specificities of MOG antibody assays of 95-100% (10), testing MOG antibodies in patients with low probability of MOGAD, e.g. including all MS-caused ON and myelitis cases, leads to a significant occurrence of false-positive test results and is therefore not recommended (10, 15, 39). As presented above, the estimated frequency of positive MRZR in the general population is more than 33 times higher than the estimated frequency of MOG seropositivity, while there are no

TABLE 7 Sensitivity, specificity, and likelihood ratios of combinations of basic CSF parameters to distinguish MOGAD from MS.

Combination of CSF parameters	MOGAD	MS	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)
1. Combination of **a)** 1 of the following parameters: - WCC>30/µl - or absence of CSF-restricted OCB and **b)** absence of positive MRZ reaction	26/30 (86.7%)	13/189 (6.9%)	86.7% (69.5-95.2)	93.1% (88.5-96.0)	**12.60** (7.32-21.69)	0.14 (0.06-0.36)
2. Combination of **a)** 1 of the following parameters: - $Q_{Alb}>10\times10^{-3}$ - or absence of CSF-restricted OCB and **b)** absence of positive MRZ reaction	26/30 (86.7%)	13/189 (6.9%)	86.7% (69.5-95.2)	93.1% (88.5-96.0)	**12.60** (7.32-21.69)	0.14 (0.06-0.36)

Bold values indicate statistical significance ($p < 0.05$).

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TABLE 8 Comparison of basic CSF parameters in MOGAD and MS patients with optic neuritis as first clinical event.

CSF parameter	Overall	MOGAD	MS	P-value
Pleocytosis, n/N (%)	47/95 (49.8%)	6/21 (28.6%)	41/74 (55.4%)	**0.047**
WCC, mean (SD)	8.7 (13.5)	9.8 (20.0)	8.4 (11.2)	**0.017**
WCC>15/µl, n/N (%)	14/95 (14.7%)	4/21 (19.0%)	10/74 (13.5%)	0.503
WCC>30/µl, n/N (%)	7/95 (7.4%)	4/21 (19.0%)	3/74 (4.1%)	**0.041**
Elevated Q_{Alb}, n/N (%)	24/95 (25.3%)	6/21 (28.6%)	18/74 (24.3%)	0.777
IgG_{IF}>0%, n/N (%)	44/95 (46.3%)	3/21 (14.3%)	41/74 (55.4%)	**0.001**
IgA_{IF}>0%, n/N (%)	6/95 (6.3%)	0/21 (0.0%)	6/74 (8.1%)	0.333
IgM_{IF}>0%, n/N (%)	10/95 (10.5%)	1/21 (4.8%)	9/74 (12.2%)	0.450
CSF-restricted OCB, n/N (%)	72/95 (75.8%)	3/21 (14.3%)	69/74 (93.2%)	**<0.001**
Positive MRZR, n/N (%)	26/95 (27.4%)	0/21 (0.0%)	26/74 (35.1%)	**<0.001**
Elevated CSF lactate, n/N (%)	2/92 (2.2%)	1/19 (5.3%)	1/74 (1.4%)	0.369
Pathologic CSF/serum glucose ratio, n/N (%)	2/93 (2.2%)	2/19 (10.5%)	0/73 (0.0%)	**0.041**

Bold values indicate statistical significance ($p < 0.05$).

reported cases of positive MRZR in MOGAD until now. Accordingly, if the pretest probability for MOG seropositivity is low, testing for MRZR should be favored over testing for MOG antibodies, and testing for MOG antibodies should be avoided if MRZR is positive.

MOGAD can occur both as a monophasic and relapsing-remitting disease (13, 14), but so far, there are no tools to predict the course at the time of diagnosis. Parameters to determine the course of the disease at an early stage would be desirable so that either an adequate immunomodulatory therapy can be initiated at an early stage, or a continuous immunomodulatory therapy is not started unnecessarily or given for too long time, respectively. In our cohort, routine CSF diagnostics did not appear useful in this regard, as there were no significant differences in terms of WCC, Q_{Alb} or intrathecal synthesis of immunoglobulins The analysis is limited by the low number of patients, variable follow-up time and different treatment strategies after the first relapse. Therefore, further work is needed to verify this in a bigger cohort.

The number of studies analyzing typical CSF profiles in MOGAD patients is low (13, 16, 23, 28–30) and most studies focus on pediatric MOGAD. The most relevant multicenter study for adult MOGAD patients involved 163 lumbar punctures in 100 adult MOGAD patients (16). Especially the absence of CSF-restricted OCB in the majority of samples (present in 19/150, 12.7%) and the absence of a positive MRZR in all patients (present in 0/48, 0.0%) were considered remarkable. The cellular immune response and function of the BSCFB varied widely within the cohort and was dependent on relapse and remission as well as the initial clinical manifestation. Of particular interest, in a notable proportion of samples, there was a moderate cell count increase above 50/µl (in 30/157, 19.1%) and 100/µl (in 19/157, 12.1%), which is considered a red flag for the diagnosis of MS, since only 5% of MS patients are found with CSF WCC>30/µl (25, 40). Regarding cell differentiation, the presence of neutrophils in 33/77 (42.9%) was particularly striking, whereas the presence of plasma cells (3/77, 3.9%) was rare. In about half of the samples, a dysfunction of the BSCFB could be detected (67/139, 48.2%) and a moderate dysfunction (defined as $Q_{Alb}>10\times10^{-3}$) as well as a severe dysfunction (defined as $Q_{Alb}>20\times10^{-3}$) occurred in a notable number of patients (exact number not stated). These results also appear useful to distinguish MOGAD from MS, as the latter has intact barrier function in approximately 90% of cases and elevation of $Q_{Alb}>10\times10^{-3}$ is an exception (25, 40). A systematic analysis to assess the usefulness of these CSF parameters, either as single parameter or in combination, to distinguish MOGAD from MS in clinical practice has not yet been conducted.

It should be noted that the vast majority of our MOGAD patients had optic neuritis as first clinical presentation, which probably influenced the comparison, as MOGAD patients with acute optic neuritis have been shown to differ significantly from patients with acute myelitis in terms of WCC, frequency of pleocytosis, BSCFB dysfunction and even CSF-restricted OCB

(16). Due to the small number of patients with myelitis, our analysis of differences between MOGAD patients with myelitis and ON was significantly limited, but a combined analysis of our work with the previously published cohort of Jarius et al. (16) not only confirms significant differences in frequency of pleocytosis, WCC>100/µl, BCSFB dysfunction and CSF lactate elevation, but revealed for the first time significant differences in the frequency of intrathecal synthesis of IgM. This could have implications for the understanding of MOGAD pathophysiology, as e.g. intrathecal IgM synthesis in MS is associated with spinal cord manifestation and with early activation of the complement cascade (41). BCSFB dysfunction has also been observed more often in MS patients with spinal lesions as compared to MS patients with supra- and/or infratentorial lesions (42), and Reiber (43) postulated that this could reflect reduced CSF- or interstitial fluid flow due to spinal lesions.

Jarius and colleagues (16) also showed CSF findings of the first-ever lumbar puncture in a subcohort, which corresponds to the diagnostic situation in our work and is suitable for comparing the data with our results. The majority of our MOGAD patients, especially if presenting with ON, had normal WCC (12/30 [40.0%)] vs. 55.7% [30.8% if ON] in Jarius et al. (16)), but the level of WCC varied widely between patients with pleocytosis. Q_{Alb} also varied widely, an elevation of Q_{Alb} was detected in 13/30 of our MOGAD cases (43% vs. 53.8% [42.4% if ON] in Jarius et al. (16)). In 5/30 of our MOGAD patients CSF-restricted OCB could be detected (16.7% vs. 9.6% in Jarius et al. (16)) and positive MRZR did not occur in either cohort. Regarding CSF white cell differentiation, our data is limited by the fact that only data from patients with pleocytosis were available and therefore the number of MOGAD patients with available data was very low (n=10), but our work confirms the increased occurrence of neutrophils and the less frequent occurrence of plasma cells in the CSF of MOGAD patients.

In order to determine their value, the PLR and NLR of single and combinational multiple parameters were calculated, and a PLR>10 and NLR<0.1 was considered meaningful (31, 32). There is a general lack of data on these ratios for diagnostic tests (32), but they are considered superior to sensitivity and specificity for clinical routine (44). Only a $Q_{Alb}>10\times10^{-3}$ (PLR=12.60) and the absence of CSF-restricted OCB (PLR=14.32) showed a useful PLR (defined as PLR>10) and the absence of a positive MRZR (NLR=0.00) showed a useful NLR (defined as NLR<0.1) to distinguish MOGAD from MS. Notably, the PLR for a decreased CSF/serum glucose ratio could not be calculated because of its specificity of 100%. These results confirm the importance of MRZR as the most specific biomarker for MS. However, in clinical routine and especially in cases with high diagnostic uncertainty, it is not the individual parameters, but patterns of several findings that are considered for diagnosis. Looking at combinations of several parameters in patients with absence of a positive MRZR, both the combination of (i) WCC>30/µl or absence of CSF-restricted OCB and (ii) $Q_{Alb}>10\times10^{-3}$ or absence of CSF-restricted OCB, both with simultaneous absence of positive MRZR, showed significant relevance (both with PLR=12.6, NLR=0.14) with the second lowest NLR overall. Thus, whereas positive MRZR can be used as a rule-out parameter for MOGAD, the absence of CSF-restricted oligoclonal bands, possibly combined with moderate-grade WCC elevation or moderate or severe dysfunction of the BSCFB can be used as a rule-in parameter for MOGAD.

A particularly interesting comparison in clinical practice is the one between MOGAD and MS patients without evidence of CSF-restricted OCB. As a complicating factor, positive MRZR is rare in OCB-negative patients and thus plays a significantly smaller role in the diagnosis of MS in these cases (45). While there is no statistically significant difference due to the small numbers of patients with OCB-negative MS in our cohort, we believe it is worthwhile to consider the direction in which the results point here: Pleocytosis, especially with intermediate cell count elevation, appears to be a typical finding in MOGAD patients, and cell counts above 15/µl did not occur within our MS patients without CSF-restricted OCB. In addition, BCSFB dysfunction was more than twice as frequent in MOGAD patients as in MS patients. No trends were apparent with respect to the humoral immune response. Of particular interest, positive MRZR was absent in both MOGAD and MS patients without CSF-restricted OCB. Unfortunately, data on cell differentiation were not available in this subcohort. In our opinion, a re-examination of these results in a larger cohort is necessary, but could prove very helpful.

Optic neuritis is a common symptom in both MOGAD and MS. While bilateral optic neuritis is an exception in MS (46), it can be a typical feature in MOGAD and occurs in up to 58% (47). In MOGAD, the optic nerve is typically affected in the proximal part and in a longitudinally extensive manner, and concomitant optic disc swelling, involvement of perineural tissue or moderate to severe edema may occur, whereas short-extent and peripheral involvement is particularly typical in MS (46, 48). While initial loss of visual acuity appears to be more severe in MOGAD, usually there is a good recovery in both diseases following corticosteroid treatment (46). Many papers have addressed the clinical and radiological differences of optic neuritis between the two disease entities (15, 48, 49), but systematic analysis of differences in CSF findings in these subcohorts is scarce. According to the current literature, optic neuritis in MOGAD presents with a normal WCC in up to two third of the cases, but can also show moderate pleocytosis and even a WCC>100/µl (16). In our cohort, MOGAD patients showed a normal WCC more frequently than MS patients, whereas in case of pleocytosis, a moderate WCC increase >30/µl was more frequent in MOGAD. Both results are thus compatible with previous work. The intrathecal synthesis of IgG, whether detected in the Reiber diagram or by detection of CSF-restricted OCB, as well as a positive MRZR, which occurred exclusively in MS patients, appear to be the best parameters to distinguish both diseases. Based on our results on the significant differences in cell differentiation between MOGAD and MS, the detection of neutrophils and plasma cells, respectively, could be helpful in clinical practice, but due to lack of data, we could not perform this analysis in the context of optic neuritis. The small number of patients limits the results of our analysis, and a larger systematic analysis is needed to confirm and further elaborate on these findings.

In summary, a number of useful pieces of information can be obtained from routine CSF clinical diagnostics to differentiate MOGAD from MS. Absence of CSF-restricted OCB and presence

of moderate blood CSF barrier dysfunction stood out as the most relevant rule-in parameters for MOGAD in this context, while positive MRZR is confirmed as by far the best rule-out parameter for MOGAD. While circumstances such as relapse, remission, and clinical phenotype have a crucial impact on routine CSF parameters, a positive MRZR is now considered a robust marker to reliably distinguish MS from MOGAD regardless of the clinical context and time point. We consider it worthwhile to verify the results of this work in other and larger cohorts.

Our study is limited by its retrospective nature, the fact that it was conducted at a single center and the overall small number of MOGAD patients. MOG antibodies, which are detected in 3-5% of MOGAD patients only in CSF and not in the serum (50–52), have not been measured in CSF in our center, but could add new information to the cohort. Furthermore, our work is limited to routine clinical diagnostics that are ubiquitously available in laboratories and does not include emerging biomarkers such as neurofilament light-chain, glial fibrillary acidic protein, myelin basic protein, or even cytokine profiles from serum and CSF, which could help differentiate both disease entities at a higher level. On the plus side, we provide robust likelihood ratios for single and combined CSF parameters that are easy to use in clinical routine practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Informed consent was obtained from all patients or relatives. Since data of all patients were anonymized for this study, the local Cantonal Ethics Committee stated that the research project does not fall within the scope of the Human Reseach Act (HRA) and therefore, an authorization from the ethics committee is not required (BASEC Nr. Req-2022-01134). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

BV had a major role in the acquisition of the data, analyzed and interpreted the data, and drafted the manuscript for intellectual content. IR, SN, MH, AL and AR acquired, analyzed and interpreted data, and revised the manuscript for intellectual content. DL, CH and AE interpreted data and revised the manuscript for intellectual content. MZ acquired and analyzed data and revised the manuscript for intellectual content. MR analyzed and interpreted data and revised the manuscript for intellectual content. IJ designed and conceptualized the study, acquired, analyzed and interpreted the data, and drafted the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

MR was supported by a research support from Euroimmun and Roche. The University Hospital and Medical University of Innsbruck Austria, employer of Dr. Reindl receives payments for antibody assays MOG, AQP4, and other autoantibodies and for MOG and AQP4 antibody validation experiments organized by Euroimmun Lübeck, Germany. AL received financial compensation and/or travel support for lectures and advice from Biogen, Merck, Novartis, Teva, Genzyme, Roche, Bayer, Celgene and he is a co-founder and co-owner of Cellerys, a company which pursues antigen-specific tolerization. He is co-inventor on a patent held by the University of Zurich on the use of peptide-coupled cells for treatment of MS. IJ has received speaker honoraria or unrestricted grants from Biogen Idec and Novartis and has received compensation for advice or lecturing by for Alexion, Biogen, Bristol Myers Squibb, Celgene, Janssen-Cilag, Neuway, Merck, Novartis, Roche and Sanofi Genzyme; none of these are related to this study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1237149/full#supplementary-material

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Epidemiology of myelin oligodendrocyte glycoprotein antibody-associated disease: a review of prevalence and incidence worldwide

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Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is an inflammatory demyelinating disease of the central nervous system (CNS) with the presence of conformation-sensitive antibodies against MOG. The spectrum of MOGAD includes monophasic/relapsing optic neuritis, myelitis, neuromyelitis optica spectrum disorder (NMOSD) phenotype without aquaporin 4 (AQP4) antibodies, acute/multiphasic demyelinating encephalomyelitis (ADEM/MDEM)-like presentation, and brainstem and cerebral cortical encephalitis. There is no apparent female preponderance in MOGAD, and MOGAD can onset in all age groups (age at onset is approximately 30 years on average, and approximately 30% of cases are in the pediatric age group). While prevalence and incidence data have been available for AQP4+ NMOSD globally, such data are only beginning to accumulate for MOGAD. We reviewed the currently available data from population-based MOGAD studies conducted around the world: three studies in Europe, three in Asia, and one joint study in the Americas. The prevalence of MOGAD is approximately 1.3–2.5/100,000, and the annual incidence is approximately 3.4–4.8 per million. Among White people, the prevalence of MOGAD appears to be slightly higher than that of AQP4+ NMOSD. No obvious latitude gradient was observed in the Japanese nationwide survey. The data available so far showed no obvious racial preponderance or strong HLA associations in MOGAD. However, precedent infection was reported in approximately 20–40% of MOGAD cases, and this is worthy of further investigation. Co-existing autoimmune disorders are less common in MOGAD than in AQP4+ NMOSD, but NMDAR antibodies may occasionally be positive in patients with MOGAD. More population-based studies in different populations and regions are useful to further inform the epidemiology of this disease.

KEYWORDS

myelin oligodendrocyte glycoprotein, MOG antibody-associated disease, neuromyelitis optica spectrum disorder, population study, prevalence, incidence, epidemiology

1. Introduction

Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is an inflammatory demyelinating disease of the central nervous system (CNS), with the presence of conformation-sensitive antibodies against MOG detected by a cell-based assay (1). The MOG antibodies were initially detected primarily in a subgroup of patients with acute/multiphasic demyelinating encephalomyelitis (ADEM/MDEM) (2, 3). Subsequent studies showed that MOG antibodies were also present in patients with optic neuritis, myelitis, neuromyelitis optica spectrum disorder (NMOSD) phenotype without aquaporin 4 (AQP4) antibodies, and brainstem and cerebral cortical encephalitis (4–10). In addition to the unique clinical spectrum, MOGAD has some distinguishing immunopathological features, such as perivenous demyelinating lesions and the fusion pattern without astrocytic damage, MOG-dominant myelin loss in some lesions, and Th17-related cytokine upregulation (11). Therefore, MOGAD is now recognized as a clinical entity distinct from multiple sclerosis (MS) and AQP4 antibody-positive NMOSD (AQP4+ NMOSD).

Recently, the international diagnostic criteria for MOGAD were published (12), and the diagnosis of MOGAD is now made based on the presence of at least one of the core clinical demyelinating events (optic neuritis, myelitis, ADEM, cerebral monofocal or polyfocal deficits, brainstem or cerebellar deficits, and cerebral cortical encephalitis often with seizures), a positive MOG-IgG test, and the exclusion of alternative diagnoses including MS. When MOG antibody is low-positive in a patient with a core clinical demyelinating event, at least one supporting clinical or MRI feature should be met to make a diagnosis of MOGAD since alternative diagnoses including MS can be low-positive (if clear-positive, such a process is unnecessary). In some core clinical demyelinating events (e.g., cerebral monofocal or polyfocal deficits), the clinical and imaging findings are not necessarily strictly defined, and occasionally it may be difficult to diagnose MOGAD in such a case when the MOG antibody is low-positive.

Unlike AQP4+ NMOSD, which has a very high female-to-male ratio (up to 9:1), there is no apparent female preponderance in MOGAD (around 1.2:1). MOGAD can onset in all age groups, with a mean/median age at onset of approximately 28–30 years. Approximately 30% of MOGAD cases are in the pediatric age group, and MOGAD comprises approximately 35–40% of cases of acquired CNS demyelinating syndrome in the pediatric population (10, 13–16). Approximately 35–50% of MOGAD cases have a relapsing course, with the relapse risk being slightly higher (~60%) in the young adult-onset group (14–16). Optic neuritis is the most common onset phenotype (~40%). Age-related onset phenotype is a feature of MOGAD, where ADEM is more common in pediatric patients <10 years old, while myelitis and brainstem encephalitis are more common in adult patients (14–16).

Almost two decades since the discovery of AQP4 antibodies, there is now accumulated data on the prevalence and incidence of AQP4+ NMOSD globally, with over 30 population-based studies published or presented from all continents except Africa (17, 18). The data showed a racial preponderance where the prevalence is higher among East Asians (~5/100,000) and Black people (up to 10/100,000) when compared to White people (~1–1.5/100,000) and Austronesians (~1.5/100,000) (17–21). Despite being less well studied, there are now a number of population-based studies on the prevalence and incidence of MOGAD being reported, and it is time to review these data from around the world.

In this article, we review population-based studies of MOGAD to determine its prevalence and incidence in all regions of the world. We also review certain epidemiological aspects such as precedent infection/vaccination, autoimmune comorbidities, and seasonal variation, as well as the available data on HLA and other genetic associations in MOGAD.

2. Prevalence and incidence of MOGAD

There have been a total of seven population-based studies that have provided data on the prevalence and incidence of MOGAD (as of June 2023). Three studies were conducted in Europe: Oxfordshire (UK) (22), Verona (Italy) (23), and the Dutch nationwide incidence study (24). The studies in Asia included a nationwide survey in Japan (16), a nationwide audit in Singapore (20), and a study in Chumphon (Thailand) (25). In the Americas and the Caribbean, there was a joint study in Olmsted County (Minnesota, USA) and Martinique Island, which was presented at a conference (ECTRIMS 2019) (26). The data from these studies are summarized and presented in Figure 1 and Table 1.

It is of note that all these studies were conducted before the international diagnostic criteria for MOGAD were proposed (12). With the new diagnostic criteria, future epidemiological data may be more standardized and accurate. It is also important to note that the majority of the studies were based on the results of MOG antibodies detected in sera. However, some patients with MOGAD are known to be MOG antibody-positive only in the cerebrospinal fluid (CSF) (27, 28), and they were not included in the prevalence and incidence calculations.

2.1. Europe

The first population-based prevalence study of MOGAD in Europe was reported from Oxfordshire (UK), with a prevalence of 2.0/100,000 (total of 14 patients, with 12 White people) and an annual incidence of 3.4 per million (22). In that study, among White people, the prevalence of MOGAD was 1.9/100,000 (12 cases), while the prevalence of AQP4-IgG+ NMOSD was 1.0/100,000 (6 cases). This study shows that in White people, MOGAD appears to be two times more common than AQP4+ NMOSD.

The MOGAD study from Verona (Italy) reported a prevalence of 2.5/100,000 (in 23 patients; 22 White people and 1 Asian) and an annual incidence of 4.4 per million (23). This prevalence in Verona is quite consistent with that reported from Oxfordshire.

In the Dutch nationwide MOGAD incidence study, the data from a single centralized laboratory that performed MOG antibody tests were analyzed. From 2015 to 2017, the average annual incidence was 1.6 per million (1.3 per million in adults, and a higher incidence of 3.1 per million in children) (24). The study investigators noted that these incidence estimates were minimum figures, and increased awareness of the antibody tests among treating physicians would likely lead to a higher incidence. For instance, in 2017, the annual incidence was 2.4 per million (children: 4.7 per million).

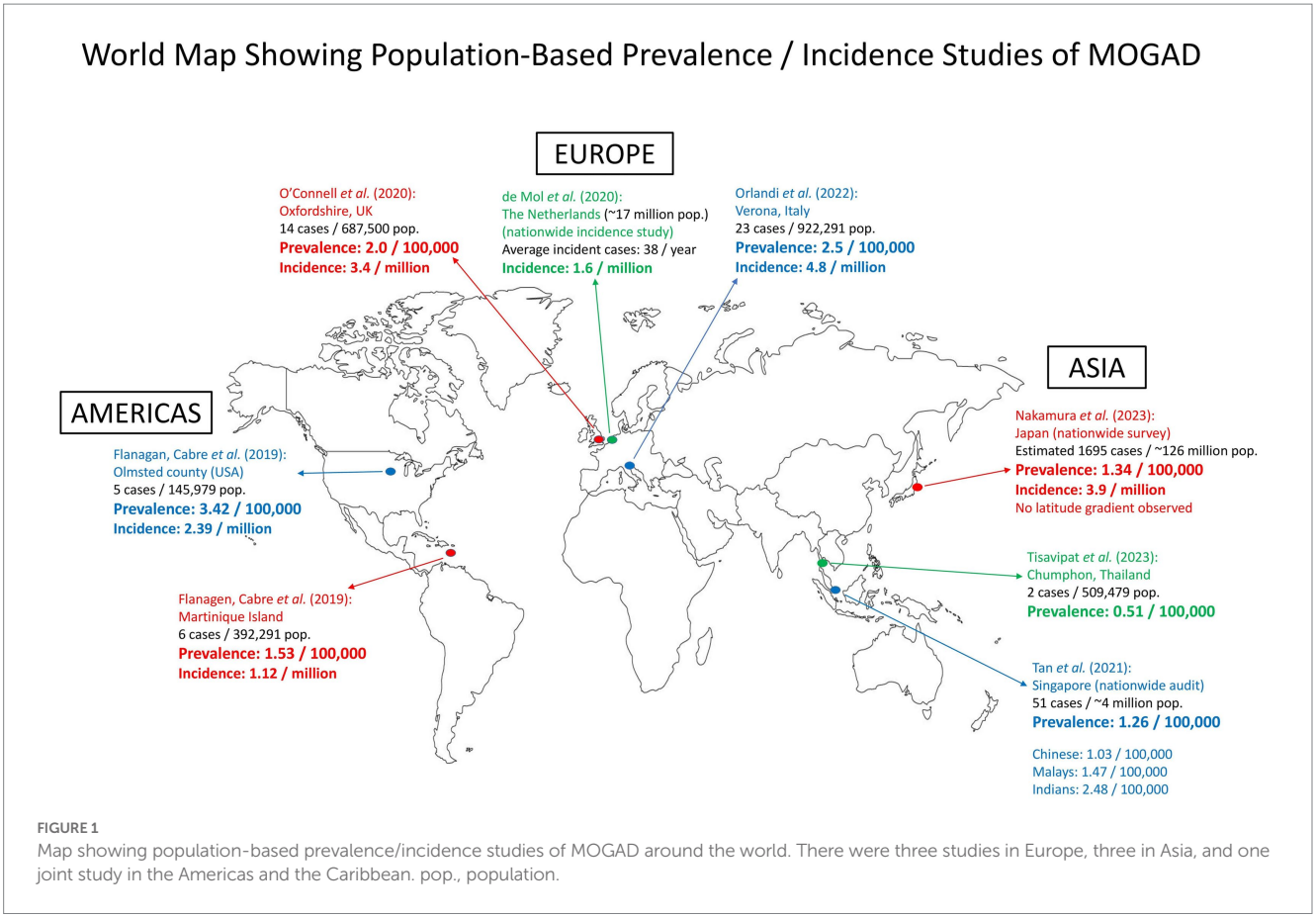

FIGURE 1
Map showing population-based prevalence/incidence studies of MOGAD around the world. There were three studies in Europe, three in Asia, and one joint study in the Americas and the Caribbean. pop., population.

There were also two population-based studies conducted in Catalonia and Portugal on the prevalence and incidence of NMOSD that included AQP4 antibody-positive cases and MOG antibody-positive cases (29, 30). However, these cases were the ones that strictly fulfilled the 2015 criteria of the International Panel on NMO Diagnosis, and therefore, for MOG antibody-positive cases, only those with an NMO phenotype were included. In Catalonia, 12% of the NMOSD cases were MOG antibody-positive, giving a prevalence of 0.11/100,000 (29). In the Portuguese nationwide study, 67/180 (37%) of NMOSD cases were MOG antibody-positive, giving a prevalence of 0.65/100,000 (30). Suffice it to say, if all phenotypes of MOGAD (e.g., those with monophasic or relapsing optic neuritis or the ones with brain syndromes) were included, the prevalence would be higher.

2.2. Asia

The Japanese nationwide MOGAD survey (Japan's population in 2020 was 126 million) published recently identified 877 MOGAD cases, including 258 new cases, and estimated there were 1,695 MOGAD cases nationwide. This gave an estimated prevalence of 1.34/100,000 and an annual incidence of 3.9 per million (16). The survey also showed that there was no obvious latitude gradient observed between the northern and southern parts of Japan for MOGAD prevalence. This study was based on data gleaned from questionnaires sent to neurology, pediatric neurology, and neuro-ophthalmology departments ($N = 3{,}790$) across the country, which is different from a conventional population-based prevalence and incidence study. In addition, the response rate in the primary survey was relatively low (36.4%). These may be the limitations of the survey.

In the multi-racial island nation of Singapore at the equator, a nationwide audit estimated a prevalence of 1.26/100,000 (20). When breaking down according to the racial groups, the prevalence was 1.03/100,000 among Chinese, 1.47/100,000 among Malays, and 2.48/100,000 among Indians, suggesting a potential influence of race on the prevalence. On the other hand, multi-center studies from Australia and the UK largely did not show significant racial preponderance (15, 31), though, in the UK study, there was a slightly increased proportion of South Asian patients in the young pediatric group (<12 years), while in the Australian cohort, there was a slightly increased proportion of South Asian patients in the adult group. Longitudinal studies and data from other regions will be useful to clarify this.

A recent study from the Chumphon province in Thailand reported two cases of MOGAD in adult females, giving a prevalence of 0.51/100,000 among the adult population (25). In the same study, the prevalence of MS was 0.77/100,000, while the prevalence of AQP4+ NMOSD was 3.08/100,000. More population-based studies of MOGAD from the diverse regions of Asia are awaited.

2.3. The Americas and the Caribbean

There was a joint study from Olmsted County (USA) and Martinique Island that was presented at the ECTRIMS 2019 congress but utilized earlier data (prevalence date: 2011) (26). In Olmsted

TABLE 1 Population-based prevalence and incidence studies of MOGAD around the world.

Population-based study	Geographical location	Area of study	Population	Prevalence date	Incidence period	Number of prevalent cases	Female-to-male ratio	Pediatric cases	Clinical phenotypes	Other clinical information	MOG antibody testing method	Prevalence per 100,000 population (95% CI)	Annual Incidence per million population (95% CI)
	Europe												
O'Connell et al. 2020 (22)	Oxfordshire, UK	Countywide	687,500	1/7/2018	2015–2018	14 (12 White people, 1 Asian, and 1 mixed)	1.8:1	N = 2	NMOSD: 3 ON: 7 Myelitis: 3 ADEM: 1	NA	Live CBA	2.0 (1.1–3.4)	3.4 (1.4–6.9)
Orlandi et al. 2022 (23)	Verona, Italy	Provincewide	922,291	1/1/2021	2016–2020	23 (22 White people and 1 Asian)	1.3:1	N = 2	Onset phenotypes: ON: 5 Myelitis: 7 Encephalopathy/brainstem syndrome: 7 Multifocal encephalomyelitis: 4	Median disease duration: 19.5 months 2 cases relapsed	Live CBA	2.5 (1.7–3.7)	4.8 (3.1–7.2)
de Mol et al. 2020 (24)	The Netherlands	Nationwide incidence study	~17 million	–	2015–2017	Average incident cases: 38 per year	–	Average incident cases: 11 per year	Phenotypes (in 61 of 92 cases): NMOSD: 21% ON: 26% Myelitis: 15% ADEM: 23% Brainstem syndrome: 2% Others: 12%	Median follow-up duration: 27.5 months 33% relapsed Median duration to 1st relapse: 8 months	Live CBA	–	1.6 (1.1–2.3) Adult: 1.3 (0.8–1.9) Children: 3.1 (1.7–5.1)
	Asia												
Nakamura et al. 2023 (16)	Japan	Nationwide survey and estimate	~126 million	03/2021	~04/2020–03/2021	1,695	1.2:1	~30%	Onset phenotypes (in 746 cases): NMOSD: 6.4% ON: 35.7% Myelitis: 12.7% ADEM: 12.5% Encephalitis: 11.8% Brainstem encephalitis: 3.9%	53.5% relapsed Median EDSS at maximum disability: 4 Median EDSS at last follow-up: 0 Median number of relapses: 1 Median duration to 1st relapse: 7 months	CBA	1.34 (1.18–1.51)	3.9 (3.2–4.4)

(Continued)

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TABLE 1 (Continued)

Population-based study	Geographical location	Area of study	Population	Prevalence date	Incidence period	Number of prevalent cases	Female-to-male ratio	Pediatric cases	Clinical phenotypes	Other clinical information	MOG antibody testing method	Prevalence per 100,000 population (95% CI)	Annual Incidence per million population (95% CI)
Tan et al. 2021 (20)	Singapore	Nationwide audit	~4 million	2020	–	51	1.2:1*	N = 10	NA	NA	CBA	1.26 (0.91–1.61) Chinese: 1.03 (0.57–1.39) Malays: 1.47 (0.45–2.48) Indians: 2.48 (0.86–4.11)	---
Tisavipat et al. 2023 (25)	Chumphon, Thailand	Provincewide	509,479	31/12/2021	2016–2021	2	Both females	0	ON: 1 ON + short myelitis: 1	Median disease duration: 10 years Both cases relapsed Median VFSS at last visit: 1.5	Fixed CBA	0.51* (0.14–1.87)	–
	Americas and Caribbean												
Flanagan et al. 2019 (26)	Olmsted County, USA	Countywide	145,979	31/12/2011	2003–2011	5	–	–	ON: 2 Myelitis: 1 ADEM: 2	Median follow-up: 8 years 20% relapsed Median EDSS: 1.5	Live CBA	3.42	2.39
Flanagan et al. 2019 (26)	Martinique Island	Island wide	392,291	31/12/2011	2003–2011	6	–	–	NMOSD: 2 ON: 3 ADEM: 1	Median follow-up: 1 year 50% relapsed Median EDSS: 2	Live CBA	1.53	1.12

*Data for adult patients. ADEM, acute disseminated encephalomyelitis; CBA, cell-based assays; EDSS, Expanded Disability Status Scale; NA, not available; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; VFSS, visual functional system score.

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County, the prevalence was 3.42/100,000 and the annual incidence was 2.39 per million. On Martinique Island in the Caribbean, the prevalence was 1.53/100,000 and the annual incidence was 1.12 per million. A follow-up study from these two areas will help provide updated data on MOGAD prevalence and incidence in the Americas and the Caribbean.

In São Paulo (Brazil), a study estimated the prevalence of MOGAD by first determining the ratio of MS to MOGAD in a university referral center and then extrapolating it by using the known MS prevalence (in 1997) in that region. With this method, the prevalence of MOGAD was estimated to be 0.4/100,000 (32). Nevertheless, there could be an underestimation as the center only treats adult patients but not pediatric patients. In a multi-center study in the province of Quebec (Canada) that involved seven major adult and pediatric academic centers, a total of 45 MOGAD cases were identified, giving a minimum prevalence of 0.52/100,000 (33). This was also likely an underestimation because some cases might not have been tested for MOG antibodies or referred to those specialized centers.

3. Precedent infection and vaccination

An important clinical aspect of MOGAD is that approximately 20–40% of the cases had infectious prodromes or precedent infections. Those precedent infections included the common cold, pharyngolaryngitis, bronchitis, pneumonia, acute gastroenteritis, and infections related to influenza, mycoplasma, streptococcus, and chlamydia (16, 31, 34–36). The Japanese study showed that this precedent infection was more frequent in the pediatric-onset group (39% for those <10 years) than in the adult-onset group (13.5%) (16). It is interesting to see how infectious diseases are involved in the pathogenesis of MOGAD (immune activation, molecular mimicry, etc.). Additionally, there were also a small number of MOGAD cases that onset after vaccination. The vaccines reported included those for influenza, Japanese encephalitis, measles/rubella, diphtheria/tetanus/pertussis, and COVID-19 (16, 34, 36–38).

4. Autoimmune comorbidities

Co-existing autoimmune diseases are observed in up to 7–10% of MOGAD patients, with Sjogren syndrome, rheumatoid arthritis, ulcerative colitis, thyroid disorder, psoriasis, and NMDAR encephalitis being commonly reported (16, 31, 34, 35, 39), but the frequency appears to be lower than that in AQP4+ NMOSD (40). In a laboratory study, the serum and/or CSF of 376 patients positive for MOG antibodies were tested for co-existent neuronal surface antibodies. A total of 14 (3.7%) patients were dual positive for MOG and NMDAR antibodies, making NMDAR antibodies the most frequent co-existent neuronal surface antibodies in MOGAD (41). In the Japanese nationwide survey, 15 (31%) of 48 selected MOGAD patients tested were positive for NMDAR antibodies (16). A systematic review showed that there have been more than 200 cases reported in the literature of either MOGAD co-existing with NMDAR encephalitis or dual positivity of MOG and NMDAR antibodies in encephalitis or MOGAD patients (42).

5. HLA and other genetic associations

For AQP4+ NMOSD, multiple studies have shown different HLA associations (both risk and protective HLA alleles) in different racial groups (Asians, White people, and Latin Americans) (19, 43–46). For MOGAD, two studies (the Netherlands and the UK) did not find any strong HLA associations (43, 47). However, a study in Guangzhou (China) found that pediatric-onset MOGAD was associated with the DQB1*05:02-DRB1*16:02 haplotype, though no HLA association was found for adult-onset MOGAD (48). Another study in Guangzhou also revealed three non-HLA susceptibility loci (*BANK1*, *RNASET2*, and *TNIP1*) for MOGAD (49).

6. Seasonal variation

Three studies [Tohoku region (Japan), Verona (Italy), and Quebec (Canada)] reported an autumn-winter predominance for the onset of MOGAD (23, 33, 50). However, a joint study from Germany and the Kanto region in Japan did not find such a trend (51). That study reported the lowest incidence of MOGAD onset during autumn in both the German and Kanto cohorts. A UK study did not observe seasonal variation in MOGAD onset either (52). More studies are needed to further clarify this aspect.

7. Conclusion

We reviewed the currently available data from population-based MOGAD studies conducted around the world. The prevalence of MOGAD is approximately 1.3–2.5/100,000, and the annual incidence is approximately 3.4–4.8 per million. As disease awareness increases, and with the ease of availability of MOG antibody assays, the prevalence is expected to rise in the future. Moreover, through the application of the international diagnostic criteria of MOGAD (12), the epidemiological data are expected to be more accurate.

Among White people, the prevalence of MOGAD appears to be slightly higher than that of AQP4+ NMOSD. Conversely, in populations or regions where the prevalence of AQP4+ NMOSD is higher (such as in Japan), MOGAD appears comparatively less common. So far, there has been no obvious racial preponderance observed in MOGAD, though the slight increase in prevalence among South Asians requires further investigation. The role of precedent infection observed in a proportion of MOGAD cases is also worthy of further research. More population-based studies in different populations and regions of the world will be very useful to further inform the epidemiology of this unique inflammatory demyelinating disease of the CNS.

Author contributions

JH and KF conceived and designed the study, collected and analyzed the data, drafted the manuscript, critically revised the manuscript for intellectual content, and approved the final manuscript.

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Conflict of interest

KF serves on scientific advisory boards or as a consultant for Biogen, Mitsubishi-Tanabe, Novartis, Chugai, Roche, Alexion, VielaBio/Horizon Therapeutics, UCB, Merck Biopharma, Japan Tobacco, Argenx, and Abbvie; has received funding for travel or speaker honoraria from Chugai, Roche, Biogen, Novartis, Alexion, Teijin, Mitsubishi-Tanabe, AsahiKasei, Eisai, Takeda, and Bayer; serves on editorial boards of *Clinical and Experimental Neuroimmunology, Frontiers in Neurology, Neurology: Neuroimmunology and Neuroinflammation, Multiple Sclerosis Journal, Multiple Sclerosis and Related Disorders, Neuroimmunology Reports* and *European Journal of Neurology*, and advisory board of *Sri Lanka Journal of Neurology*; and has been funded by the Grants-in-Aid for Scientific Research from the Ministry of Education, Science and Technology of Japan and by the Grants-in-Aid for Scientific Research from the Ministry of Health, Welfare and Labor of Japan.

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Delimiting MOGAD as a disease entity using translational imaging

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The first formal consensus diagnostic criteria for myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) were recently proposed. Yet, the distinction of MOGAD-defining characteristics from characteristics of its important differential diagnoses such as multiple sclerosis (MS) and aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorder (NMOSD) is still obstructed. In preclinical research, MOG antibody-based animal models were used for decades to derive knowledge about MS. In clinical research, people with MOGAD have been combined into cohorts with other diagnoses. Thus, it remains unclear to which extent the generated knowledge is specifically applicable to MOGAD. Translational research can contribute to identifying MOGAD characteristic features by establishing imaging methods and outcome parameters on proven pathophysiological grounds. This article reviews suitable animal models for translational MOGAD research and the current state and prospect of translational imaging in MOGAD.

KEYWORDS

myelin oligodendrocyte glycoprotein associated disease, imaging, translational research, EAE, animal models

1 Introduction

Myelin oligodendrocyte glycoprotein (MOG) is a minor transmembrane glycoprotein located in the outermost membranes of the myelin sheath (1) that has long been an important target molecule for animal models of demyelinating diseases. Only in recent decades, antibodies against MOG (MOG-IgG) have been identified in people who were previously diagnosed with various other autoimmune-neurological diagnoses such as multiple sclerosis (MS), aquaporin-4-antibody (AQP4-IgG) seronegative neuromyelitis optica spectrum disorder (NMOSD), and acute disseminated encephalomyelitis (ADEM), as well as in isolated and recurrent optic neuritis (ON) and transverse myelitis (TM) (2–6). Furthermore, MOG-IgG can be discovered "false positively" in several other conditions, as demonstrated in several cases of peripheral neuropathy (7, 8) and tumor/lymphoma (9–11). Thus, care needs to be taken as to when MOG-IgG measurement should be performed as well as to the interpretation and consideration of possible differential diagnosis thereof, as has been pointed out in the formal consensus diagnostic criteria for MOG-IgG-associated diseases (MOGAD) that were recently established for the first time (12). Yet, clinical features of MOGAD partly overlap with its differential diagnoses, most importantly NMOSD and MS, delaying the time required until the correct treatment is applied, thus increasing relapse probability. Clinical and imaging studies until now also often included MOGAD

patients grouped together with MOG-IgG seronegative patients (for example, as AQP4-IgG seronegative NMOSD), further limiting the discovery of MOGAD-specific features. This is not only true for clinical research: MOG-induced animal models, such as experimental autoimmune encephalomyelitis (EAE), have been widely used as models of demyelinating diseases in general and MS in particular. With the definition of MOGAD as a separate disease entity, it needs to be reevaluated to which extent the generated knowledge from MOG-induced models is specifically applicable to MOGAD vs. what should be considered valid for its differential diagnosis (13).

Imaging can significantly aid differential diagnosis early in the disease course and guide the application of cell-based MOG-IgG assays (if available) (14–16). By using a back-translational approach to investigate disease-specific imaging features in preclinical models, imaging can also be used to improve the understanding of (A) distinct pathophysiology by using methods with single-cell resolution and (B) the pathophysiological basis of distinct imaging characteristics by using feature-specific histopathology. This article reviews translational imaging techniques in MOGAD and its animal models. It also discusses the current and potential future relevance of MOGAD-specific animal models and translational imaging for defining distinct pathophysiological features in MOGAD compared with important differential diagnoses, especially MS (17) and AQP4-IgG seropositive NMOSD (18).

2 The pathophysiology of MOGAD

There is very little autopsy and/or biopsy material that documents MOGAD pathology specifically (13, 19–22). Furthermore, these studies were conducted mostly on cerebral samples; there is only one reported case of spinal cord pathology (Carta et.al). Optic nerves are missing in these evaluations. From the presented material, it can be deduced that there are clear histopathological differences discerning MOGAD from both NMOSD and MS, including a CD4+ dominated infiltrate, with fewer B cells, a moderate number of granulocytes (eosinophils and neutrophils), and many/abundant macrophages, some containing early myelin degradation products. While AQP4 and AQP1 were preserved in MOGAD, reactive astrogliosis and even scarring in and around the demyelinating lesions were observed. Axons and oligodendrocytes were unaffected or variably destructed, with a moderate number of axons showing disturbed fast axon transport and axonal spheroids, especially at the lesion rim. Demyelinating lesions occur usually in white matter in a mixed perivenous and confluent pattern of several perivenous lesions, with affection of cortico-medullary junctions and leptomeningeal areas of the cortex as well as the cerebral white matter. Furthermore, there are no "smoldering" radially expanding lesions with microglial/macrophage rim, as would be seen in progressive MS. A meningeal inflammation in 86% of biopsy cases could be seen. The studies, however, do not agree about complement deposition, one describing complement deposition/activation in white matter lesions (13) and the other describing only occasional perivascular-activated complement and IgG deposition (19), which however could be attributed to differences in staining protocols (personal communication). In the latter study and the study by Spadaro et al., MOG-dominated myelin loss with preserved oligodendrocytes was observed (20), whereas the previous one did not discern preferential loss of MOG (13). The pathology of one patient with a fulminant MOGAD-like disease including meningoencephalitis and leptomeningeal enhancement and positive MOG-IgG in the cerebrospinal fluid only showed relative axonal sparing, primary confluent demyelination, reactive gliosis, and CD4+ dominated inflammatory infiltrates (22).

There have also been attempts to define the cytokine profile in patients with MOGAD. A study by Nakajima et al. found elevated levels of serum IL-1ra, IL-5, and TGF-α as compared to MOG-negative patients (23). IL-6 was found to be elevated in the CSF of MOG-IgG seropositive children (24). In the study by Bauer et al., serum cytokine levels of MOG-IgG positive/AQP4-IgG positive NMOSD were compared to those measured in MS patients (25). They discovered 36 analytes being increased from MOGAD compared with MS (IL-8, SDF-1a, MCP-1, GRO-a, IL18, MIP-1b, Fractalkine, HGF, IP-10, SCF, VEGF-A, BAFF, IL-7, TWEAK, MIP-3a, M-CSF, CD40L, MMP-1, IL-27, MIG, LIF, MIP-1a, IL-17A, IL-23, TNF-β, IL-1a, IL-6, IL-21, IL-5, MDC, IL-9, FGF-2, Eotaxin-3, IL-10, Eotaxin-2, and IL-31). Only five cytokines differed between AQP4-IgG seropositive NMOSD and MOGAD, all being lower expressed in MOGAD (APRIL, TNFR2, TRAIL, MCP-2, and CD30). No differences were found in MOGAD/NMOSD with regard to disease activity (relapse/remission and amount of relapses), disease course (monophasic/relapsing), treatment modality, sex, or age; however, the availability of clinical data were incomplete.

3 Clinical features and clinical imaging in MOGAD

MOGAD affects pediatric and adult patients and shows no sex or ethnic predominance (26). Typical clinical attacks include ON, TM, and, to a lesser extent, cranial neuropathies, brainstem and cerebellar demyelinating attacks, tumefactive brain lesions, mono- and polyfocal CNS deficits, and white matter leukodystrophy-like damage, as well as encephalitis with seizures and neuropsychiatric symptoms (27–30). The most common first manifestation in adults is ON (>55%), whereas the most common first pediatric manifestation is ADEM (with or without ON, >45%) (31–33).

In contrast to the recurrent disease course in MS and NMOSD, MOGAD can be monophasic (~22–56%) (4, 13), preferentially in children (16, 34–36), or recurrent. The current estimation is limited by the short follow-up lengths of published studies, but only one in three MOGAD patients seems to have a relapse within a year after their initial manifestation (3, 4, 37). The risk is higher with steroid tapering and shortly after the initial attack (3, 4, 38, 39). Other longer studies with a small sample size suggest that the long-term risk for recurrent attacks is higher and that attacks can still occur up to >40 years after onset (40, 41). The risk of relapse is lower in pediatric patients; only one in five kids is affected (16, 31, 42, 43). In contrast to MS, clinical progression independent of attacks has not been widely reported in MOGAD so far (41, 44, 45). Histopathological analysis of autopsies/biopsies did not reveal "smoldering" (i.e., slowly expanding) lesions in

patients with MOGAD, suggesting a different etiology, if there was a clinically progressive, meaning an attack-independent, disease course in MOGAD as compared to MS. Yet, the current state of research cannot shed light on the possibility of clinical or subclinical progression in MOGAD (46, 47). In a few cases in our outpatient clinic, we observed that patients experience relapse-free worsening of their symptoms over time; however, a thorough investigation on this matter is still needed.

3.1 Brain and brainstem

Cerebral manifestations and imaging findings in MOGAD are diverse. In adults with MOGAD, brain MRI findings are usually sparse and rarely occur in isolation without cerebral syndrome or concurrent optico-spinal lesions (3, 48). Silent lesions are seen in <5% of adult MOGAD patients and even those are usually associated with subsequent relapses (49). Cortical and infratentorial lesion locations are the most common, but large T2-hyperintense white matter lesions can occur (13, 48). In rare cases, tumefactive lesions with a risk for herniation are seen (50).

People with MOGAD have a higher frequency of cortical and juxtacortical lesions compared with people with AQP4-IgG seropositive NMOSD. Yet, the number of lesions in MOGAD is usually lower than in MS, especially at onset (3). Matthews et al. and Juryńczyk et al. specifically proposed that lesions close to the lateral ventricle and/or in the inferior lobe, subcortical U-fiber lesions, and Dawson's finger-type lesions strongly suggest a diagnosis of MS vs. MOGAD (51, 52). For infratentorial lesions, the brainstem, especially the pons, close to the 4th ventricle and the middle cerebellar peduncle, are the most common locations in MOGAD—lesions can be found in up to 30% of patients (3, 53, 54). Lesion demarcation is usually poor and can disperse over time (4, 48). Particularly, lesions in the middle cerebellar peduncle can distinguish MOGAD from MS and AQP4-IgG seropositive NMOSD (54). Area postrema syndrome, however, is less common in MOGAD compared with AQP4-IgG seropositive NMOSD (55–57). In contrast to MS and AQP4-IgG seropositive NMOSD, the application of gadolinium rarely reveals a lesion enhancement pattern in MOGAD but can lead to unspecific leptomeningeal enhancement around the brainstem or in uni- or bilateral cortical areas, especially in MOGAD with cortical encephalitis.

In pediatric patients, the most common onset syndrome is ADEM, which typically presents on MRI with large asymmetric and diffuse, supra- and infratentorial T2-hyperintense white matter lesions (58–60). ADEM can also rarely occur in adults—with similar MRI features. Compared with MOG-IgG seronegative ADEM, MOGAD-ADEM more often involves the thalamus (61). MOG-IgG-associated autoimmune encephalitis, a second common pediatric manifestation, presents with large subcortical and/or cortical lesions (31, 62). In contrast to autoimmune encephalitis with other antibodies, normal MRI findings in MOG-IgG-associated autoimmune encephalitis are rare (63). A leukodystrophy-like phenotype of MOGAD, a rarer pediatric manifestation, also presents with large symmetric confluent white matter lesions, yet they are usually clinically progressive (47).

Advanced MRI techniques have been used for a limited number of MOGAD studies so far. Combining fluid-attenuated inversion recovery sequences (FLAIR) with traditional MRI metrics, hyperintense cortical lesions and numerous T2-hyperintense lesions in various locations were identified, respectively, in a subgroup of MOGAD referred to as FLAMES (*FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures*) (29, 64, 65). FLAMES can further be characterized by hyperperfusion of lesions on single photon emission computed tomography (SPECT) (56). Using diffusion-tensor imaging (DTI) and resting state functional MRI, reduced axial diffusivity in line with microstructural white matter damage, and interhemispheric functional connectivity changes of the motor, sensorimotoric and frontal lobe networks, respectively, were identified in MOGAD compared with healthy controls (66, 67). Applying volumetric analyses, no loss of gray or white matter was observed in adult MOGAD patients compared with healthy controls (66, 68). In pediatric ADEM, however, the brain volume as well as the expected brain growth were reduced (69). So far, no advanced MRI marker has been suggested to distinguish MOGAD from its differential diagnoses.

3.2 Spinal cord

TM in MOGAD can manifest as sensory, motor, and sphincter dysfunctions (70). It can occur in isolation or combined with other manifestations such as ADEM or ON. Despite often severe impairment in the acute stage, most patients have a good recovery. Yet, especially sexual, bladder, and bowel dysfunction can remain (44, 71). Persisting pain or spasms are uncommon and seen more often in AQP4-IgG seropositive NMOSD than in MOGAD. The MOGAD-associated spinal cord involvement in adult and pediatric patients is largely comparable (72).

Initial spinal cord MRI can be normal in 10% (73, 74). The most common finding on spinal cord MRI in MOGAD, however, is the so-called longitudinally extensive transverse myelitis (LETM) presenting as a hyperintense T2-lesion spanning over three or more segments and mainly affecting the cervical and/or thoracic cord (Figures 1A–D) (74–77). LETMs rarely occur in MS (78). While LETMs can also be seen in AQP4-IgG seropositive NMOSD, MOGAD patients present more often with multiple lesions and conus involvement (75, 79–81). Also, shorter TM, as typical for MS, can be seen in MOGAD and is more common compared with AQP4-IgG seropositive NMOSD (77, 79, 82).

Up to 75% of lesions in MOGAD are centrally located and up to 50% of lesions are restricted to gray matter, which can often be identified as the characteristic H-sign on axial scans (Figures 1C, D) (73, 79, 81). This is particularly interesting since MOGAD is a highly inflammatory condition primed to the white matter. As discussed below, data from rodent models suggest that this severe white matter inflammation correlates with gray matter hypoxia and increased variation in oxygenation in the gray matter potentially leads to gray matter damage (83), as has been similarly suggested in MS (84, 85). Still the pathomechanism of gray matter damage remains to be elucidated and more autopsy/biopsy samples, especially in MOGAD, need to be analyzed to this end.

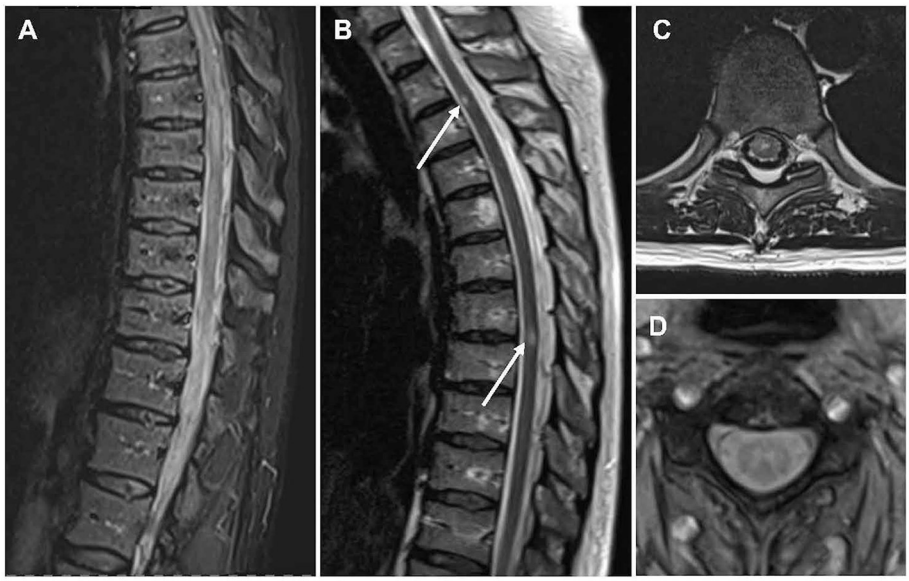

FIGURE 1
MR imaging of the spinal cord in people with MOGAD. Sagittal T2-weighted MRI showing hyperintense lesions in line with **(A)** an LETM and **(B)** shorter lesions. Axial T2-weighted MRI showing **(C)** a centrally located lesion and **(D)** the characteristic H-sign. LETM, longitudinally extensive transverse myelitis; MOGAD, myelin oligodendrocyte glycoprotein antibody associated disease; MRI, magnetic resonance imaging.

In contrast to both MS and AQP4-IgG seropositive NMOSD, gadolinium-enhancement is less common in MOGAD (∼50%) (72, 75). However, contrast enhancement of the pia and cauda as well as contrast enhancement and thickening of dorsal nerve roots can occur (28, 72).

The application of advanced spinal cord imaging in MOGAD has so far been very limited. Spinal cord atrophy as measured by volumetric MRI has been only seen after severe attacks (86, 87). Silent spinal cord lesions can occur during an attack of the brain or optic nerve but are extremely rare outside of attacks in MOGAD, making spinal cord involvement outside of acute attacks unlikely (49).

3.3 Retina and optic nerve

Optic neuritis (ON) is the most frequent onset feature in adults and one of the most common manifestations of MOGAD in general (88). Thus, imaging of the visual system is a promising approach for diagnosis and differential diagnosis (89, 90). In MOGAD, ON is often bilateral and mostly located in the anterior segment causing severe edema (39, 91, 92). Although single ON attacks often do not lead to tremendous retinal neurodegeneration, the high frequency of attacks in MOGAD can accumulate significant damage (92). Due to its severe symptoms, silent ON is uncommon in MOGAD, yet a bilateral ON can remain unrecognized due to stronger symptoms in one eye.

Lesions on optic nerve MRI usually show T2-hyperintensity and gadolinium enhancement on T1-weighted imaging (Figure 2A). In MOGAD, drastic nerve swelling and characteristic perineural/periorbital gadolinium enhancement are often seen (93, 94). Hemorrhages can occasionally occur, particularly in peripapillary regions. Optic nerve lesions are also extensive, involving more than half of the pre-chiasmic optic nerve, which distinguishes optic nerve lesions in MOGAD from shorter lesions in MS (95, 96). The optic nerve MRI can show the characteristic anterior involvement, which distinguishes optic nerve lesions in MOGAD from the also often extensive but mostly posterior lesions in AQP4-IgG seropositive NMOSD (96, 97). Simultaneous bilateral involvement is more common in MOGAD than in both MS and AQP4-IgG seropositive NMOSD (98).

ON leads to retrograde retinal neurodegeneration, which can be monitored using spectral domain optical coherence tomography (OCT). OCT is a non-invasive imaging method using the interference of low coherent light to produce high-resolution images of the retina (99). Neurodegeneration after ON is quantified by OCT measuring the peripapillary retinal nerve fiber layer (pRNFL) and the combined ganglion cell and inner plexiform layer (GCIPL), which contain the axons and cell bodies of retinal ganglion cells, respectively (Figures 2B, C) (99, 100). Whereas, the pRNFL usually undergoes swelling during the acute phase before experiencing volume loss due to subsiding edema and concurrent degeneration; the GCIPL is less affected by swelling and undergoes a steadier volume loss due to neurodegeneration. According to the current consensus, the majority of retinal neurodegeneration happens within the first 6 months after the acute ON attack independent of the underlying disease. Yet, the acute pRNFL swelling in MOGAD is described to be more severe and is suggested as a diagnostic marker distinguishing MOGAD from MS (101). This might lead to a prolonged (more than 6 months) pRNFL reduction in MOGAD (102, 103).

To diagnose a history of ON, the use of the absolute or relative differences in pRNFL and GCIPL between both eyes of patients,

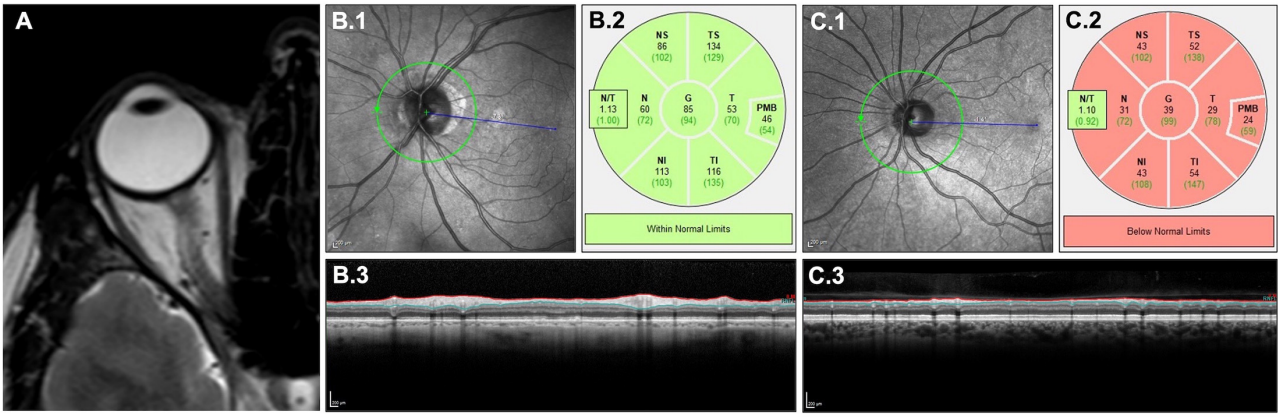

FIGURE 2
Clinical imaging of retina and optic nerve. T2-weighted MRI of the optic nerve **(A)** showing a longitudinal lesion with edema. OCT quantifying retinal neuroaxonal content measured by pRNFL around the optic nerve head in a retina without a history of ON **(B)** and with a history of ON **(C)** in MOGAD: scanning laser ophthalmoscopy **(B.1, C.1)**, color-coded comparison with a healthy control cohort **(B.2, C.2)** and cross-sectional B-scans showing pRNFL atrophy in **(C.3)** compared with **(B.3)**. MOGAD, myelin oligodendrocyte glycoprotein antibody associated disease; MRI, magnetic resonance imaging; OCT, optical coherence tomography; ON, optic neuritis; pRNFL, peripapillary retinal nerve fiber layer.

the so-called inter-eye-difference (IED), has been suggested (104). Due to a higher frequency of unilateral ON, the application of IED is very high in MS and reasonable in NMOSD (105–108). Yet, the use of IED has not been investigated in MOGAD and seems limited due to the high frequency of bilateral ON. When comparing absolute values of pRNFL and GCIPL after ON, MOGAD patients usually have more severe retinal neurodegeneration (ergo thinner pRNFL and GCIPL) than patients with MS. pRNFL and GCIPL after ON are comparable in people with MOGAD and AQP4-IgG seropositive NMOSD (109). Yet, several publications suggest that the neuronal loss per ON is lower in MOGAD, and only the higher frequency of ONs leads to damage that is comparable with AQP4-IgG seropositive NMOSD patients with less frequent but more severe ONs (109, 110). Despite the neuroaxonal loss being comparable, people with MOGAD often have a better long-term visual outcome compared with AQP4-IgG seropositive patients—the pathophysiological explanation for this difference is still pending (111–115).

Retinal and optic nerve damage independent of ON has been shown in MS, where it can also be used to predict disease activity (116–120) and, to a lesser extent, in AQP4-IgG seropositive NMOSD (121–126). Advanced OCT imaging suggests that ON-independent retinal changes in AQP4-IgG seropositive NMOSD are related to primary astrocytopathy (127). So far, no ON-independent neurodegeneration above aging-related standard and no primary and/or outer retinopathy has been shown in MOGAD, potentially aiding differential diagnosis (102, 103, 128). First applications of OCT angiography showed a significant decrease in vessel density after ON in MOGAD, which exceeded the changes in AQP4-IgG seropositive NMOSD (129, 130). A new generation of advanced OCT imaging methods including 3D-shape analyses and feature recognition can potentially contribute to a better understanding of ON-dependent and -independent changes in MOGAD and their use for differential diagnoses in the future (131–134).

4 Are MOG and MOG-IgG-induced animal models good models for MOGAD?

Animal models that induce encephalitis to mimic autoimmune-mediated disease in the CNS include approaches of active immunization, passive transfer, antibody (co-)mediated disease induction or exacerbation as well as transgenic/genetic modifications to mention the most common ones. MOG-mediated disease is one of the most commonly used to model MS and has been used in many variations that have been described and reviewed extensively elsewhere (135–164). However, with the emergence of MOGAD as a separate disease entity and considering that these models do present drawbacks in reproducing MS characteristics (mainly CD4+ mediated, no MOG-IgG present in any form of MS, etc.) (2, 12, 35, 165–168) the issues in their translation into new therapeutic modalities for MS could be viewed in a new light (169–171). In this review, we will discuss to what extent (some selected) MOG-induced animal models as well as some non-MOG-induced models resemble human MOGAD disease and to what extent they could be employed for diagnostic, prognostic, and therapeutic approaches.

4.1 MOG-induced animal models

The course and development of EAE are dependent on many different factors and their ratio to each other (172) including the conformation, concentration, solubility, specificity of the antigen used (135), age, species and genetic background of the experimental animals (139, 173–175), the adjuvant (176–179), and timing of immunizations/transfer to name just some variable instances. It has been shown, for instance, that the disease course—monophasic, relapsing, primary/secondary progressive, or chronic progressive

(with disability accrual)—can be regulated by the immunization protocol of Lewis (LEW.1AV1) rats with MOG (135).

4.2 MOG-IgG-mediated models

In patients, MOG-IgG was shown to be present during very early stages of disease onset and to persist over long periods of time even during remission. The MOG-IgG titer is dependent on disease activity; however, the antibodies cannot independently induce the disease. In contrast, MOG-IgG has been found in early, intermediate, and late stages of EAE; however, the titer was not disease activity-dependent, being low at the beginning and higher in the end, with the amount being similar during the acute and remission phases (135). Complement-mediated pathology/demyelination could be induced in EAE (180, 181) in line with findings of complement deposition in MOGAD autopsy material. In a constitutively MOG-IgG-producing transgenic mouse model, EAE could be induced in the absence of B cells but required T cells (182).

Experimental studies suggest that MOG-IgG mediates a pathogenic effect in EAE (181, 183, 184). It seems, however, that circulating MOG-IgG require the presence of complement, cytokines, and/or a (T cell-induced) inflammatory milieu to trigger demyelination/enhance inflammation via CDC/antibody mediated cellular cytotoxicity (ADCC), as alone, they are not able to do so (152, 185–187). It was shown in naive recipient animals that primary demyelination restricted to CNS nerve fibers could be induced via injection of a monoclonal MOG-IgG (the 8-18C5) into their cerebrospinal fluid. In adult Sprague-Dawley rats, an association between antibody titer and degree of demyelination could be demonstrated after infusion of sera from Hartley guinea pigs previously immunized with homologous spinal cord lysate in adjuvant into their subarachnoid space. The presence of MOG-IgG in injected sera was demonstrated via an anti-MOG ELISA (185). The direct translational value of these experiments seems tenuous as the blood-brain barrier (BBB) was circumvented in these experiments. The demyelinating effect of antibodies directed against MOG was also demonstrated in a Sprague-Dawley animal model in which monoclonal MOG-IgG-producing B cell hybridomas were implanted into the right lateral ventricle (188). MOG-IgG titers could not be linked to disease outcome in MOGAD patients to this date (189); however, a longitudinally persistent MOG-IgG positivity seems to be associated with a higher risk for relapse (190, 191). Furthermore, it was shown that children with monophasic ADEM lose MOG-IgG over time (192). This is mirrored in animals as high frequencies of relapses are associated with permanent damage. MOG-IgG injection was lethal when injected into SJL mice repeatedly challenged with passive MBP-specific T cell transfers (mimicking a relapsing disease course) that had not yet completely recovered from the previous relapse as opposed to no negative effect of the antibody if the disease score was zero (193). In another experiment with repeated passive transfer of T cells and subsequent antibody application, formation of large demyelinating lesions accompanied by lack of remyelination could be observed, with pronounced astrocytic scar formation traversed by "naked" axons, both characteristic of MS, and not described thus in the available MOGAD autopsy/biopsy cases (194). In mice engineered to produce high MOG-IgG titers, pathology could only be seen after immunization with MOG antigen, without regard to the genetically more (SJL) or less (C57BL/6) EAE-susceptible background (195). This is in line with experiments showing that B cells are not critical for the development of MOG-induced EAE (B cell-deficient muMT mice on C57BL/10 and DBA/1 genetic backgrounds and X-linked immunodeficiency (xid) mice on DBA/1 background) but contribute to the severity, i.e., demyelination rather than inflammation (196). However, the effect of the autoantibodies seems to differ regarding their enhancing characteristics of demyelination/inflammation depending on the agent EAE was induced with. Thus, MOG-specific T-cell-mediated inflammation can be enhanced via augmented antigen presentation (197), whereas in EAE induced by non-MOG-specific T-cells, demyelination is triggered but no enhancement of inflammation is observed (184).

4.3 Animal models targeting MBP

In the passive transfer EAE model (transfer of antigen-specific T cells propagated *in vitro*) with intravenous injection of MBP-specific T cells and subsequent intravenous (i.v.) MOG-IgG injection at the onset of the disease, a massive augmentation of clinical affection as well as primary demyelination could be observed in Lewis rats. Similarities to MOGAD include lesions located predominantly in the spinal cord and medulla oblongata at circumventricular organs (BBB is more transmissible at these points), predominantly mononuclear cell infiltrate with some granulocytes, perivascular, or focal confluent demyelinated lesion formation (75% of T cells infiltrate to the parenchyma), depending largely on the amount of injected T cells, extensive gliosis, preservation of axons, and remyelination of demyelinated lesions (20, 151, 198). There is a clear macrophage-dominated infiltrate seen in MBP EAE (macrophage: T cell ratio of approximately 6:1); in some cases of MOGAD histopathology, the amount of both cell types seems to be near to equal (1:1.2, respectively) (19), while in others, T cells seem to be somewhat outnumbered by macrophages, especially in the parenchyma [no ratios given, (13, 22)]. Furthermore, the relevance of complement involvement, in the form of membrane attack complex (MAC) formation as well as ADCC, was demonstrated in this model as well as MAC formation in PVG/c rats (±C6 complement component, immunized with guinea pig myelin basic protein (gpMBP) and Complete Freund's Adjuvants (CFA) containing *Mycobacterium tuberculosis* H37Ra) (199), which is in line with findings of complement deposition, to varying degrees, in MOGAD patients' biopsies/autopsies (200, 201).

Active EAE to MBP immunization has been induced in Lewis rats with subsequent MOG-IgG injection (MoAb 8-18C5) 10 days after sensitization. Antibody injection led to significant worsening of clinical and histopathological observations compared to the disease course without the addition of antibody (193, 202), granulocytic infiltrate, perivascular complement deposition, and inflammatory cuff formation, which could be observed similarly to histopathology found in MOGAD patients. The disease course after MBP immunization, with or without subsequent antibody

injection, was monophasic; progression or relapse was not recorded after an observation period of 13 weeks (193).

4.4 Animal models induced by MOG-specific T cells

In animals (Lewis rat) with passive MOG-EAE (T cells raised against the MOG_{35-55} peptide, with and without MOG-IgG transfer), however, inflammatory changes were induced in the spinal cord without producing an according clinical correlate of typical EAE symptoms (tail tonus loss, gait instability, and severe weight loss) (173, 203). The macrophage: T cell ratio was clearly shifted toward T cells (1:6, respectively), and a few cells (7–20%) of the inflammatory perivascular infiltrate left the perivascular space toward parenchymal infiltration. Contrary to all previously analyzed passive EAE models [induced with MBP, S100β, PLP nicely reviewed in (140, 204, 205)], no peripheral affection was noted. Severe blood-brain barrier dysfunction was induced by passive MOG-EAE and subsequent intravenous injection of a demyelinating MOG-specific monoclonal antibody that induced severe clinical disease. Furthermore, it has been shown that the location of lesions was dependent on the antigen used to raise the T cells (204).

4.5 Animal models induced by MOG peptide immunization

Immunization (active MOG-EAE) in Lewis rats via a highly purified recombinant protein, mMOG, spanning its N-terminal domain (a.a 1–125 + CFA) failed to activate immunodominant T cell epitopes, producing an inflammatory non-demyelinating phenotype as seen previously with passive transfer EAE (206). No clinical symptoms could be observed, at least partly attributable to reduced macrophage recruitment as compared to immunization with MBP/PLP protein/peptide (173). Antibodies to MOG_{1-25} were induced by mMOG immunization and production could be enhanced by repeated immunization (booster) after 4 weeks; however, this epitope does not seem to produce a demyelinating phenotype. Again, extensive perivascular and subpial demyelination could be produced by co-injection of the MOG-specific mAb 8-18C5 on day 10 post-immunization. Thus, immunization with mMOG seems to reproduce MOGAD histopathology rather poorly. Contrary to these findings, immunization with MOG isolated from human/rat brain tissue as well as immunization with MOG_{35-55} peptide were able to induce a severe relapsing-remitting disease course in Lewis rats presenting with inflammatory demyelinating lesions and perivascular cuffs (mononuclear, including myelin debris) with accompanying MOG specific IgG production (in the former) (207). Different rat strains (BN, DA, Lewis.1N, Lew1AV1, and Lew1A) were challenged with different MOG compositions [soluble or precipitated in complete or incomplete Freund's Adjuvants (CFA/IFA)] and varying immunization protocols (205). This study shows a very good reproduction of core MOGAD characteristics, more or less expressed depending on strain/regime/immunogen composition, in all the animals. These include the development of a chronic relapsing disease course in 111/156 animals, 16/156 developed chronic progressive disease, 17/156 showed stable course with neurological deficit. Development of predominant or selective ON was seen in some animals. Neuropathology (in 133/156 animals) featuring perivenous inflammation, confluent demyelinating plaques with complement deposition at sites of active demyelination, relative axonal sparing, inflammatory perivenous infiltrates, and meninges with parenchymal infiltration adjacent to the pia mater with predominant T cell/macrophage infiltration as well as polymorphonuclear infiltrates (mostly in animals with ON/spinal cord affection) and frequent remyelination. Of the observed pathology, glial scar formation is not readily found in current reports of MOGAD histopathology. Acute disseminated leukoencephalomyelitis was seen in the other 23 animals, which is about ∼15 of animals; in comparison, in human children ADEM occurs in >45% cases and in adults in ∼10%, featuring severe perivenous inflammation and little/absent demyelination. Major patterns of lesion distribution across the CNS (optic nerve/spinal cord, isolated ON, spinal type, cerebellar type, periventricular type, acute disseminated leukoencephalomyelitis type, and destructive transverse myelitis) go along well with lesion distribution seen in MOGAD (classified by these authors at that time as neuromyelitis optica). In this study, the authors showed that optic nerve involvement was independent of MHC genes; in addition, it was shown by others that MHC haplotype seems to influence disease susceptibility to a certain amount (174, 208). Differences in these models compared to MOGAD were seen in relation to sex-associated characteristics, specifically in DA rats. It could be observed that female rats had a high incidence of ON, whereas none was seen in male rats. In a study by the Mayo Clinic, the authors observed that of the 87 MOGAD patients presenting with ON, 57% were female (92). Another clear sex difference was seen in eosinophilic granulocyte infiltration, which was seen only in female rats; however, this phenomenon was not mentioned by any of the MOGAD autopsy/biopsy studies cited above. In a transgenic mouse study with MHC II-restricted animals, immunodominant MOG epitopes were identified and EAE could be induced (209). This is in line with findings that CD4+ T cells (HLA class II) dominate cell infiltrates in MOGAD patients' lesions. In a Dutch and UK study, no negative association of MOGAD to an HLA subtype could be discerned to date, whereas a Chinese study suggested an association of DQB1*05:02-DRB1*16:02 alleles to pediatric-onset MOGAD (210–212). Notably, to this date, no definite genetic association could be shown in MOGAD; specifically, no strong HLA dependence, which is in contrast to what has been suggested in MS (210–212).

One of the most widely used EAE animal models to date is the C57BL/6 mouse MOG_{35-55} EAE (213, 214). Similar to MOG-induced EAE in Lewis rats, injection with only MOG_{35-55} peptide (and CFA, with and without *pertussis toxin* PT) was able to induce neurological impairment in C57BL/6J mice featuring a chronic, non-remitting disease course and mild clinical presentation usually restricted to paralysis in the tail and hind legs. Mice did not

recover after immunization even after long-term observation (3 months), which, however, could not be observed in other studies (215). Lesions included perivascular infiltration of mononuclear cells and secondary demyelination. PT was observed to enhance EAE moderately and lead to earlier disease onset, however, PT is not needed to induce overt clinical disease *per se* (213).

It was shown in active C57BL/6 mouse MOG_{35-55} EAE (with CFA and PT) that natural killer cells (NK-cells) are involved in preventing EAE development, as Th1 response (including Th1 specific cytokine production, IFN-γ, and TNF-α) seemed to be elevated in NK-cell depleted animals (216). However, a reduced amount of NK-cells could only be seen in NMOSD but not MOGAD when compared to each other (217).

There have been some attempts to define the cytokine profile in patients with MOGAD (see above). In a study using actively induced MOG35-55-EAE in mice (induced with MOG35-55, CFA, PT) changes in cytokine production largely overlapping with MOGAD (IL-4, IL-6, IL-10, IL-12, IL-17, IL-23, TNF-α, IFN-γ and TGF-β) were observed (218). In EAE, the involvement of IL-6 has been extensively studied. It has been shown that IL-6 (conditionally) deficient mice are resistant to EAE (219–221), that IL-6 is involved in the induction phase of EAE (222) (MOG_{35-55} induced), that IL-6 inhibits T cell conversion to the Treg phenotype (Foxp3+) (223), and is (224, 225) or is not (223) involved in conversion to Th17 type T cells. It has been shown that tissue damage occurs preferentially at sites of IL-6 production (226, 227) and that induced antibodies against IL-6 are protective against EAE (228). Interestingly, PT which is often used to enhance EAE has been shown to induce IL-6 (229). In a mouse line deficient in the IL-6 gene (129/SvXC57BL/6), immunization with MOG_{35-55} peptide showed abrogated EAE induction (230). These findings are in line with the seemingly beneficial effect of Tocilizumab/Satralizumab (recombinant, monoclonal antil-IL6 receptor antibodies) on relapse prevention in MOGAD patients (231–236). IL-23 involvement was shown in EAE induction (237), as well as the development of Th1 and Th17 cells (238–240) but is not necessary in the effector phase of the disease.

It was demonstrated in different rodent animal models that IL-10 is involved in EAE via increased disease severity when deleted, and IL-10 contributed to disease course duration (shorter) and recovery (241, 242). In a passive transfer EAE with anti-MOG T cells into MyD88 animals, it was shown that resistance to EAE was mediated via the secretion of IL-10 by recipient T cells (243). Further, it was shown that immunization with MOG_{35-55} in susceptible (SJL and NOD) vs. resistant strains (B10.S or III) differed in the amount of cytokines produced, resistant strains secreting primarily IL-4/IL-10 and transforming growth factor (TGF)-β, vs. susceptible strains with predominant IFN-γ production (244). In contrast, 129/Sv mice knocked out for the gene coding for the ligand-binding chain of the IFN-γ receptor developed severe EAE (129/Sv are resistant to MOG-induced EAE), indicating that IFN-γ was involved in ameliorating EAE during both the effector and induction phase (245, 246). IFN-γ involvement in the determination of lesion location was shown in passive MOG-EAE induced in C57BL/6 mice lacking the IFN-γ receptor (IFNγR) (247) and it was shown that CFA/PT alone do not induce IFN-γ production, but immunization together with MOG is necessary (248).

The above-described patient cytokine profile points toward the direction of TH17 involvement (IL-17A, IL-23, IL-6, and IL-21) in the pathogenesis/disease course of MOGAD (249). The involvement of Th17 T cell subsets has been under discussion since their discovery in 2005 (250, 251), allocating a role for them in EAE induction/autoimmunity (252–256) or not (257) in different MOG-induced animal models [reviewed elsewhere (249)], going so far as to implicating the intestinal microbiome to EAE resistance of mice deficient in IL-17A and IL-17F (258). In a passive transfer model with MOG-specific T cells derived from 2D2 mice, it was shown that both Th1/Th17 cells are able to induce EAE; however, Th17 induce an atypical phenotype in half the cases (beginning with ataxia instead of paralysis, only developing paralysis later). Interestingly, histopathology [severe immune cells infiltration (CD4+ T cells and macrophages), astrogliosis, microglia activation, demyelination, and axonal damage] as well as lesion location (throughout the CNS as well as inflammatory infiltrates/demyelination in the PNS) were similar in both Th1 and Th17 recipients (259). A higher frequency of ataxia was found in children with ADEM positive for MOG-IgG compared to MOG-IgG negative cases (60). No involvement of IL-5 could be detected in the initiation or effector phases after immunization of C57BL/6J (or $IL5^{-/-}$) mice with MOG_{35-55} (260). Likewise, IL-21 was found irrelevant for Th17 induction (261).

Cerebral cortical encephalitis is one of the core clinical demyelinating events suggested by Banwell et al. in the diagnostic criteria for MOGAD (12). Current models of EAE do not reflect cortical demyelination ideally. One model trying to recapitulate these lesions targeted the cerebral cortex by stereotactical injection of pro-inflammatory mediators into Lewis rats challenged with MOG_{1-125} (262). Inflammatory, demyelinating lesions were induced including complement deposition, and as seen in MOGAD autopsy cases, ready remyelination was observed. In a model of Dark Agouti rats immunized with MOG, inflammatory agents were injected into the subarachnoidal space to avoid parenchymal damage. Here as well, IgG and complement deposition were observed, the amount of inflammatory infiltrate was little and mostly limited to meninges, and as in the model described by Merkler et al., repair was rapid (263).

4.6 Transgenic animal models

There is a wealth of genetically modified/transgenic/humanized animal models that have been reviewed in more detail elsewhere (264–266). We will discuss some of those models in this review in regard to their similarities as models for MOGAD. In MOG_{35-55}-induced active EAE in non-obese diabetic (NOD) mice, some groups showed that a switch from relapsing-remitting (RRMS) to secondary progressive (SPMS) can be induced and this model is considered to reflect the pathology of SPMS well (267, 268). Other groups could not observe the switch of clinical symptoms to a progressive disease course (269). When disease was induced in NOD mice via immunization with MOG_{35-55} and CFA/PT, inflammatory/demyelinating lesions developed preferentially in

brain white matter (fimbria/internal capsule) and also in the spinal cord with macrophage infiltration. Microglia/astrocyte activation could be observed (268). Interestingly, disease development and progression could be prevented via anti-IL-12 antibodies in this model (270). NOD mice with transgenic TCR recognizing MOG_{35-55} were generated (1C6 TCR) (267) and showed development of spontaneous optic neuritis/EAE in around 1% of the animals, distributed similarly in both male and female animals. Upon passive transfer EAE, these mice developed preferentially spinal cord lesions and optic neuritis. When immunized with MOG_{35-55} and CFA, these mice developed chronic disease after the second relapse with CD4+ T cells predominating over CD8+ T cells at a ratio of 30:1 in the lesions, with elevated production of IFN-γ and IL-17. In following experiments, 1C6 TCR mice were crossed with Ig heavy-chain knock-in mice (IgH^{MOG} or Th mice) on a C57BL/6 background (195). IgH^{MOG} mice harbor autoreactive B cells producing anti-MOG antibodies with the heavy chain of the 8.18C5 demyelinating MOG-specific antibody; however, they do not develop spontaneous disease but were shown to both accelerate and exacerbate EAE irrespective of the inducing agent. The frequency of spontaneous disease was higher in 1C6 x IgH^{MOG} mice (45% males, 79% females), CD4+ T cells still outnumbering CD8+ T cells 7:1, the amount of CD8+ T cells, however, being higher compared to 1C6 TCR mice. Lesions were located mostly in the spinal cord, with around 40% of the mice showing optic nerve lesions, and no formation of ectopic follicle-like structures was observed in the CNS of the animals. A large part (75%) of asymptomatic 1C6 × IgH^{MOG} animals showed exclusively cerebellar lesions upon histopathological examination.

Also, in the Biozzi EAE model (271), chronic relapsing disease could be induced via subcutaneous injection at days 0 and 7 in both hind flanks with an emulsion spinal cord homogenate and CFA complemented with *M. Butyricum*. In these animals partial closing of the BBB, meningeal ectopic lymphoid tissue with adjacent subpial demyelinating lesions and a switch from T cell to B cell predominance and serum MOG-IgG generation in later chronic disease stages could be observed (272).

Another study in a transgenic mouse model, GFAPγR1Δ, induced EAE by active immunization with MOG_{35-55} to gain a progressive phenotype with sustained inflammation and increasing clinical disease. This study suggests that tumor necrosis factor (TNF) is predominantly produced by CNS infiltrating macrophages rather than microglia after the acute disease stage (273). Contrary to promising preclinical results of TNF blockade, however, the success of TNF suppression in MS patients did not yield uniformly positive results (274). For MOGAD in relation to TNF treatment, little is known and data from a small retrospective study (n = 5) is inconclusive regarding negative effects, and no clear positive outcome is documented (275). Primary progressive-EAE (PP-EAE) was further established in A.SW mice sensitized with MOG_{92-106} and SJL/J mice sensitized with MOG_{92-106} and curdlan (276). A.SW mice develop large areas of demyelination, immunoglobulin deposition, and neutrophil infiltration in the absence of a T cell infiltrate (14, 16) while SJL mice show T cell infiltration and paralysis. Both models generated an anti-MOG antibody response (276).

Another model is the "genetic 2D2" EAE model (TCR^{MOG}) in which mice were generated with a TCR that is directed against MOG_{35-55} (with a C57BL/6 background), about 5% of the animals develop EAE spontaneously with inflammatory/demyelinating lesions in brain, spinal cord, and optic nerves (277). Furthermore, a large proportion of non-clinically symptomatic mice showed ocular abnormalities, and around 15% of the 2D2 transgenic mice developed isolated optic neuritis in the absence of clinical/histological signs of EAE. These lesions showed macrophage infiltration, demyelination, and axonal damage. Interestingly, the challenge with PT alone was sufficient to induce clinical EAE in 39% and histological EAE in 56% of 2D2 mice. The GF-IL23 model, with astrocyte-specific IL-23 secretion on a 2D2 background (most CD4+ have TCR specific for MOG_{35-55}), showed a spontaneous EAE induction with chronic disease course, clinical affection (ataxia/paraparesis), and a high proportion of B cells. A pronounced B cell accumulation and B cell follicle-like infiltrates have not been reported as such in MOGAD yet (160).

To generate double transgenic opticospinal EAE (OSE) mice (277–280), 2D2 mice were then crossed with IgH^{MOG} (with a transgenic B cell receptor to MOG, described above). The offspring of these mice spontaneously develop ON and severe inflammatory spinal cord lesions, whereas the brain remains relatively spared, which is very similar to NMOSD/MOGAD disease in humans. A gene expression profiling study sought to discern whether spontaneous OSE or MOG-induced EAE reproduced the genetic contribution to MS pathogenesis more closely, and concluded that the OSE model is probably linked more closely to human MS risk genes due to differentially higher expressed Th1 genes (281). A thorough gene expression profile for MOGAD still needs to be generated; however, the cytokine profile (see above) is rather indicative of a predominant Th17 response in MOGAD, which needs to be verified.

It has been suggested that most axonal damage in MOGAD happens during the initial attack, measuring neuroinflammatory biomarkers (such as MBP, sNFL, GFAP, and Tau), and relapses are associated with increased myelin damage (282). It has been suggested that antineurofascin antibodies contribute to axonal pathology in a passive transfer MOG-EAE model (283). It has been shown in double-transgenic OSE mice that when MOG is knocked out, the autoimmune response of MOG TCR-specific T cells is redirected toward the medium-sized neurofilament (NF-M) (278). Subsequently, the same group was able to demonstrate that due to inefficient exposure to two self-antigens, these bi-specific T cells managed to escape tolerization (284). Interestingly, there are only few reports of MOG-IgG/AQP4-IgG double positivity in MOGAD/NMOSD patients (285–287), and peripheral involvement in MOGAD is rarely reported (288).

The major drawback of TCR transgenic 2D2 mice and double transgenic OSE mice is that there is no complement deposition or granulocyte recruitment present (277, 279). Several humanized models have been established (265). It was shown in a transgenic mouse line that was generated to express human fragment crystallizable gamma receptors (hFcgRs) that recognize Immunoglobulin G antibodies, nicely reviewed in (289), that FcgRs but not complement activation contribute to EAE and that the

exacerbation is dependent on MOG recognition by the human-derived antibodies (290). However, it is unclear which disease should be mimicked with this model, as it was shown that MS does not harbor anti-MOG autoantibodies and MOGAD probably has a complement-activating component driving lesion formation (13, 35) although the extent of complement involvement in human pathology is under debate.

Other transgenic mouse models investigated the relevance of IL-6, TH17 cells, oligodendrocytes, Nrf2, and CXCR3 (225, 227, 240, 291–293). The presence of MOG-IgG in MOGAD patients suggests B cell involvement that could be mirrored in several EAE models (294–297). SJL/J mice expressing a MOG_{92-106}-specific transgenic TCR^{1640} with high frequency (99% proportion of transgenic $V\alpha8.3^+/V\beta4^+CD4^+$ T cells) spontaneously produced pathogenic MOG-specific IgG1 antibodies (162).

4.7 MOG induced EAE in non-human primates

Different EAE models in monkeys have been reviewed elsewhere (298–300). EAE models developed in the rhesus macaque (*Macaca mulatta*) and the cynomolgus monkey (*Macaca fascicularis*) tend to replicate acute disseminated (leuko)encephalomyelitis well (301). In all, the non-human primates (NHP) disease course varies with a more acute/relapsing or chronic disease course depending on the adjuvant used, complete or incomplete Freund's Adjuvants, respectively.

In the common marmoset monkey (*Callithrix jacchus*), extensive cortical demyelination could be induced upon immunization with $rMOG_{1-125}$ and CFA (302). Lesions were dominated by macrophage/microglia activation and T cell infiltration (mostly perivascular) with few B cells, the cellular infiltrate was generally lower than in the parenchyma. Furthermore, IgG infiltration and complement deposition were observed. No subpial demyelination could be observed which is in contrast to patients with MOGAD, as well as in another study that observed subpial lesions in all experimental animals (303). Another study with marmoset monkeys immunized with $rMOG_{1-125}$ and CFA found inflammatory lesions in cerebral white matter with some animals being affected in the spinal cord and optic nerve. Lesion composition was similar to activated macrophages/microglia, T cell infiltrate, few B cells, IgG and complement deposition, and large confluent demyelinating lesions with some perivascular preference. The authors mentioned some axonal damage and indications for early remyelination (304). The encephalitogenic epitope inducing EAE in marmosets in mixed human myelin and CFA-induced immunization was shown to be MOG_{14-36} and not MBP (305); however, it could be shown that EAE could also be induced with myelin (from both WT and $MOG^{-/-}$ C57BL/6 mice) but severity/disease progression was dependent on the presence of MOG-IgG (306). IL17-A production was found to be elevated compared to IFN-γ when marmoset monkeys were challenged with synthetic MOG_{34-56} peptide alone (307), which is in line with the cytokine profile suggested in MOGAD; however, although treatment with an anti-IL17-A antibody delayed onset of EAE, it did not abrogate its development (308). Another study found elevated levels of IL-6, G-CSF, IL-8, and IFN- γ in cynomolgus macaques immunized with rhMOG and IFA which was similar to CSF analyzed from children with acquired autoimmune disease positive for anti-MOG antibodies who had elevated levels of IL-6 and G-CSF (309).

4.8 Infection-induced animal models—Are they relevant models for MOGAD?

MOGAD has been associated with preceding infection or vaccination (310, 311) in ∼20% of cases although a causal relationship to any specific agent has not been discerned yet. Recently, cases of MOGAD after infection or vaccination with COVID-19 vaccines (both mRNA and vector-based) were reported, some with detectable persistent long-term MOG-IgG (311–323). Different types of coronaviruses have been used extensively to induce EAE, resembling different aspects of MS/MOGAD in different species over the last six to seven decades to just give a few examples (205, 324–329). Biphasic disease with a short fulminant acute phase and a 1-month long chronic phase characterized by ongoing inflammatory demyelination can develop in mice infected with Theiler's murine encephalomyelitis virus (TMEV), which is not the case in all species (330–332). Similar to MOGAD, TMEV infection in mice features perivascular immune cell infiltrates, leptomeningeal and white matter mononuclear cell infiltrates in the spinal cord, and primary demyelination around day 15 after viral intracerebral inoculation (333–336). Spontaneously occurring ADEM-like disease could be observed in a Japanese macaque (JM) colony at the Oregon National Primate Research Center (ONPRC) that has been linked to infection by a gamma-herpesvirus, JM rhadinovirus (JMRV) (337). A case report from Japan with high titer MOG-IgG links influenza-A infection to longitudinally extensive TM (338).

Besides *M. tuberculosis* (339) and Pertussis toxin (induces IL-6 and reduces Treg compartment) (340) that are usually used for immune stimulation to induce EAE in mice, other infectious agents have been used prior or post-immunization with MOG_{33-35} like SEB (341) or LPS (342), exacerbation of MOG-induced EAE by intraperitoneal injections of a viral mimetic, polyinosinic-polycytidylic acid (PIC) (343), Cytomegalovirus infection (344) which induces susceptibility to EAE in resistant BALB/c mice (345), Influenza virus infection (346) by enhanced type I T cell infiltration. 2′-5′ oligoadenylate synthetase-like 1 (OASL1) deficient ($Oasl1^{-/-}$) mice are resistant to viral infections, as OASL1 specifically inhibits the translation of interferon regulatory factor 7 (IRF7), the master transcription factor for interferon-1 (IFN-I). Thus, IFN-I production is negatively regulated upon viral infection and ($Oasl1^{-/-}$) mice seem to have an enhanced resistance toward MOG-induced EAE (347). Protective effects toward EAE were also shown in a model of sepsis (348) and some malaria strains (349). Interestingly, it could be seen in a study by Nourbakhsh et al. that predominantly children seronegative for EBV presented with MOG-IgG (44%) compared to only 5.5% MOG+ in EBV+ children (350); likewise, no correlation between MOG+/EBNA+ was found in children in another study (351), suggesting that if infectious agents were involved/associated in

the development of both diseases, they would be distinct. Cases linking LETM to *M. tuberculosis* infection have been reported (352, 353). Molecular mimicry between MOG_{18-32} and Semliki Forest Virus (SFV) could be demonstrated after demyelination-inducing immunization of C57Bl6/J mice (354). Infection with *S. pneumoniae* was shown to upregulate IL-6 and TNF-α in mice immunized with MOG_{35-55} (355).

In several animal models [Brown Norway rats challenged with MOG (356), rats challenged with replication-deficient adenovirus vector carrying IL-1β cDNA (AdIL-1β) (357)] a beneficial effect on EAE outcome was demonstrated with IFN beta-1a. It was also demonstrated in a mouse model (TMEV-infected SJL/J mice) that a shorter duration of treatment was associated with remyelination, whereas long-term treatment seemingly promoted demyelination (358).

5 Preclinical imaging in MOGAD animal models

Many clinical imaging methods can be applied to preclinical research in animal models with minimal adaptations. Additional methods beyond what is possible in clinical research allow imaging with higher up to single-cell resolution and better labeling of key players in pathophysiological processes. There are several applications for preclinical imaging: Firstly, comparing imaging features between MOGAD and its potential animal models can be used to validate the model's suitability. Secondly, imaging can be useful in traditional animal research investigating disease cause and pathophysiology by allowing longitudinal high-resolution analyses and the definition of time points based on imaging features, thereby reducing the number of needed animals. Thirdly, it can aid image marker development: New imaging methods can be tested in animal models for potential clinical application, especially regarding their safety, sensitivity, and correlation with histological features. When clinically established imaging methods are used to describe new distinct features in a disease, assumptions are often made about their pathophysiological origin. By back-translating these imaging methods and findings into an animal model, these assumptions can be tested using histology or molecular analyses. Finally, during drug development and testing, translatable methods can be extremely useful since future clinical trial endpoints can already be tested early on.

5.1 Brain and brainstem

As described above, actively induced MOG_{35-55}-EAE (induced by MOG_{35-55}, CFA, and PT) only has a low affection of the brainstem and cerebellum and mostly absent inflammation and tissue damage in the forebrain. Although this picture closely resembles the brain involvement of many MOGAD patients, it limits the use of this model for the investigation of MOGAD brain lesions. Using T1-weighted imaging with contrast enhancement, the brain involvement in $2D2^{+}$ mice was also shown to be little or non-existent (359). Only actively induced MOG_{35-55}-EAE (induced by MOG_{35-55}, CFA, and PT) in non-obese diabetic (NOD) mice, a model with relapsing-remitting disease course, leads to MRI gadolinium-enhanced lesions in T1-weighted imaging, located in corpus callosum, fimbria, and internal capsule (268). Although promising, this lesion pattern is more in line with MS pathology. In common marmoset monkeys, MOG_{1-125}-induced EAE causes small T2 hyperintensities within the white matter with histopathologically confirmed demyelination, which can subsequently develop into expanding confluent lesions. This model might be suitable to model MOG-IgG seropositive ADEM, but further confirmatory research is warranted (268, 360).

Absent microstructural brain damage in actively induced MOG_{35-55}-EAE in C57BL/6 mice (induced by MOG_{35-55}, CFA, and PT) was confirmed by a DTI study, which did not detect differences in DTI parameters of anterior commissure, corpus callosum, cerebral peduncle, and external capsule between MOG_{35-55}-EAE and controls (361). Similarly, the application of magnetization transfer ratio (MTR), which is suggested to be a sensitive method to detect demyelination, did not find any changes in actively induced MOG_{1-125}-EAE in C57BL/6 mice (induced by MOG_{1-125}, CFA, and PT) in line with absent histopathological findings, which is in contrast to results in monkeys described above (362). No in-depth diffusion-weighted MR studies in people with MOGAD exist yet. Lesion load, volumetric analyses, and diffusion-weighted imaging have also been applied in the preclinical testing of new and established therapeutic agents (363–366). Although easily translatable into clinical research, one has to be aware that preclinical MRI markers are not well-validated in distinct models so far.

However, some clinical imaging features of MOGAD patients can be reproduced: using serial post-contrast FLAIR (*fluid-attenuated inversion recovery)* sequences after gadolinium administration in actively induced MOG_{35-55}-EAE (induced by MOG_{35-55}, CFA, and PT) in C57BL/6 mice, Pol and colleagues showed leptomeningeal contrast enhancement in all mice that decreased during the chronic stage and correlated with the leptomeningeal invasion of macrophages as well as T- and B-cells in histology, which elucidates the leptomeningeal enhancement described in many MOGAD patients (367). Furthermore, two studies investigated the use of superparamagnetic iron oxide-enhanced MRI in MOG-EAE rats, which were actively induced by recombinant human MOG in 1AV1 congenic Lewis rats, and showed a demarcation of lesions in the cerebellum, brainstem, and periventricular regions, which were corresponding to lesional iron-laden macrophages in histology, suggesting that superparamagnetic iron oxide-enhanced MRI might be useful for the detection and demarcation of inflammatory CNS lesions (368, 369).

In the process of developing new imaging methods, preclinical research can help to establish the pathophysiological grounds. Especially when developing methods with potential side effects for patients, such as testing new positron emission tomography (PET) tracers, prior extensive preclinical research is warranted. In the CNS, translocator protein (TSPO) is thought to be mainly expressed in activated microglia cells, and TSPO ligands have been used to detect inflammatory CNS processes. Widespread accumulation of two different TSPO ligands was shown in actively induced MOG_{35-55}-EAE in C57BL/6 mice (induced by MOG_{35-55},

CFA, and PT) with and without additional cuprizone treatment including the spinal cord, cerebellum, cortex, striatum, and hippocampus (370, 371). Neuropathological analyses confirmed microglial activation and were correlated with tracer uptake, thereby validating the method. In a similar approach, tracers for CD19 and the cystine/glutamate antiporter were validated in actively induced MOG-based animal models in C57BL/6 mice (Hoehne et al.: MOG_{35-55}, CFA, PT, Stevens et al.: MOG_{1-125}, CFA, PT) (372, 373). Fluorinated molecules might be another promising and non-toxic option for MR-detectable tracers to study neuroinflammation in the near future (374–378).

Going one step further, preclinical research allows more invasive imaging approaches with up to single-cell resolution such as real-time confocal imaging and two-photon excitation microscopy. The latter uses the simultaneous non-linear excitation by two photons of fluorophores to report on the sequential order and interaction of different key players during a pathological process. Particularly interesting is the application in adoptive transfer models using autofluorescent lymphocytes, which can then be tracked longitudinally throughout the disease. By transferring MOG-sensitized lymphocytes isolated from green fluorescent protein (GFP)-transgenic mice to C57BL/6 mice, Yura et al. were able to track widespread invasion of these GFP-labeled CD4+ in the brain and spinal cord using confocal imaging and detected nearly exclusive production of T helper cell type 1 using real-time PCR (379). In a different approach, Siffrin and colleagues used the actively induced MOG_{35-55}-EAE model (induced by MOG_{35-55}, CFA, and PT) in mice with enhanced GFP (eGFP) expression in neurons and neuronal processes and red fluorescent protein in bone marrow-derived peripheral immune cells, as well as adoptive transfer models (stimulation performed with MOG_{35-55}), to investigate neuron-immune cell interaction and to show that Th17 cells induce early neuronal damage (380).

5.2 Spinal cord

So far, only a few studies implemented preclinical spinal cord MRI: T1-weighted imaging with contrast enhancement was used to characterize spinal cord involvement in $2D2^+$ mice showing enhancement in half of the mice that correlated with histologically confirmed immune cell infiltration (359). Employing *in vivo* lumbar DTI, axial and radial diffusivity changes in line with microstructural axonal and myelin pathology in the spinal cord, respectively, have been shown in actively induced MOG_{35-55}-EAE in C57BL/6 mice (induced by MOG_{35-55}, CFA, only) and in an adoptive transfer model of MOG-reactive TH1 cells in C57BL/6 mice (stimulated with MOG_{35-55}) (381, 382). In both models, exploratory treatments were suggested to improve DTI parameters toward control values, pointing toward a relative sensitivity of these metrics.

Spinal cord MRI has also been performed in two studies *ex vivo* post-fixation, potentially limiting morphometric analyses (383). Derdelinckx and colleagues treated actively induced MOG_{35-55}-EAE in C57BL/6 mice (induced by MOG_{35-55}, CFA, and PT) with myelin antigen-presenting tolerogenic dendritic cells and observed a stabilized EAE disability score and an inhibited T cell response (32). In this study, *ex vivo* gadolinium-enhanced spinal cord MRI was implemented post-fixation to confirm a reduced lesion load after treatment and to localize lesional and non-lesional tissue for histological analyses (32). Cahill and colleagues developed a new $PPAR\alpha^{mut/WT}$ $2D2^+$ animal model with a mild relapsing-remitting disease course and increasing hind limb clasping during the disease process (384). Apart from histological analyses showing T cell and microglial activation as well as axonal and myelin damage at several locations in the brain, brainstem, spinal cord, and optic nerve, they also applied *ex vivo* post-fixation MRI analyses after 9 months to confirm spinal cord atrophy compared with $2D2^-$ littermates (384). Neither study generated imaging data that can easily be transferred/translated into clinical application.

In one recent study using advanced preclinical imaging, two-photon excitation microscopy was applied to the spinal cord in actively induced MOG_{35-55}-EAE (induced by MOG_{35-55}-EAE, CFA and PT) for the first time: Steudler et al. used *ODCmitoGFP-Tomato* mice, which have GFP-labeled mitochondria in tdTomato-labeled oligodendrocytes (385). They applied two-photon excitation microscopy to reveal the complex evolution of the mitochondrial redox state with increased and decreased oxidation at the preclinical and chronic stages, respectively, suggesting an early involvement of oligodendrocyte mitochondria in the inflammatory process in EAE (385).

5.3 Retina and optic nerve

Many techniques investigating the visual system in patients can directly be translated to their application in animals with only minimal technical adaptations, for example, to correct for differences in refraction. When back-translating OCT imaging to rodents, the inner retinal layer (IRL) is usually quantified, instead of separating pRNFL and GCIPL, due to the lower retinal neuroaxonal content and lower resolution in mice. Cruz-Herranz et al. performed comparative OCT in different neuroinflammatory mouse models: Actively induced MOG_{35-55}-EAE (induced by MOG_{35-55}, CFA, and PT) in C57BL/6 mice led to severe thickening of the IRL with subsequent thinning; a 32% retinal ganglion cell loss within 120 days (54% in 9 months) and T cell and microglia invasion were later confirmed by histopathology (386). In contrast, actively induced MBP-EAE (induced by MBP, CFA, and PT) led to a much milder disease course with stable IRL measurements and no retinal ganglion cell loss. Active MOG_{35-55} -EAE induction in TCR^{2D2} mice (induced by MOG_{35-55}, CFA, and PT) led to an earlier IRL thinning without edema, yet the extent (49% within 120 days) was nearly comparable with C57BL/6 mice after MOG_{35-55} -EAE induction (386). Uninduced TCR^{2D2} mice also underwent IRL thinning and thereby neurodegeneration within a 120-day period suggesting an underlying process in the mouse line (386). In a similar fashion, actively induced $PLP_{139-151}$-EAE in SJL/J mice (induced by $PLP_{139-151}$, CFA, and PT) led to IRL atrophy, yet wild-type uninduced SJL/J mice also showed IRL thinning (386). This is most likely due to a homozygous $Pde6b^{rd1}$ mutation for retinopathy these mice carry (386). In marmoset monkeys actively induced with MOG_{1-125}-EAE (induced by recombinant rat MOG_{1-125} and CFA), only 50% have an ON at all (387).

Taken together, Cruz-Herranz and other independent studies imply a strong resemblance of actively induced MOG_{35-55}-EAE in C57BL/6 with adult MOGAD-ON, describing features such as early edema and severe neuroaxonal loss over an extended period after ON, while other models might closer resemble the milder course in MS-ON (386).

Actively induced MOG-EAE models gained further stand as a MOGAD model by a recent study confirming bilateral ON in 70% of MOG_{1-125}-EAE in Brown Norway (BN) rats (induced by MOG_{1-125}, CFA only) using visually evoked potentials (VEPs) (388). In Dark Agouti rats actively induced with MOG_{1-125}-EAE (induced by MOG_{1-125}, CFA only), a VEP latency delay could be observed even before first motor deficits were present, i.e., during an inflammatory state, demyelination and axonal loss were observed at later disease stages (389). Severe ON was caused in Brown Norway (BN) rats actively induced with the same model (390). Induced apoptosis of retinal ganglion cells (RGCs) in this model in BN rats could be seen as independent of optic nerve involvement (391). Two additional studies employing OCT and histopathology measured early, inflammation-preceding, RNFL thickness reduction in this actively induced MOG_{1-125}-EAE model in BN rats (induced by MOG_{1-125}, CFA only) (392, 393), respectively. Later, an increase in oligodendrocyte alphaB-crystallin, a heat-shock protein induced by cellular stress, was observed during the preclinical stages, particularly in the optic nerve head in this actively induced MOG_{1-125}-EAE model in BN rats (induced by MOG_{1-125}, CFA only) (394). This is in line with measurements gained in an MS study (395, 396). Contrary to these observations, RGC loss induced in C57/B6 mice by actively induced MOG_{35-55} –EAE (induced by MOG_{35-55}, CFA, and PT) occurred only in late stages of the disease (post-immunization day 42), whereas CD4+Tcell infiltration, demyelination, microglial, and astrocyte activation were induced in the optic nerve by PID 16 (397). Further late events include degeneration of retinal neurites and synapses as well as glial cell activation in the inner retina. Similarly, in actively induced $PLP_{139-151}$-EAE in SJL/J mice (induced by $PLP_{139-151}$, CFA, and PT), RGC loss was detected by PID14, which in this model was however after cell infiltrates had been detected in the optic nerve around PID 9, pointing toward inflammation preceding RGC loss in this model (398).

As a potentially promising development for pediatric MOGAD-ON, the OSE model shows good results: OCT in OSE mice with spontaneous encephalomyelitis starting on day 26 after birth showed retinal neurodegeneration, which was confirmed by histopathology as 38% loss at 6 weeks of age (399). The functional relevance of RGC loss was confirmed by electroretinogram (ERG) (399).

Due to the close correlation between structural and functional metrics, multimodal assessment including OCT and functional assessments is common in rodents. Functional metrics back-translated from clinical applications include ERGs and VEPs, usually performed as flash-VEP. As a metric for vision in mice, the optomotor response (OMR) is assessed, which quantifies the compensatory head movement when the mouse is exposed to a moving light-dark pattern. Despite being the current gold standard for vision in mice, the OMR was critiqued for (A) the interference of vision and motor function, (B) the overlay with the optokinetic response, and (C) the inability to depict the (retina–lateral geniculate nucleus—primary visual cortex)-pathway usually associated with vision in humans. Outputs of VEP, ERG, and OMR have been shown to correlate very well with the neuroaxonal content measured by OCT and by histopathology, for example, in actively induced MOG_{35-55}-EAE in mice (induced with MOG_{35-55}, CFA, and PT) (400, 401).

Applying visual outcome parameters in animal research currently serves two major purposes: Firstly, we can use animal models to better understand the pathophysiological basis of our functional metrics. Recently, VEP became an outcome parameter for myelin in clinical trials investigating potentially remyelinating agents. Although the measurement of conduction speed seems like a feasible metric for myelin, the pathophysiological basis of this assumption was never validated and the sensitivity of VEPs for myelin content was never shown. Using different demyelinating animal models including actively induced MOG_{35-55}-EAE in C57BL/6J mice (induced with MOG_{35-55}, CFA, PT), Cordano and colleagues now demonstrated that quantitative measurements of myelination and remyelination correspond well with VEP latency, thereby validating it as a tool (402). This VEP change also correlates well with the dysregulation of potassium channels around the nodes of Ranvier as shown during inflammatory demyelination in actively induced MOG_{35-55}–EAE (induced by MOG_{35-55}, CFA, and PT) (403, 404). So far, only one VEP study has been performed in actively induced MOG_{1-125}-EAE in marmoset monkeys (induced by rat recombinant MOG_{1-125}, CFA only). Unfortunately, this study only reports a loss of amplitudes in line with neurodegeneration in the later course of the disease but does not report potential latency delays (405).

Secondly, functional outcome parameters can be used in animal research to show functional relevance very early in the development and testing of new therapeutic agents. The visual system is especially suitable for early drug testing for neuroprotective agents due to the clear association of one localized lesion in the optic nerve with subsequent neurodegeneration in the retina and functional decline (406–411). A single study also used the rodent visual system in actively induced MOG_{35-55}-EAE transgenic mice backcrossed to a C57BL/6 background (induced with MOG_{35-55}, CFA, and PT) to investigate the functional effects of remyelinating with the agent chloroindazole using VEP and ERG, yet the structure-function correlation was less robust (412). The only study so far using the rodent visual system in actively induced MOG_{35-55}-EAE in mice (induced with MOG_{35-55}, CFA, PT) to investigate the effects of anti-inflammatory treatment with anti-IL-17 antibodies showed that retinal neurodegeneration as measured by OCT, but not motor symptoms, was completely prevented by neutralizing IL-17 (413). This is particularly interesting since MOGAD patients were shown to have more IL-17-positive central memory cells than healthy controls with a particular increase in IL-17-positive IFN- γ positive central memory cells during relapses, again suggesting important parallels between MOG-EAE and MOGAD (282).

Optic nerve MRI using T_1- and T_2-weighted imaging has been validated in actively induced MOG_{35-55}-EAE in C57Bl/6 mice (induced with MOG_{35-55}, CFA, and PT) but sparsely performed (414). Qi et al. were able to establish volumetric optic nerve analysis using T1-weighted 3D 4.7-tesla MRI (415). As suggested

from clinical experience, they were able to show significant optic nerve swelling and subsequent volume loss in an EAE model induced by CFA and homologous spinal cord emulsion. Reducing mitochondrial reactive oxygen stress by increasing SOD2 gene expression using virally mediated gene transfer led to less edema and prevented significant volume loss, which the analysis was sensitive enough to detect (415). The involvement of the optic nerve, optic tract, and chiasm was also shown for $2D2^{+}$ mice by contrast-enhanced T1-weighted imaging.

Interestingly, DTI has been applied to the visual system in rodents but not yet specifically in MOGAD patients. Manogaran et al. performed a multimodal study including OCT, T2-weighted imaging, and DTI in actively induced MOG_{35-55}–EAE in C57BL/6J mice (induced by MOG_{35-55}, CFA, and PT). They confirmed signal increase around the optic nerve in T2-weighted MRI in line with significant inflammation. DTI showed a decrease in axial diffusivity and an increase in radial diffusivity in the optic nerve and optic tract compared with controls. These changes were correlated with neuroaxonal parameters from OCT (416). DTI changes were confirmed by other independent studies in actively induced MOG_{35-55}–EAE (induced by MOG_{35-55}, CFA, and PT) (361, 417). A newer diffusion MRI approach called diffusion basis spectrum imaging (DBSI) was specifically developed to separate axonal and inflammatory pathologies. In its first application in actively induced MOG-EAE in C57BL/6J mice (induced by unspecified MOG peptide, CFA, and PT), the DBSI data suggest that axonal loss in ON occurs early and in parallel to the optic nerve edema (417). The application of DTI to the visual system in people with MOGAD is still pending.

The possibilities of retinal imaging in rodents exceed the options in clinical research. One example is confocal scanning laser ophthalmoscopy (CSLO), which is a non-invasive technique for real-time imaging of autofluorescent targets in the retina. In actively induced MOG_{35-55}–EAE (induced by MOG_{35-55}, CFA, and PT), CSLO has been applied to track myeloid cells in $CX3CR1^{GFP/-}$ mice (expressing a green fluorescent protein under control of the endogenous CX3C locus chemokine receptor 1) (418, 419). CSLO was then used to characterize microglial activation longitudinally during the course of actively induced MOG_{35-55}–EAE and to define time points of maximum microglial activation for further analyses (418). In the long term, this imaging method might be used with different targets and animal models. The more invasive alternative with better single-cell tracking is two-photon excitation microscopy, which can nowadays also be co-registered with OCT (420). Yet, it has been so far only applied to actively induced experimental autoimmune uveitis in $CX3CR1^{eGFP/-}$ mice [induced by $IRBP_{1-20}$ (*interphotoreceptor retinoid-binding protein*), CFA, and PT], an inflammation localized in the iris and ciliary body (421). Uveitis also occurs in MOGAD patients (422) and MOGAD-depicting animal models (423). Histopathological findings in uveitis are comparable in actively induced MOG_{35-55}-EAE in (C57BL/6 x SJL) F1 and C57BL/6 mice (induced by MOG_{35-55}, CFA, and PT) and mice with passive transfer of T cells specific to MOG_{35-55}, suggesting a T-cell-mediated origin of autoimmune uveitis in MOGAD (423). Translational imaging including co-registered OCT and two-photon excitation microscopy can help to further elucidate the cause.

6 Concluding remarks

Separating MOGAD as a disease entity presents a unique challenge since researchers have investigated MOG-IgG-based animal models and MOG-IgG seropositive patients for decades as models for or as part of other conditions. This review is a first step toward understanding how the generated knowledge is specifically applicable to MOGAD. Translational imaging in MOGAD has provided useful information on disease pathophysiology, commonalities between animal models and disease, and potential imaging markers. Yet, true translational imaging research including clinical and preclinical aspects within the same study is still warranted. Also, many open questions remain such as: (1) Is the histopathology of the optic nerve and spinal cord comparable between MOG animal models and MOGAD patients (due to the lack of human pathology studies), and which would be the closest to reflect human disease? (2) What causes the gray matter involvement in MOGAD? (3) Is there a relevant portion of MOGAD patients developing a clinically progressive disease course and do we need a disease-specific definition of neuropathological progression? and (4) Should current treatment regimens for MOGAD be reevaluated because (A) no adverse events to, e.g., Fingolimod/Natalizumab (as seen in AQP4-IgG seropositive NMOSD) were observed in MOG-IgG seropositive patients (217) and (B) many treatments have been shown to be beneficial in MOG-induced EAE that are less used in or have been unsuccessful in MS (160, 424–426). In the future, translational and advanced imaging might provide answers to these questions and support the development of biomarkers for the diagnosis and monitoring of MOGAD.

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FO and MH participated in the original conceptualization and initial draft of the manuscript. FP contributed to substantial revisions of the manuscript. All authors contributed to the revisions of the manuscript and approved the submitted version.

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Publisher's note

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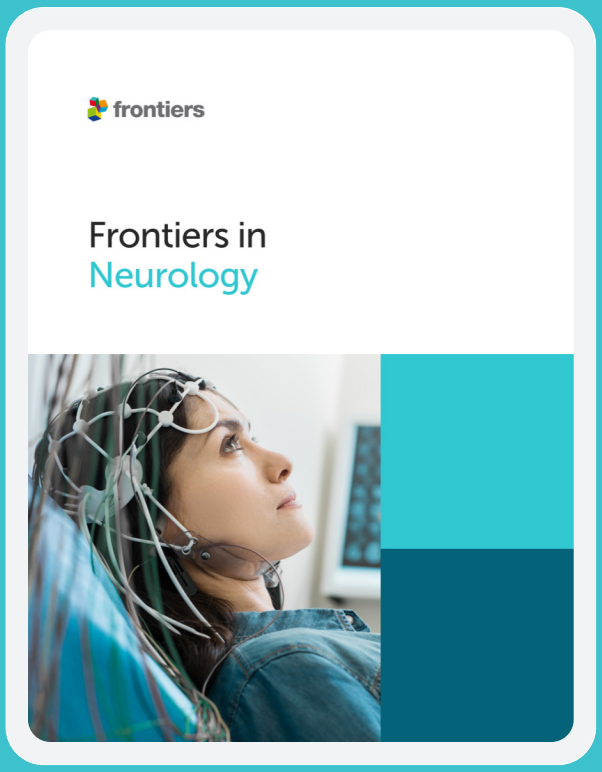

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