Characterising a Clinical and Laboratory Patient Profile That Predicts Relapse in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease

A THESIS

Submitted to fulfil the requirements of the degree of

Master of Philosophy

By

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June 2025

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Statement Of Originality

This is to certify that the content of this thesis is my own work. This thesis has not been submitted for any other degree or purpose.

I certify that the intellectual content of this thesis is the product of my own work, and that all assistance received in preparing this thesis and all sources have been acknowledged.

Jane Andersen

30 June 2025

Acknowledgements

Thank you, Professor Fabienne Brilot-Turville. I am immensely grateful for your kindness, encouragement, and compassion, which has been a fundamental support for me throughout this project. I hold so much admiration for your intelligence, vision, and attention to detail and feel deeply proud of the work we have produced together.

Thank you, Professor Russell Dale, Associate Professor Sudarshini Ramanathan, and Dr Benjamin Trewin for your invaluable clinical expertise, which strengthened the quality of this project.

Thank you to the Brain Autoimmunity Group at the Kids Neuroscience Centre and the University of Sydney Faculty of Medicine and Health for allowing me the opportunity to further my education, gain instrumental skills, and grow as a researcher all while working within a field that I feel passionately about.

Thank you to my family – Mum, Dad, Peter, Steve, Melissa, Kelly, Nina, David, Eloise, Adaline, Zoe, Lizi, George, Olly, Frankie, Jimmy, Bobby, Clancy, Annie, and Pippa! I am grateful every day for your love. Thank you, Jay, for brightening each day and making me laugh.

Author Attribution Statement

This thesis contains material from previously published work as outlined below.

Chapter 1 of this thesis is presented as a peer-reviewed publication:

- **Andersen J**, Brilot F. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): Insights into pathogenesis and biomarkers of prognosis. Semin Immunol. 2025 Jun;78:101944. doi: 10.1016/j.smim.2025.101944. Epub 2025 Mar 14. PMID: 40088708
- I reviewed published literature, prepared the figures, and drafted the manuscript. Together, Professor Fabienne Brilot-Turville and I conceptualised the study and edited the final manuscript.

Chapter 2 of this thesis is presented as a manuscript that has been accepted for publication on 1 September 2025 in the Journal of Neurology, Neurosurgery & Psychiatry:

- **Andersen J**, Trewin B, Dale R, Ramanathan S, Brilot F. Laboratory biomarkers for the prediction of relapse in myelin oligodendrocyte glycoprotein antibody-associated disease: a systematic review and meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry.
- I reviewed published literature, performed data extraction, analysis, and interpretation, prepared figures and tables, and drafted the manuscript. Together, Professor Fabienne Brilot-Turville and I conceptualised the study. The final manuscript was edited by myself, Dr Benjamin Trewin, Professor Russell Dale, Associate Professor Sudarshini Ramanathan, and Professor Fabienne Brilot-Turville.

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In addition to the statements above, permission to include the published material has been granted by the corresponding author, Professor Fabienne Brilot-Turville.

Jane Andersen

30 June 2025

Supervisor Statement

As lead supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Fabienne Brilot-Turville

30 June 2025

Artificial Intelligence

During the preparation of the thesis, ChatGPT was used for the purpose of minimal editing of code. I confirm that where code was modified by generative AI, the content was reviewed for possible errors, inaccuracies, and bias. No generative AI tools were used to assist with writing. I take full responsibility for the submitted thesis and ensure the work is my own.

Australian Government Support

This research was supported by an Australian Government Research Training Program fee offset.

Conference Presentations

- **11th Neuroimmunology Australia (NIA) Workshop**
    - 13th June 2025, Brisbane, Queensland, Australia
    - Selected abstract and oral presentation
- **3rd Asia-Pacific School of Neuroimmunology (APSNI) Course**
    - 14th–16th February 2023, Sydney, New South Wales, Australia
    - Selected abstract, poster, and oral presentation

Abbreviations

ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ADEM	Acute Disseminated Encephalomyelitis
AQP4	Aquaporin-4
AQP4-IgG	Aquaporin-4 Immunoglobulin G
BBB	Blood-Brain Barrier
BCR	B-Cell Receptor
CBA	Cell-Based Assay
CCE	Cerebral Cortical Encephalitis
CDC	Complement-Dependent Cytotoxicity
CNS	Central Nervous System
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-Linked Immunosorbent Assay
GFAP	Glial Fibrillary Acidic Protein
Ig	Immunoglobulin
IgG	Immunoglobulin G
MOG	Myelin Oligodendrocyte Glycoprotein
MOG-IgG	Myelin Oligodendrocyte Glycoprotein Immunoglobulin G
MOGAD	Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease
MS	Multiple Sclerosis
NfL	Neurofilament Light Chain
NMOSD	Neuromyelitis Optica Spectrum Disorder
ON	Optic Neuritis
TCR	T-Cell Receptor
TM	Transverse Myelitis

Abstract

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an inflammatory demyelinating pathology of the central nervous system (CNS). The mainstay of laboratory diagnosis is the detection of antibodies targeting oligodendrocyte-expressed MOG (MOG-IgG). The disease course is either monophasic or relapsing. Residual neurological disability, such as visual acuity loss, motor deficits, sensory deficits, cognitive impairment, and sphincter dysfunction, appears to accumulate with relapse and the associated morbidity burden is significant. Laboratory biomarkers have the potential to improve prediction of disease course and activity, thus, ensuring early and appropriate initiation of immunosuppression in individuals at risk of relapse-associated disability accrual, while minimising unnecessary exposure to immunosuppression in monophasic individuals. A widespread challenge of MOGAD research has been the rarity of its incidence, which often translates to limited sample sizes. For these reasons, we first summarized the literature on biomarkers of prognosis and reviewed pathological mechanisms of disease. We then conducted a systematic review with meta-analysis to investigate the capability of laboratory biomarkers to predict disease course, as well as differentiate remission compared to attack disease activity. When possible, laboratory biomarkers were additionally assessed alongside clinical factors in multivariable analyses.

Meta-analysis allowed the quantitative assessment of ≥1710 individuals from a total of 106 included studies. Relapsing disease course was associated with persistent seropositivity (OR 2.7 (95% CI 1.8–4.0), $p<0.0001$), lower likelihood of seroreversion to negative status (HR 0.19 (95% CI 0.14–0.26), $p<0.0001$), and delayed seroreversion compared to monophasic participants (median 19 years versus 2.5 years, respectively, $p<0.0001$). The highest rate of seroreversion to negative status occurred within 12 months following disease onset; hence, serial measurement of serum MOG-IgG at 3-6 month intervals in the 12 months following disease onset may be adopted by clinicians to assist with relapse risk stratification and guide therapeutic decisions. Other biomarkers assessed at disease onset or in the first collected biospecimen included serum MOG-IgG titre, cerebrospinal fluid (CSF) white cell count (WCC), CSF protein, and CSF oligoclonal bands (OCB); none of these variables were significantly associated with relapsing course.

Furthermore, biomarkers sampled throughout disease were assessed for capability to differentiate between remission and attack. In individuals with known MOGAD diagnosis,

serum MOG-IgG titre – classified semi-quantitatively as ‘negative’, ‘low positive’, or ‘clear positive’ in accordance with the 2023 international MOGAD diagnostic criteria – effectively discriminated between remission and attack. Attack was associated with clear positive titre (OR 3.6 (95% CI 2.6–5.0), p<0.0001) but not negative titre (OR 0.073 (95% CI 0.028–0.19), p<0.0001). Moreover, CSF leukocytosis (≥5 cells/μL), compared to a normal WCC, was significantly associated with attack (OR 3.1 (95% CI 1.7-5.9), p=0.0004). These findings highlighted the diagnostic utility of serum MOG-IgG titre and CSF WCC in settings of clinical uncertainty.

We also identified a multitude of novel biomarkers for prediction of disease course and activity, which we assessed qualitatively and, ultimately, require further investigation with prospective observational studies.

Our work marks a significant contribution to the landscape of relapse prediction in MOGAD. This systematic review with meta-analysis was the first of its kind to examine biomarkers of disease course and activity in MOGAD. Thus, our recommendations are informed with the highest quality evidence available and may be readily adopted into clinical practice to improve prognostication with the goal of securing better outcomes for individuals living with MOGAD.

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Chapter 1 | MOGAD: Insights into Pathogenesis and Biomarkers of Prognosis

This introductory chapter is a comprehensive narrative literature review outlining the historical and current understanding of MOGAD. There is a particular focus on the neuroimmunological concepts that underpin pathogenesis as well as the present landscape of prognostic biomarkers, with insights into their strengths and weaknesses.

The contents of Chapter 1 have been published in:

Andersen J, Brilot F. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): Insights into pathogenesis and biomarkers of prognosis. Semin Immunol. 2025 Jun;78:101944. doi: 10.1016/j.smim.2025.101944. Epub 2025 Mar 14. PMID: 40088708.

Seminars in Immunology 78 (2025) 101944

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD): Insights into pathogenesis and biomarkers of prognosis

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ARTICLE INFO

Keywords:
Myelin oligodendrocyte glycoprotein
MOGAD
Pathogenesis
Biomarker
Prognosis

ABSTRACT

MOG antibody-associated disease (MOGAD), an inflammatory demyelinating pathology, is typically associated with the clinical phenotypes acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), or transverse myelitis (TM). The mainstay of diagnosis is detection of antibodies targeting oligodendrocyte-expressed MOG (MOG-IgG). MOG-IgG-mediated demyelination occurs via complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), enhanced cognate T-cell CNS infiltration and activation, and oligodendrocyte cytoskeleton disruption, but the exact role of the immune system in MOGAD is still poorly understood. The disease course is either monophasic or relapsing, with relapsing course affecting approximately two-thirds of individuals. Neurological disability accumulates with relapse and may manifest as visual, motor, sensory, and cognitive deficits. Thus, accurate disease course prediction is of paramount importance. Prognostic biomarkers, implemented at a global scale, have the potential to guide timely therapeutic decisions to limit relapse-associated disability accrual while simultaneously avoiding unnecessary immunosuppression in monophasic individuals. This review explores recent insights in the understanding of MOGAD pathogenesis as well as advances in prognostic biomarkers of relapsing course and disease activity.

1. An historical overview

Myelin oligodendrocyte glycoprotein (MOG) was first identified as a target of demyelinating antibodies in experimental autoimmune encephalomyelitis (EAE) – an animal model of central nervous system (CNS) demyelination – in guinea pigs almost 40 years ago [1]. Although immunisation of nonhuman primates with the extracellular domain of MOG also elicits an EAE response [2], the EAE model in rats, originally induced by passive transfer of either myelin-basic protein (MBP)-activated splenocytes or MBP-specific T-cells with subsequent intravenous injection of monoclonal antibodies (mAbs) against MOG, remains a cornerstone animal model in this field [3,4]. Originally, interest was piqued in the role of MOG in multiple sclerosis (MS). Electron microscopy examining CNS tissue from *C. jacchus* marmosets with MOG-induced EAE and three humans with acute MS lesions revealed that myelin breakdown occurred in a similar structural pattern between groups, suggestive of a common mechanism, and that antibodies to MOG (MOG-IgG) were directly identified in all actively demyelinating lesions [5]. Although the clinical importance of MOG-IgG was initially investigated in clinically isolated syndrome (CIS) – a standalone demyelinating lesion of the CNS which, in 90 % of individuals with MS, is retrospectively identified as the first presentation of disease – the association between MOG-IgG and MS has been difficult to ascertain [6–12].

Historically, Western blot and enzyme-linked immunosorbent assay (ELISA) techniques were the mainstay of MOG-IgG detection; however, these techniques identified antibodies against linear epitopes, which were not exposed in the native conformational structure of MOG [11,13,14]. In 2007, O'Connor, *et al.* published the seminal study demonstrating that assays, in which MOG was expressed in its native conformation, addressed this limitation and enabled the identification of clinically relevant MOG-IgG in a subset of individuals with acute disseminated encephalomyelitis (ADEM), but rarely MS [15]. The methodology of cell-based assays (CBAs) was subsequently refined, inspired by advances in other autoimmune neurological diseases such as anti-NMDA receptor encephalitis [16–19]. Fixed CBA, employing fixed MOG-transfected cells, has been shown to have lower sensitivity and

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https://doi.org/10.1016/j.smim.2025.101944
Received 21 December 2024; Received in revised form 6 March 2025; Accepted 6 March 2025
Available online 14 March 2025

specificity for MOG-IgG detection than live CBA [18,20,21]. The intracellular domain of MOG appears essential to induce MOG clustering and facilitate optimal MOG-IgG binding; thus, the current gold standard of MOG-IgG detection is live CBA utilizing full-length MOG [22]. This advancement paved the way for the recognition that MOG-IgG occurred in a clinically distinct population of individuals, who would later be characterised as having MOG antibody-associated disease (MOGAD) [23–25].

2. Clinical features

The recently published International MOGAD Panel proposed criteria outlined that MOGAD is typically associated with the clinical phenotypes ADEM, optic neuritis (ON), or transverse myelitis (TM), and is less commonly associated with cerebral cortical encephalitis (CCE), brainstem presentations, or cerebellar presentations [26]. The disease course is either monophasic or relapsing, with a recent systematic review reporting that relapsing disease course occurs in 72 % of individuals when follow-up is extended beyond 5-years [27]. The incidence of MOGAD has been estimated at 1.6–3.4 per 1000,000 person-years [28,29]. Female and male sexes appear to be affected relatively equally [30,31], though there may be a female predominance [32,33]. Studies from Europe and North America have observed predominantly white patient cohorts [31,34,35]; other studies have asserted that no definitive racial or ethnic predilection can be concluded at this stage [32,33,36]. MOGAD affects both children and adults; however, there is a distinct divergence of phenotype – ADEM is the most frequent paediatric phenotype compared to ON as the primary manifestation in adults [37]. Antecedent infection is common and has been reported in 20–57 % of individuals with MOGAD [31,38–40]. Two key differential diagnoses of MOGAD include the inflammatory demyelinating conditions neuromyelitis optica spectrum disorder (NMOSD) and MS. Demyelination in NMOSD is primarily autoantibody-mediated as most individuals have been shown to harbor a pathogenic autoantibody against the astrocyte water channel aquaporin-4 (AQP4) termed AQP4-IgG [41,42]. In contrast, the pathomechanism underpinning demyelination in MS is more heterogeneous; nevertheless, lesions are mostly composed of activated macrophages and microglia, and CD8 + T-cells, with fewer numbers of CD4 + T-cells and B-cells [43]. While there are clinical similarities between individuals with MOGAD, AQP4-IgG seropositive NMOSD, and MS, these disease entities are thought to be distinct [43].

3. Insights into pathogenesis

MOG is a glycoprotein expressed at the extracellular surface of the myelin sheath and oligodendrocyte processes in the CNS [44–46]. MOG has a 218 amino acid sequence and is structurally characterised by an immunoglobulin (Ig)-like extracellular domain, for which it belongs to the Ig superfamily, as well as transmembrane and cytoplasmic domains [47,48]. The putative role of MOG has yet to be fully elucidated; however, it has been theorised to act as an adhesion molecule, regulator of microtubule stability, and marker of oligodendrocyte maturation due to its differential temporal expression [46,49]. Furthermore, MOG has been shown to bind and sequester nerve growth factor (NGF) to modulate axon growth and survival, with deletion of MOG resulting in aberrant sprouting of nociceptive neurons in the spinal cord [50]. Autoantibodies targeting MOG are predominantly of the Ig G type, hence, the nomenclature MOG-IgG [39,51]. IgG subclass analysis of MOG-IgG isolated from the sera of individuals with MOGAD has revealed IgG1 predominance [39,51]. Other isotypes have been detected; however, they occur less frequently and are less defined, thus, current diagnosis of MOGAD requires the detection of IgG1 [26,39]. Nonetheless, it is important to consider that the use of IgG1 subclass-specific CBAs does not identify individuals with MOGAD in whom other IgG subclasses, such as IgG3, are the predominant subclass [52]. Moreover, a recent cohort study identified a subgroup of individuals with demyelinating CNS disease who tested positive for MOG-IgA, while testing negative for both AQP4- and MOG-IgG [53].

MOGAD is an autoantibody-mediated pathology that arises due to the cooperation of MOG-specific B- and T-cells (Fig. 1). The first step in this process is antigen recognition. MOG is surface-expressed and, thus, is a biologically plausible and accessible autoantigen for immune cell recognition. Historically the CNS was considered an "immune ignorant" environment with little-to-no interaction with the peripheral immune system; however, a recent literature review proposed an updated model of the CNS as a complex orchestration of immune surveillance [54]. Antecedent infection occurs commonly in the development of MOGAD; symptoms consistent with an infectious prodrome have been reported in 20–57 % of individuals [31,38–40]. Antecedent infection may facilitate antigen recognition and precipitate the breakdown of self-tolerance via the following pathways: (1) molecular mimicry: cross-reactivity of self-antigens such as MOG with microbial antigens may result in the inappropriate activation of self-reactive B- and T-cells, (2) bystander activation: infection-induced pro-inflammatory cytokines and co-stimulatory signals can lead to the activation of self-reactive B- and T-cells, which may have otherwise remained quiescent, and (3) disruption of the highly-regulated CNS may expose normally-sequestered self-antigens such as MOG to peripheral immune cells [55]. Human leukocyte antigen (HLA) class II molecules are fundamental for antigen presentation and activation of CD4 + T-cells. Specific HLA class II alleles have been associated with celiac disease, type 1 diabetes mellitus, and MS and likely represent a genetic vulnerability for autoimmunity via mechanisms such as enhanced presentation of self-antigens, presentation of cryptic epitopes, or failing to maintain self-tolerance [56–58]. In Han Chinese individuals, the frequency of the HLA class II DQB1 * 05:02 allele was significantly higher in individuals with MOGAD compared to healthy controls at 18.95 % and 10.71 %, respectively [59]. No significant HLA associations with MOGAD were observed in either Dutch or United Kingdom cohorts [60,61]. While multiple stimulatory T-cell epitopes have been identified in the transmembrane and cytoplasmic domains of MOG [62], other studies have not observed significant peripheral T-cell reactivity to MOG peptides in individuals with MOG-IgG [63,64]. Whether this represents peripheral T-cell ignorance due to MOG CNS sequestration or a tissue-restricted T-cell response remains to be clarified. Nonetheless, crosstalk between MOG-specific B- and T-cells is required following antigen recognition to facilitate antibody class-switching to IgG as well as B-cell differentiation into memory B-cells and MOG-IgG-secreting cells – the source of MOG-IgG in MOGAD. Notably, MOG-specific B cells have been detected and differentiated into MOG-IgG-secreting cells via toll receptors 7 and 8 in vitro stimulation in 60 % of MOGAD patients [65].

MOG-IgG synthesis appears to occur primarily in the periphery, though intrathecal synthesis has also been reported [23,66–68]. Individuals with intrathecal MOG-IgG synthesis have exhibited comparable clinical and pathological characteristics as their counterparts with peripheral MOG-IgG synthesis and, as such, the International MOGAD Panel proposed criteria supported testing of cerebrospinal fluid (CSF) for MOG-IgG in seronegative individuals whose pre-test assessment was suggestive of MOGAD [26,69–71]. Nonetheless, caution is warranted when interpreting CSF-restricted MOG-IgG. The frequency of CSF-restricted MOG-IgG has been reported as 0.7 % of samples tested for workup of diverse CNS inflammatory syndromes, with an alternative diagnosis such as MS and CNS vasculitis, as opposed to MOGAD, identified in over half the cases [72]. Consequently, serum is the preferred biospecimen for diagnostic identification of MOG-IgG [26,72]. Endpoint titres are an important consideration in MOG-IgG testing; a study of 1260 individuals reported that 49 % (20/41) of low titre (1:20–1:40) serum samples were false positives compared to 18 % (6/33) of medium titre (1:100) and 0 % of high titre serum samples [73]. This challenging lack of low-titre specificity may, in part, be attributed to CBA limitations as well as detection of non-pathogenic variants of MOG-IgG and

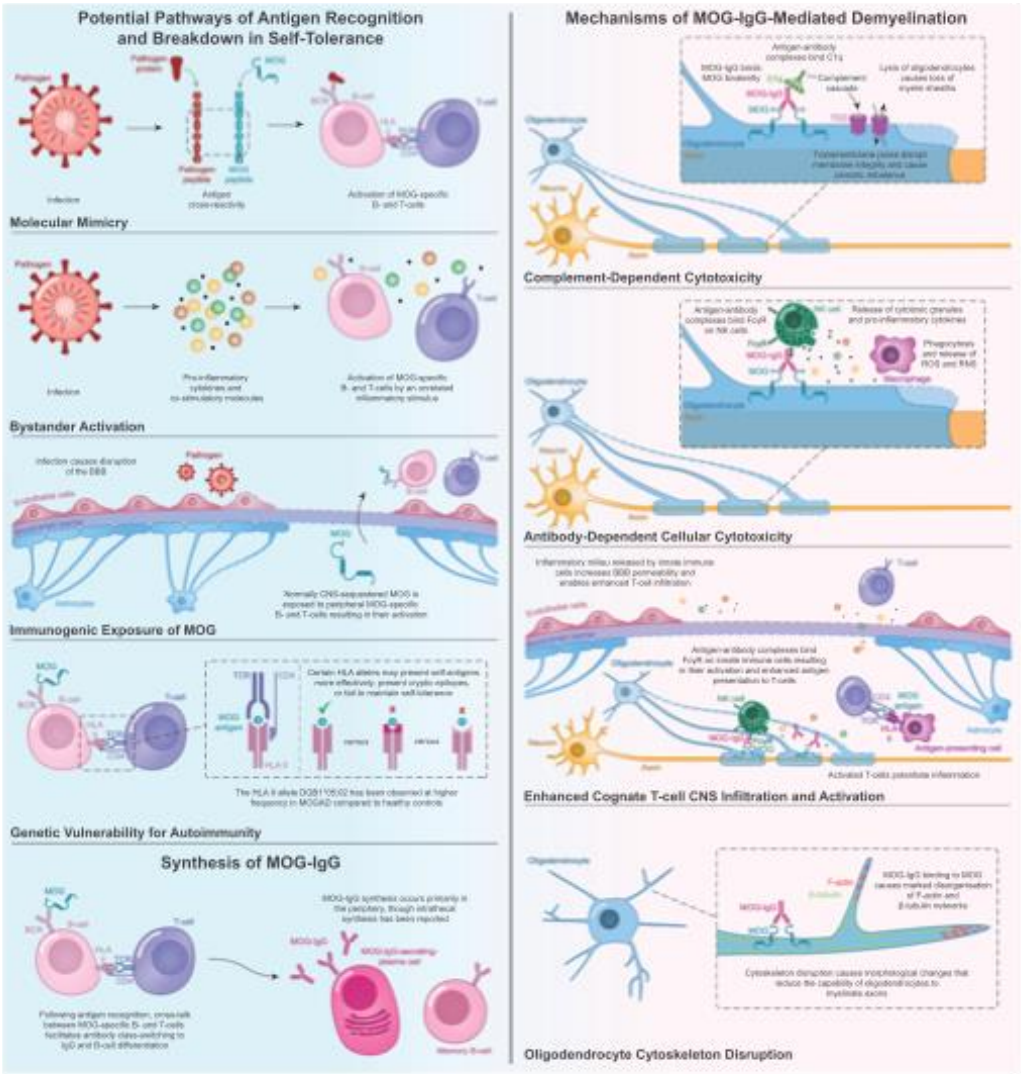

Fig. 1. Schematic overview of the potential pathways of antigen recognition and breakdown in self-tolerance in MOGAD, synthesis of MOG-IgG, and mechanisms of MOG-IgG-mediated demyelination. BBB, blood-brain barrier; BCR, B-cell receptor; FcγR, Fcγ receptor; HLA II, human leukocyte antigen class II; NK cell, natural killer cell; MOG, myelin oligodendrocyte glycoprotein; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; TCC, terminal complement complex; ROS, reactive oxygen species; RNS, reactive nitrogen species; TCR, T-cell receptor.

production of polyspecific antibodies against antigens such as MOG in other settings of CNS inflammation, as seen in MS [74,75]. Initially, the pathogenic capability of MOG-IgG was ambiguous when a transgenic murine model producing high levels of MOG-IgG did not exhibit spontaneous neurological disease nor pathological evidence of demyelination, suggesting that the presence of MOG-IgG alone was insufficient to trigger demyelination [76]. Subsequent transfer experiments of human MOG-IgG to rodents demonstrated that MOG-IgG was indeed pathogenic but required T-cell interaction to elicit demyelination [77].

MOG-IgG acts as a pathogenic perpetrator of demyelination via a multitude of mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), enhanced cognate T-cell CNS infiltration and activation, and oligodendrocyte cytoskeleton disruption (Fig. 1) [23,37,49,51,68,78–80]. As aforementioned, MOG-IgG isolated from the sera of individuals with MOGAD is predominantly of the IgG1 subclass [39,51]. It is well established that IgG1 antibodies engage C1q and Fcγ receptor (FcγR) more efficiently than other IgG subclasses, and thus, IgG1 antibodies are potent triggers

of pro-inflammatory effector mechanisms [81]. AQP4-IgG observed in NMOSD is also primarily of the IgG1 subclass [82]. MOGAD and AQP4-IgG seropositive NMOSD have often been investigated in parallel with regards to the role of complement activation. It has been reported that MOG-IgG requires bivalent recognition of MOG and, thus, may engage C1q less efficiently thereby generating less complement activation compared to AQP4-IgG, which recognises AQP4 in a monovalent capacity [22,83]. This aligns with the observation that, while both MOG-IgG-positive and AQP4-IgG-positive serum samples induced CDC and terminal complement complex (TCC, also known as membrane attack complex (MAC)), AQP4-IgG-positive serum samples did so to a greater extent [78]. Interestingly, both MOG-IgG and AQP4-IgG titres positively correlated with CDC and TCC levels [78]. When compared to MS, levels of CSF-C3a and CSF-C5a were similarly significantly elevated in both MOGAD and AQP4-IgG seropositive NMOSD – supporting complement pathway activation in both pathologies – while CSF-C5b-9 (TCC/MAC) levels were significantly lower in MOGAD compared to AQP4-IgG seropositive NMOSD [84]. Multiple studies have corroborated the capability of MOG-IgG isolated from individuals with MOGAD to induce CDC and ADCC [23,37,51,79]. Complement consumption, which occurs with activation of the complement pathway, has also been investigated via C3 and C4 levels measured in remission serum samples from individuals with MOGAD, AQP4-IgG seropositive NMOSD, CIS or relapsing remitting MS (RRMS), and healthy controls (HCs) [85]. C4 levels were found to be significantly lower in individuals with AQP4-IgG seropositive NMOSD compared to individuals with MOGAD, CIS/RRMS, and HCs, suggesting that complement consumption may be a more prominent feature of AQP4-IgG seropositive NMOSD than MOGAD even when disease is clinically quiescent [85]. Systemic complement activation has also been interrogated by direct measurement of proteins (C5a, SC5b9, C3a, Ba, Bb, and Factor H) associated with activated classical and alternative complement pathways from attack and remission serum samples of individuals with MOGAD, AQP4-IgG seropositive NMOSD, relapsing MS (RMS), and paediatric and adult controls [86]. Overall, systemic complement activation was significantly more prominent in MOGAD [86]. An important caveat of this study was that 77 % (10/13) of individuals with AQP4-IgG seropositive NMOSD had already received immunotherapy at time of sampling whereas the treatment status of 73 % (80/109) of individuals with MOGAD at time of sampling was unknown due to limited clinical records [86]. This somewhat aligned with the finding that complement activation products were significantly elevated in the serum of individuals with NMOSD (a combined cohort of MOG-IgG seropositive, AQP4-IgG seropositive, and antibody negative individuals) compared to MS and HCs and, when the NMOSD group was discriminated by antibody status, the following trends were observed: (1) AQP4-IgG seropositive > MOG-IgG seropositive > antibody negative for Bb, C4d, and C5a, and (2) MOG-IgG seropositive > AQP4-IgG seropositive > antibody negative for iC3b and TCC [87]. Shifting the investigative lens from serum to CSF revealed that individuals with monophasic acquired demyelinating syndrome (ADS), among whom 53 % (9/17) were MOG-IgG seropositive, had significantly elevated levels of CSF C5a, C3a, C4a, IL-6, and IgG compared to individuals with other neurologic diseases (OND) as well as significantly elevated levels of CSF C5a and IL-6 compared to individuals with MS, among whom 12 % (2/17) were MOG-IgG seropositive [88]. Overall, complement activation, CDC, and ADCC play a prominent role in the pathogenesis of MOGAD; however, the extent of complement activation compared to AQP4-IgG seropositive NMOSD is uncertain – complement activation appears more prominent *in vitro* in AQP4-IgG seropositive NMOSD, while *in vivo* studies have yielded mixed results.

Examinations of postmortem autopsy and brain biopsy specimens of individuals with MOGAD have shed further light on its pathogenesis [66,89–91]. Spadaro, *et al.* reported the first histopathological insight into MOGAD – a right-sided splenium brain biopsy from an individual with relapsing encephalomyelitis [89]. Within the active lesion, there was infiltration of T-cells as well as activated macrophages and microglia; profound reactivity for C9neo indicative of terminal complement activation alongside significant IgG accumulation was also observed [89]. Jarius, *et al.* reported complement and IgG deposition in a single brain biopsy from their centre [90]. Hoftberger, *et al.* assessed the immunopattern of eight brain biopsy cases and similarly observed complement deposition in all specimens [66]. Discordantly, only minor complement and IgG deposition was observed by Takai, *et al.* in their assessment of 11 brain biopsy specimens [91]. Interestingly, lymphocytic infiltrates were consistently dominated by CD4 + T-cells, which contrasts the predominant CD8 + T-cell presence classic of MS [66,90,91]. Furthermore, AQP4 was preserved and dystrophic astrocytes were absent – a clear contrast to AQP4-IgG seropositive NMOSD [66,89–91]. Together, these findings served to clarify the interplay of humoral and cellular immunity underlying MOG-IgG-associated demyelination while also further distinguishing MOGAD, AQP4-IgG seropositive NMOSD, and MS as distinct immunopathogenic processes.

Beyond the requirement of CD4 + T-cell co-stimulation for MOG-specific B-cell activation and antibody class switching to IgG – a T-cell-dependent Ig class, cognate T-cells have been shown to infiltrate the CNS and potentiate inflammation [80]. 13 Fc-mutated variants of a MOG-specific mAb were created and, in particular, one mutated mAb with abolished C1q binding but maintained FcγR binding was instrumental in demonstrating that MOG-IgG enhanced infiltration and activation of cognate T-cells via FcγR engagement, possibly through enhanced antigen uptake by local antigen-presenting cells (APCs) and augmented co-stimulatory signals [80]. This complement-independent FcγR-mediated pathomechanism of MOG-IgG was responsible for approximately half of the observed demyelination and raised next-generation FcγR blocking reagents as a potential therapeutic avenue for MOGAD [80]. Peripheral blood mononuclear cells (PBMCs) have also been useful in the assessment of cellular immunity in MOGAD. PBMCs collected at onset in individuals with MOGAD were cultured with recombinant human MOG (rh-MOG) protein and the T-cell immunophenotype was examined [92]. Following stimulation with rh-MOG, a significant increase in CD4 + T helper 2 (Th2) and T helper 17 (Th17) cells was observed in individuals with MOGAD but not in MS or control groups [92]. In a similar vein, PBMCs were collected at both attack and remission timepoints from individuals with MOGAD and compared to HCs [93]. Levels of activated follicular regulatory T (Tfr)-cells – found to have the strongest inhibitory potential on plasmablast expansion among the three assessed Tfr-cell subgroups – were significantly decreased in MOGAD [93]. Furthermore, the percentage of circulating follicular helper T (Tfh)-cells – contrastingly observed to promote the differentiation of plasmablasts – were significantly elevated at MOGAD attack compared to remission and HCs [93]. Interestingly, the percentage of plasmablasts was significantly increased in MOGAD compared to HCs and positively correlated with the ratios of Tfh/Tfr cells [93]. In concert, these findings gave rise to a hypothesis that disturbance of the immune balance between Tfh- and Tfr-cells was contributory to the pathogenesis of MOGAD [93]. Cytokine and chemokine profiling highlighted another facet of adaptive immunity. Examination of the CSF of children with MOG-IgG seropositive and MOG-IgG seronegative ADEM and TM alongside a control group with various non-inflammatory neurologic diseases revealed that 79 % (27/34) of measured CSF cytokines and chemokines were elevated in the MOG-IgG seropositive group compared to the control group [94]. Moreover, concentrations of cytokines and chemokines related to B-cell (CXCL13, CCL19, CXCL12) and Th17-cell (G-CSF, IL-17A) function were significantly higher in the CSF of MOG-IgG seropositive individuals compared to their MOG-IgG seronegative counterparts [94]. Both MOG-IgG seropositive and MOG-IgG seronegative groups exhibited evidence of elevated T helper 1 (Th1) and Th2-cell function compared to controls [94]. This aligned with an earlier finding that MOG-IgG serum titres had a significant positive correlation with CSF IL-6 levels, another cytokine intimately related to Th17-cell function [88]. Concordantly, another evaluation of CSF from children and adults with MOGAD,

AQP4-IgG seropositive NMOSD, and MS demonstrated that MOGAD and AQP4-IgG seropositive NMOSD groups both had significantly elevated cytokines, chemokines, and related molecules associated with Th17-cell (IL-6, GM-CSF), Th1-cell (IFN-γ) and regulatory T-cell (Treg) (IL-10) function compared to MS [95]. IL-6 is a pleiotropic cytokine which is involved in the differentiation of CD4 + T-cells into Th17-cells as well as the terminal differentiation of B-cells and production of immunoglobulins [96–98]. IL-6 has been implicated in autoimmunity, including rheumatoid arthritis and Takayasu arteritis, wherein it has been shown to enhance excessive pro-inflammatory pathways [99,100]. Therapeutic blockade with tocilizumab, an anti-IL-6-receptor (IL-6R) mAb, has been efficacious in these conditions [101,102]. Moreover, Th17-cells exert a pro-inflammatory function by recruiting and promoting the maturation and activation of both granulocytes and macrophages [103,104]. Rheumatoid arthritis has logically been highlighted as an example of Th17-mediated autoimmunity, with abrogation of this pathway using ixekizumab and secukinumab, anti-IL-17-receptor (IL-17R) mAbs, also exhibiting therapeutic potential, albeit with limited evidence base at this stage [105].

An alternative model of MOG-IgG-induced demyelination related to cytoskeleton disruption has also been proposed [49,68]. It was demonstrated using cultured oligodendrocytes that MOG-IgG binding induced MOG crosslinking, repartitioning, and facilitated novel protein-protein interactions within lipid rafts [49]. This resulted in cellular morphological alterations, specifically, dramatic retraction of myelin-like membrane sheets and cellular processes [49]. This was consistent with the observation that oligodendrocytes treated with MOG-IgG exhibited marked loss of organisation in both F-actin and β-tubulin networks; no difference was observed in cell viability at 45-minute and 10-hour timepoints [68].

To summarise, MOG is an accessible autoantigen surface-localised on myelin sheaths and oligodendrocyte processes in the CNS [44–46]. The interplay of MOG-specific B- and T-cells results in the autoantibody-mediated pathology MOGAD. MOG-IgG-induced demyelination occurs via CDC, ADCC, enhanced cognate T-cell CNS infiltration and activation, and oligodendrocyte cytoskeleton disruption [23,37,49,51,68,78–80].

4. Determinants of prognosis

The morbidity burden associated with MOGAD is significant, with residual neurologic disability manifesting as visual acuity loss, motor deficits, sensory deficits, cognitive impairment, and sphincter dysfunction [33,38,106]. TM phenotype and higher expanded disability status scale (EDSS) at onset attack have been associated with a greater long-term burden of disability [31,38]. Furthermore, it has been reported that the median EDSS at recovery following later episodes was higher than the median EDSS at recovery following earlier episodes, suggestive of disability accumulation with relapse [38]. A recent review reported that relapsing disease course occurs in 72 % of individuals when follow-up is extended beyond 5-years [27]. Male sex, age at onset older than 16-years, TM onset attack phenotype, and corticosteroid wean ≥ 1-month duration have all been associated with a reduced risk of relapse [33]. Conversely, rapid corticosteroid taper and corticosteroid withdrawal have been shown to confer increased risk of relapse [32,38,107]. The greatest risk of relapse appears to be within the first 12-months following onset attack [32,33].

It is a paramount yet elusive goal to predict the likelihood of relapsing disease course. Accurate disease course prediction has the potential to facilitate early institution of maintenance immunotherapy, thus, limiting the accrual of disability that occurs with relapse while simultaneously avoiding unnecessary immunosuppression in monophasic individuals. The ideal biomarker could be sampled at disease onset or at remission prior to relapse. Numerous candidates have been investigated (Table 1 and Fig. 2).

Persistent seropositivity on serial MOG-IgG measurement has been significantly associated with relapsing disease course [108–110]; however, the literature lacks consensus regarding this relationship [33,111]. Conversion to MOG-IgG seronegative status appears to confer a reduced risk of subsequent relapse [33,111].

Assessment of MOG epitope recognition pattern has yielded promising insights. Liyanage, *et al.* evaluated MOG epitope binding by serum MOG-IgG collected from adults with MOGAD [112]. They demonstrated that individuals whose MOG-IgG did not recognise the P42 epitope (non-P42 MOG-IgG) – the most frequently recognised epitope (74 %, 150/202) – had a 70 % increased risk for relapsing disease course compared to individuals whose MOG-IgG did recognise P42 (P42 MOG-IgG) [112]. This association was strengthened when onset attack phenotype was considered. It was reported that non-P42 MOG-IgG alongside unilateral ON (uON) carried more than double the risk of relapsing course compared to P42 MOG-IgG with uON [112], and was also associated with a higher risk of relapse in paediatric MOGAD [115]. Seok, *et al.* similarly examined MOG epitope binding by MOG-IgG isolated from individuals with MOGAD [113]. Of the individuals with > 1-year follow-up, 0 % (0/10) in the non-P42 MOG-IgG group exhibited a monophasic course compared to 18.3 % (2/11) of the P42 MOG-IgG group [113]. A lower total number of attacks was observed during follow-up in the P42 MOG-IgG group compared to the non-P42 MOG-IgG group [113]. It is important to note that neither these findings, nor any other differences in demographic or clinical characteristics between the groups, reached statistical significance [113]. Mayer, *et al.* did not identify an association between MOG epitope recognition pattern and disease course in their analysis of 111 individuals [114]. While MOG epitope recognition pattern has been shown to be highly stable over time, which would enable the use of serum collected at onset or remission prior to first relapse, the current evidence is mixed with regards to its utility as a disease course biomarker [89,112,114,115].

PBMCs have also been investigated for biomarker capability. Horellou, *et al.* sampled PBMCs collected at onset in individuals with MOGAD, cultured these PBMCs with rh-MOG protein for stimulation, and examined T-cell immunophenotype [92]. The following statistically significant findings were observed: (1) Th-17 cells increased in monophasic individuals (2) CD4 + Treg cells increased in monophasic individuals, and (3) CD45RA-Foxp3 + Tregs decreased in relapsing individuals [92]. It was hypothesised that the reduction in Tregs following rh-MOG stimulation observed in relapsing individuals represented intermittent loss of tolerance toward MOG manifesting as multiphasic disease [92]. While PBMCs could be sampled at onset attack, pragmatically, these tests are more suited to the research laboratory than the commercial setting due to the requirement of extended cell culture and specialised flow cytometric analysis.

In line with this practical consideration, index ratios derived from peripheral blood counts may represent a more accessible avenue for biomarker consideration. Lin, *et al.* examined the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) collected at disease onset and pre-treatment in individuals with MOGAD, MS, and HCs [116]. Individuals with MOGAD had significantly elevated NLR, PLR, and MLR measurements compared to HCs as well as significantly elevated NLR and PLR measurements compared to individuals with MS, highlighting usefulness of these metrics for disease discrimination [116]. Moreover, PLR was found to be significantly positively associated with relapsing disease course, albeit the conferred increased risk was modest with an odds ratio (OR) of 1.016 [116].

Finally, Sun, *et al.* investigated the HLA locus in 95 Han Chinese individuals with MOGAD [59]. Stratification of the paediatric-onset cohort by DQB1 * 05:02–DRB1 * 16:02 carriers and DQB1 * 05:02–DRB1 * 16:02 non-carriers revealed that carriers exhibited more severe clinical symptoms evidenced by significantly higher initial EDSS scores and more frequent relapsing disease course [59].

Biomarkers of disease activity may be diagnostically useful in

Table 1
Characteristics and key findings of studies reporting biomarkers of prognosis.

Biomarker	Sample Size (n)	Study	Specimen	Key Findings	Classification of Evidence[a]
Serial MOG-IgG status	51 total; 25 MOGAD	[108]	Serum	• 89 % (8/9) of children and 88 % (7/8) of adults with persistent MOG-IgG seropositivity had a relapsing course compared to 0 % (0/4) of children and 25 % (1/4) of adults with transient MOG-IgG seropositivity ($p = 0.002$ and $p = 0.03$, respectively)	Class III
	210 total; 65 MOGAD	[109]	Serum	• Persistent MOG-IgG seropositivity occurred more frequently in children with a relapsing course ($p = 0.01$)	Class II
	8	[110]	Serum	• All (8/8) children had a relapsing course and persistent MOG-IgG seropositivity	Class III
	76	[33]	Serum	• No significant difference between proportion of monophasic (47 %, 15/32) and relapsing (62 %, 24/39) individuals who remained MOG-IgG seropositive at last follow-up ($p = 0.229$) • Conversion to MOG-IgG seronegative status conferred a significantly reduced risk of subsequent relapse ($p < 0.001$)	Class II
	102	[111]	Serum	• No significant difference between proportion of monophasic (43 %, 25/58) and relapsing (36 %, 16/44) individuals who converted to MOG-IgG seronegative status ($p = 0.55$) • Conversion to MOG-IgG seronegative status conferred a significantly reduced risk of subsequent relapse ($p < 0.001$)	Class II
MOG-IgG titre	50	[67]	Serum	• MOG-IgG titres were significantly higher at attack (median 1:2560, IQR 1:1280–1:5200) compared to remission (median 1:320, IQR 1:160–1:640) ($p < 0.0001$)	Class II
	102	[111]	Serum	• MOG-IgG titres were significantly higher at attack (median 1:1280, IQR 1:320–1:4480) compared to remission (median 1:640, IQR 1:160–1:2560) ($p = 0.001$)	Class II
	130 total; 65 MOGAD	[117]	Serum	• High (≥1:160) MOG-IgG titres were only observed within 4-months of attack	Class II
MOG epitope recognition pattern	202	[112]	Serum	• Non-P42 MOG-IgG conferred significantly increased risk for relapsing course compared to P42 MOG-IgG (HR 1.7, 95 % CI 1.15–2.60) ($p = 0.009$) • Among individuals with uON at onset, non-P42 MOG-IgG conferred significantly increased risk of relapsing course compared to P42 MOG-IgG (HR 2.7, 95 % CI 1.06– 6.98) ($p = 0.038$) • Epitope recognition pattern was highly stable over time	Class II
	55	[113]	Serum	• 0 % (0/10) of individuals with non-P42 MOG-IgG had a monophasic course compared to 18.3 % (2/11) with P42 MOG-IgG ($p = 0.476$) • P42 MOG-IgG was associated with fewer total attacks during follow-up (median 2.0, IQR 1.8–3.5) compared to non-P42 MOG-IgG (median 2.5, IQR 2.0–5.0) ($p = 0.722$)	Class III
	111	[114]	Serum	• No significant association between MOG epitope recognition pattern and disease course	Class II
PBMCs	29 total; 12 MOGAD	[92]	Serum	• PBMCs collected at onset were stimulated with rh-MOG • Th17-cells increased significantly in individuals with a monophasic course but not a relapsing course ($p = 0.03$ and $p = 0.25$, respectively) • CD4 + Foxp3 + Tregs increased significantly in individuals with a monophasic course but not a relapsing course ($p = 0.046$ and $p = 0.375$, respectively) • CD45RA-Foxp3 + Tregs decreased significantly in individuals with a relapsing course but not with a monophasic course ($p = 0.021$; p-value for monophasic group not stated)	Class III
	96 total; 26 MOGAD	[118]	Serum	• Th17-cells were significantly increased in MOGAD, AQP4-IgG seropositive NMOSD, and MS compared to HCs at attack ($p = 0.001$, $p < 0.001$, and $p = 0.005$, respectively) and remission ($p = 0.033$, $p = 0.005$, and $p = 0.004$, respectively) • Th17/Treg ratios were significantly increased in MOGAD, AQP4-IgG seropositive NMOSD, and MS compared to HCs at attack ($p = 0.004$, $p < 0.001$, and $p = 0.006$, respectively) and remission ($p = 0.019$, $p < 0.001$, and $p = 0.005$, respectively) • Th17-cells were significantly increased in MOGAD, AQP4-IgG seropositive NMOSD, and MS at attack compared to remission (paired sample comparison) ($p = 0.015$, $p = 0.012$, and $p = 0.018$, respectively)	Class II
	41 total; 17 MOGAD	[119]	Serum	• Plasmablasts were significantly lower at attack in MOGAD compared to AQP4-IgG seropositive NMOSD ($p < 0.05$) • Transitional B-cells were significantly elevated at remission in MOGAD compared to HCs and AQP4-IgG seropositive NMOSD (all $p < 0.01$) • MOGAD attack and remission B- and T-cell subsets were not explicitly compared	Class II
Peripheral blood count index ratios, including N%, NLR, PLR, MLR, and ELR	81 total; 31 MOGAD	[116]	Serum	• NLR, PLR, and MLR collected at onset were significantly elevated in MOGAD compared to HCs (all $p < 0.001$) • NLR and PLR collected at onset were significantly elevated in MOGAD compared to MS ($p < 0.001$ and $p = 0.001$, respectively) • PLR was significantly positively associated with relapsing course in MOGAD (OR=1.016, 95 % CI 1.001–1.031) ($p = 0.038$)	Class II
	39	[120]	Serum	• NLR, PLR and N% were significantly elevated at attack compared to remission (all $p < 0.001$)	Class II

(continued on next page)

Table 1 (*continued*)

				• ELR was significantly lower at attack compared to remission ($p < 0.001$)	
	304 total; 26 MOGAD	[121]	Serum	• Total white blood cell count, neutrophil count, monocyte count, NLR, and MLR were all significantly elevated at attack compared to controls ($p = 0.0001$, $p < 0.0001$, $p = 0.0191$, $p = 0.0002$, and $p = 0.0320$, respectively)	Class II
	156 total; 17 MOGAD	[122]	Serum	• NLR was significantly elevated at attack compared to remission in MOGAD ($p < 0.001$) • NLR was significantly elevated at attack in MOGAD compared to MS ($p < 0.001$)	Class II
HLA genotype	576 total; 95 MOGAD	[59]	Serum	• Frequency of DQB1 * 05:02 allele was significantly higher at 18.95 % in MOGAD compared to 10.71 % in controls (OR=1.95, 95 % CI 1.25–3.0) ($p = 0.002$) • Age subgroup analysis revealed a significant association for paediatric-onset MOGAD with DQB1 * 05:02 (OR=2.43, 95 % CI 1.39–4.11) ($p = 0.001$) and DRB1 * 16:02 (OR=3.28, 95 % CI 1.55–6.25) ($p = 0.001$) but no significant associations for adult-onset MOGAD • 80 % (8/10) of paediatric-onset MOGAD carriers of the DQB1 * 05:02–DRB1 * 16:02 haplotype had a relapsing course compared to 37 % (15/41) of non-carriers ($p = 0.030$)	Class II
Nfl	152 total; 42 MOGAD	[124]	Serum	• Nfl levels were significantly higher in AQP4-IgG seropositive NMOSD (median 17.6, IQR 9.6–48.1 pg/mL), MOGAD (median 27.2, IQR 10.8–54.8 pg/mL), and RRMS (median 24.5, IQR 14.5–58.3 pg/mL) compared to HCs (median 7.4, IQR 5.6–9.4 pg/mL) (all $p < 0.001$) • Nfl levels were significantly higher at attack (median 34.1, IQR 17.6–64.3 pg/mL) compared to remission (median 2.5, IQR 9.1–48.4 pg/mL) in MOGAD ($p = 0.049$)	Class I
	120 total; 49 MOGAD	[125]	Serum	• Nfl levels in adults were significantly higher at attack (median 31.0, IQR 15.8–81.2 pg/mL) compared to remission (median 8.1, IQR 5.7–14.4 pg/mL) and HCs (median 10.3, IQR 8.1–13.3 pg/mL) ($p = 0.001$ and $p = 0.004$, respectively) • Nfl levels in children were significantly higher at attack (median 46.8, IQR 5.8–130.2 pg/mL) compared to remission (median 13.1, IQR 4.7–35.7 pg/mL) and HCs (median 8.2, IQR 6.4–11.3 pg/mL) ($p = 0.001$ and $p = 0.007$, respectively)	Class I
	164 total; 19 MOGAD	[126]	Serum	• Nfl levels collected within 3-months of onset were significantly higher in children with MOGAD (median 56.7, range 4.1–372.8 pg/mL), other ADS (median 26.5, range 1.5–2444.3 pg/mL), and MS (median 39.1, range 4.2–474.7 pg/mL) compared to controls with other neurological diseases (median 7.5, range 3.0–31.8 pg/mL) (all $p < 0.001$)	Class I
	41 total; 15 MOGAD	[127]	Serum	• Nfl levels were elevated in all (17) attack samples compared to 24 % (14/59) of remission samples ($p < 0.0001$)	Class II
	36 total; 18 MOGAD	[128]	Serum	• Nfl levels were increased at onset then stable or decreased with no significant elevation at subsequent attacks	Class III
	49 total; 16 MOGAD	[129]	Serum	• No significant difference between Nfl levels at attack and remission	Class I
Tau	49 total; 16 MOGAD	[129]	Serum	• Tau levels were significantly higher at attack (median 0.5, IQR 0.4–0.5 pg/mL) compared to remission (median 0.2, IQR 0.1–0.3 pg/mL) ($p = 0.027$)	Class I
GFAP	152 total; 42 MOGAD	[124]	Serum	• GFAP levels were significantly elevated in AQP4-IgG seropositive NMOSD (median 274.1, IQR 109.2–1680.6 pg/mL) and MOGAD (median 136.7, IQR 97.8–220.1 pg/mL) compared to HCs (median 61.4, IQR 49.7–81.0 pg/mL) (all $p < 0.001$)	Class I
	41 total; 15 MOGAD	[127]	Serum	• GFAP levels were not significantly elevated at attack	Class II
	49 total; 16 MOGAD	[129]	Serum	• No significant difference between GFAP levels at attack and remission	Class I
IL−1β	93 total; 21 MOGAD	[130]	Serum	• IL−1β levels were significantly increased at attack compared to remission ($p = 0.002$)	Class I
MFAP4	152 total; 22 MOGAD	[131]	CSF	• MFAP4 levels were significantly reduced at attack compared to remission ($p = 0.001$)	Class II
sTREM2	38 total; 19 MOGAD	[132]	Serum and CSF	• sTREM2 levels were significantly elevated in serum and CSF of children with MOGAD compared to non-neuroinflammatory disorder controls ($p = 0.0012$ and $p < 0.001$, respectively); all samples were collected at attack	Class III
TNFAIP3	68 total; 24 MOGAD	[133]	Serum	• TNFAIP3 levels were significantly reduced at attack compared to remission and HCs ($p = 0.04$ and $p = 0.0001$, respectively)	Class II
Thiol homeostasis	85 total; 8 MOGAD	[134]	Serum	• Total thiol and native thiol levels were significantly lower in samples collected at attack compared to remission in a combined cohort of MOGAD, AQP4-IgG seropositive NMOSD, and MS	Class III
Prolactin	138 total; 15 MOGAD	[135]	Serum	• No significant difference between prolactin levels in MOGAD at attack and remission	Class II
UCHL1	225 total; 7 MOGAD	[136]	Serum	• UCHL1 levels were not elevated (> 2 SDs of HD means) at baseline in any individuals with MOGAD nor was any significant attack-related pattern observed	Class I

[a] Classification of evidence was assessed using the American Academy of Neurology (AAN) Criteria for Rating Diagnostic Accuracy Studies.

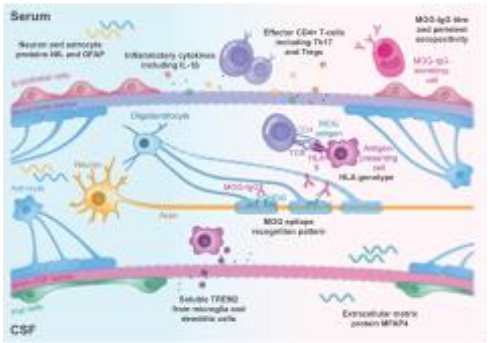

Fig. 2. : Schematic overview of the potential biomarkers of prognosis in MOGAD. Biomarkers are reviewed in further detail in Table 1. CSF, cerebrospinal fluid; HLA II, human leukocyte antigen class II; IL-1β, interleukin-1 beta; MFAP4, microfibrillar-associated protein 4; MOG, myelin oligodendrocyte glycoprotein; MOG-IgG, myelin oligodendrocyte glycoprotein immunoglobulin G; TCR, T-cell receptor; Th17, T helper 17 cells; Tregs, T regulatory cells; TREM2, triggering receptor expressed on myeloid cells 2; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein.

settings of clinical uncertainty to discriminate whether symptoms represent a MOGAD attack as opposed to an alternate pathology (Table 1 and Fig. 2). Naturally, MOG-IgG titres have been interrogated in this context. Median MOG-IgG titres have been shown to be significantly elevated at attack compared to remission [67,111]. This aligned with another report whereby stratification of MOG-IgG titres revealed that high (≥1:160) titres were only observed within 4-months from an attack [117]. Nevertheless, there are two important caveats to the interpretation of MOG-IgG titres for disease activity correlation: firstly, longitudinal sampling has revealed that titres may fluctuate independent of attacks [111]; secondly, the International MOGAD Panel proposed criteria outlined 'low positive' and 'clear positive' reference thresholds for many CBAs although further reference data to characterise additional thresholds appropriately sensitive and specific for prediction of attack or remission disease activity are currently lacking [26].

Exploratory analyses have interrogated the utility of PBMC immunophenotyping as a biomarker of disease activity in MOGAD [118,119]. PBMCs were isolated from individuals with MOGAD, AQP4-IgG seropositive NMOSD, MS, and HCs and T-cell subsets were measured – with respect to HCs, the proportions of Th17-cells and the Th17/Treg ratios were significantly increased in all three disorders at both attack and remission timepoints [118]. Additionally, a comparison of paired attack and remission samples revealed that the proportions of Th17-cells in MOGAD, AQP4-IgG seropositive NMOSD, and MS were all significantly increased at attack compared to remission [118]. Contrastingly, another study compared both B- (transitional B-cells, naïve B-cells, memory B-cells, and plasmablasts) and T-cell (natural killer (NK) cells, CD4 + T-cells, CD8 + T-cells, and Treg-cells) subsets from individuals with MOGAD, AQP4-IgG seropositive NMOSD, and HCs [119]. Plasmablasts were significantly lower at attack in MOGAD compared to AQP4-IgG seropositive NMOSD, and transitional B-cells were significantly higher at remission in MOGAD compared to HCs and AQP4-IgG seropositive NMOSD [119]. The presence or absence of differences between B- and T-cell subsets at attack compared to remission in MOGAD was not explicitly stated [119]. Theoretically, there is potential for PBMC immunophenotyping as a biomarker of disease activity in MOGAD; however, the discriminatory capacity between other autoimmune inflammatory demyelinating conditions appears limited due to apparent common immunologic mechanisms.

Index ratios derived from peripheral blood counts have also been evaluated for their usefulness as biomarkers of disease activity in MOGAD [120–122]. NLR, PLR, and neutrophil percentage (N%) were all found to be significantly elevated at attack compared to remission while eosinophil-to-lymphocyte ratio (ELR) was significantly lower at attack [120]. Values for areas under the receiver operating characteristic (ROC) curve for each parameter were modest – NLR, ELR, PLR, and N% were 0.68, 0.69, 0.61, and 0.68, respectively [120]. Other studies have similarly observed significantly elevated NLR in samples collected at attack in MOGAD [121,122]. Peripheral blood count index ratios are an accessible metric and have potential as supportive biomarkers; however, a fundamental limitation will be that neutrophilia occurs in a multitude of other circumstances.

Neurofilament light chain (NfL) and tau are proteins specific to neurons – particularly axons – while glial fibrillary acidic protein (GFAP) is a protein specific to astrocytes; elevated levels of these biomarkers in the serum or CSF may reflect damage to their respective cells [123]. It has been shown that serum NfL levels in MOGAD are significantly elevated at attack compared to HCs [124–126] and also compared to remission samples [125,127]. In contrast, it has been reported that serum NfL levels increased at onset of MOGAD but were subsequently stable or decreased irrespective of attacks [128]. There has not been consensus regarding elevation of serum NfL at attack in MOGAD [129]. Serum tau has been observed to increase significantly at attack [129]. It has primarily been reported that serum GFAP does not increase significantly at attack [127,129], though increased levels have been observed but to a lesser degree than seen in AQP4-IgG NMOSD – an astrocytopathy [124]. A challenge of these biomarkers is that elevated levels can occur with a multitude of neurological disorders beyond demyelination, such as stroke, traumatic brain injury, and Parkinson's disease [123]. Nonetheless, the married pattern of all three biomarkers may improve interpretation as this appears distinct at least between MOGAD and AQP4-IgG seropositive NMOSD [129].

Numerous other novel biomarkers have been investigated for association with disease activity in MOGAD (Table 1 and Fig. 2). Significant correlations have been observed with serum IL-1β [130], CSF microfibrillar-associated protein 4 (MFAP4) [131], CSF secreted ectodomain of soluble triggering receptor expressed on myeloid cells 2 (sTREM2) [132], tumour necrosis factor alpha-induced protein 3 (TNFAIP3) [133], and serum total thiol and native thiol [134]. In contrast, no correlation was observed with disease activity and serum prolactin levels [135] or serum ubiquitin C-terminal hydrolase L1 (UCHL1) [136].

5. The current treatment landscape

Current treatment pathways for MOGAD are largely based on clinical expertise and are highly variable. A survey of 52 neurologists who practice internationally found that all treat acute attacks with high dose corticosteroids [137]. Intravenous corticosteroids have been shown to achieve dramatic symptom improvement [32,67,138,139]. An example proposed regimen is 30 mg/kg per day or 1 g per day for 3–5 days [140]. Escalation therapies for an acute attack include intravenous immunoglobulin (IVIg) and/or plasma exchange (PLEX) [141,142]. Notably, a recent cohort study supported early first-line PLEX with concomitant disease-modifying therapy to achieve complete remission and minimise residual disability [143]. Rapid corticosteroid taper and corticosteroid withdrawal have been shown to confer increased risk of relapse [32,38]. Varied regimens of oral prednisone dosing have been proposed and include 12.5 mg daily for adults and 0.16 mg/kg/day for children for a minimum of 3-months, and 60 mg daily for adults reduced by 5 mg weekly for a total 12-week course [107,144].

After onset attack, 60 % of neurologists reported starting steroid-sparing maintenance therapy, and this increased to 92.3 % of neurologists after an individual had experienced two or more attacks [137]. The most commonly used steroid-sparing agents include azathioprine, mycophenolate mofetil, and rituximab, which all aim to deplete B-cells

in the context of this autoantibody-associated pathology [30,33,137,139]. While rituximab does reduce relapse rates, it appears less efficacious in MOGAD than in AQP4-IgG seropositive NMOSD [145]. Biologic agents such as tocilizumab and satralizumab, which target IL-6R, have yielded promising results in small case series of individuals with treatment-refractory MOGAD [146,147].

6. Future directions

MOGAD is a relatively newly defined clinical entity, though significant progress has already been made toward its characterisation. The vast majority of the existing primary literature is observational cohort studies and, thus, there is a need for progression up the hierarchy of evidence with randomised controlled trials, systematic reviews, and meta-analyses, particularly with regard to biomarker prognostication and therapeutic strategies. It is anticipated that the recently published International MOGAD Panel proposed criteria will assist with standardising future research approaches in the field.

7. Conclusions

MOGAD is an inflammatory demyelinating pathology characterised by the presence of pathogenic autoantibodies targeting MOG. MOG-IgG elicits demyelination via a multitude of mechanisms, including CDC, ADCC, enhanced cognate T-cell CNS infiltration and activation, and oligodendrocyte cytoskeleton disruption. There is an imperative need to improve prediction of disease course and disease activity to limit relapse-associated disability accrual and minimise unnecessary exposure to immunosuppression in monophasic individuals. Several biomarkers have been identified as potential candidates associated with relapsing disease course and disease activity. Despite their potential, widespread implementation in laboratories and clinics is challenging due to technological issues and low prevalence of MOGAD. International validation studies are warranted to ensure global application in clinical practice.

Funding

Authors' work was supported by grants from the National Health Medical Research Council (Australia, FB GNT2016841).

CRediT authorship contribution statement

Brilot Fabienne: Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Andersen Jane:** Writing – review & editing, Writing – original draft, Visualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

There was no use of Generative AI or AI-assisted technologies.

Declaration of Competing Interest

JA and FB have no competing interest.

References

[1] R. Lebar, M. Baudrimont, C. Vincent, Chronic experimental autoimmune encephalomyelitis in the guinea pig. Presence of anti-M2 antibodies in central nervous system tissue and the possible role of M2 autoantigen in the induction of the disease, J. Autoimmun. 2 (2) (1989) 115–132.

[2] C.P. Genain, M.H. Nguyen, N.L. Letvin, R. Pearl, R.L. Davis, M. Adelman, M. B. Lees, C. Linington, S.L. Hauser, Antibody facilitation of multiple sclerosis-like lesions in a nonhuman primate, J. Clin. Invest 96 (6) (1995) 2966–2974.

[3] C. Linington, M. Bradl, H. Lassmann, C. Brunner, R. Vass, Augmentation of demyelination in rat acute allergic encephalomyelitis by circulating mouse monoclonal antibodies directed against a myelin/oligodendrocyte glycoprotein, Am. J. Pathol. 130 (3) (1988) 443–454.

[4] H. Lassmann, M. Bradl, Multiple sclerosis: experimental models and reality, Acta Neuropathol. 133 (2) (2017) 223–244.

[5] C.P. Genain, B. Cannella, S.L. Hauser, C.S. Raine, Identification of autoantibodies associated with myelin damage in multiple sclerosis, Nat. Med 5 (2) (1999) 170–175.

[6] T. Berger, P. Rubner, F. Schautzer, R. Egg, H. Ulmer, T. Mayringer, B. Dilitz, F. Deisenhammer, M. Reindl, Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event, N. Engl. J. Med. 349 (2) (2003) 139–145.

[7] J.I. O'Riordan, A.J. Thompson, D.P. Kingsley, D.G. MacManus, B.E. Kendall, P. Rudge, W.I. McDonald, D.H. Miller, The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up, Brain 121 (Pt 3) (1998) 495–503.

[8] E.T. Lim, T. Berger, M. Reindl, C.M. Dalton, K. Fernando, G. Keir, E.J. Thompson, D.H. Miller, G. Giovannoni, Anti-myelin antibodies do not allow earlier diagnosis of multiple sclerosis, Mult. Scler. 11 (4) (2005) 492–494.

[9] R. Pelayo, M. Tintoré, X. Montalban, A. Rovira, C. Espejo, M. Reindl, T. Berger, Antimyelin antibodies with no progression to multiple sclerosis, N. Engl. J. Med. 356 (4) (2007) 426–428.

[10] J. Kuhle, C. Pohl, M. Mehling, G. Edan, M.S. Freedman, H.-P. Hartung, C. H. Polman, D.H. Miller, X. Montalban, F. Barkhof, L. Bauer, S. Dahms, R. Lindberg, L. Kappos, R. Sandbrink, Lack of association between antimyelin antibodies and progression to multiple sclerosis, N. Engl. J. Med. 356 (4) (2007) 371–378.

[11] S. Rauer, B. Euler, M. Reindl, T. Berger, Antimyelin antibodies and the risk of relapse in patients with a primary demyelinating event, J. Neurol. Neurosurg. Psychiatry 77 (6) (2006) 739.

[12] H. Wang, K.L. Munger, M. Reindl, P.J. O'Reilly, L.I. Levin, T. Berger, A. Ascherio, Myelin oligodendrocyte glycoprotein antibodies and multiple sclerosis in healthy young adults, Neurology 71 (15) (2008) 1142–1146.

[13] S.J. Pittock, M. Reindl, S. Achenbach, T. Berger, W. Bruck, F. Konig, Y. Morales, H. Lassmann, S. Bryant, S.B. Moore, B.M. Keegan, C.F. Lucchinetti, Myelin oligodendrocyte glycoprotein antibodies in pathologically proven multiple sclerosis: frequency, stability and clinicopathologic correlations, Mult. Scler. 13 (1) (2007) 7–16.

[14] M. Khalil, M. Reindl, A. Lutterotti, B. Kuenz, R. Ehling, C. Gneiss, P. Lackner, F. Deisenhammer, T. Berger, Epitope specificity of serum antibodies directed against the extracellular domain of myelin oligodendrocyte glycoprotein: influence of relapses and immunomodulatory treatments, J. Neuroimmunol. 174 (1–2) (2006) 147–156.

[15] K.C. O'Connor, K.A. McLaughlin, P.L. De Jager, T. Chitnis, E. Bettelli, C. Xu, W. H. Robinson, S.V. Cherry, A. Bar-Or, B. Banwell, H. Fukazawa, T. Fukazawa, S. Tenembaum, S.J. Wong, N.P. Tavakoli, Z. Idrissova, V. Viglietta, K. Rostasy, D. Pohl, R.C. Dale, M. Freedman, L. Steinman, G.J. Buckle, V.K. Kuchroo, D. A. Hafler, K.W. Wucherpfennig, Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein, Nat. Med. 13 (2) (2007) 211–217.

[16] P. Waters, M. Woodhall, K.C. Connor, M. Reindl, B. Lang, D.K. Sato, M. Jurynczyk, G. Tackley, J. Rocha, T. Takahashi, T. Misu, I. Nakashima, J. Palace, K. Fujihara, M.I. Leite, A. Vincent, MOG cell-based assay detects non-MS patients with inflammatory neurologic disease, Neurol. - Neuroimmunol. Neuroinflamm. 2 (3) (2015) e89.

[17] Y. Kim, J.-W. Hyun, M.R. Woodhall, Y.-M. Oh, J.-E. Lee, J.Y. Jung, S.Y. Kim, M. Y. Lee, S.-H. Kim, W. Kim, S.R. Irani, P. Waters, K. Choi, H.J. Kim, Refining cell-based assay to detect MOG-IgG in patients with central nervous system inflammatory diseases, Mult. Scler. Relat. Disord. 40 (2020) 101939.

[18] P.J. Waters, L. Komorowski, M. Woodhall, S. Lederer, M. Majed, J. Fryer, J. Mills, E.P. Flanagan, S.R. Irani, A.C. Kunchok, A. McKeon, S.J. Pittock, A multicenter comparison of MOG-IgG cell-based assays, Neurology 92 (11) (2019) e1250.

[19] J. Dalmau, T. Armangué, J. Planagumà, M. Radosevic, F. Mannara, F. Leypoldt, C. Geis, F. Lancaster, M.J. Titulaer, M.R. Rosenfeld, F. Graus, An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models, Lancet Neurol. 18 (11) (2019) 1045–1057.

[20] M. Reindl, K. Schanda, M. Woodhall, F. Tea, S. Ramanathan, J. Sagen, J.P. Fryer, J. Mills, B. Teegen, S. Mindorf, N. Ritter, U. Kraemmel, W. Stöcker, J. Eggert, E. P. Flanagan, M. Bamberger, H. Hegen, K. Rostasy, T. Berger, M.I. Leite, J. Palace, S.R. Irani, R.C. Dale, C. Probst, M. Probst, F. Brilot, S.J. Pittock, P. Waters, International multicenter examination of MOG antibody assays, Neurol. Neuroimmunol. Neuroinflamm. 7 (2) (2020).

[21] F. Tea, J.A. Lopez, S. Ramanathan, V. Merheb, F.X.Z. Lee, A. Zou, D. Pilli, E. Patrick, A. van der Walt, M. Morsli, E.M. Tantsis, E.M. Yiu, S. Vucic, A.P. D. Henderson, A. Peak, C.L. Fraser, J. Lechner-Scott, S.W. Reddel, S. Broadley, M. H. Barnett, D.A. Brown, J.D. Lunemann, R.C. Dale, F. Brilot, Australasian; New Zealand, M. O. G. S. G., Characterisation of the human myelin oligodendrocyte glycoprotein antibody response in demyelination, Acta Neuropathol. Commun. 7 (1) (2019) 145.

[22] C. Macrini, R. Gerhards, S. Winklmeier, L. Bergmann, S. Mader, M. Spadaro, A. Vural, M. Smolik, R. Hohlfeld, T. Kümpfel, S.F. Lichtenthaler, H.G. Franquelim, D. Jenne, E. Meinl, Features of MOG required for recognition by patients with MOG antibody-associated disorders, Brain 144 (8) (2021) 2375–2389.

[23] F. Brilot, R.C. Dale, R.C. Selter, V. Grummel, S.R. Kalluri, M. Aslam, M. Phil, V. Busch, D. Zhou, S. Cepok, B. Hemmer, Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease, Ann. Neurol. 66 (6) (2009) 833–842.

[24] J. Kitley, M. Woodhall, P. Waters, M.I. Leite, E. Devenney, J. Craig, J. Palace, A. Vincent, Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype, Neurology 79 (12) (2012) 1273–1277.
[25] S. Mader, V. Gredler, K. Schanda, K. Rostasy, I. Dujmovic, K. Pfaller, A. Lutterotti, S. Jarius, F. Di Pauli, B. Kuenz, R. Ehling, H. Hegen, F. Deisenhammer, F. Aboul-Enein, M.K. Storch, P. Koson, J. Drulovic, W. Kristoferitsch, T. Berger, M. Reindl, Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders, J. Neuroinflamm. 8 (2011) 184.
[26] B. Banwell, J.L. Bennett, R. Marignier, H.J. Kim, F. Brilot, E.P. Flanagan, S. Ramanathan, P. Waters, S. Tenembaum, J.S. Graves, T. Chitnis, A.U. Brandt, C. Hemingway, R. Neuteboom, L. Pandit, M. Reindl, A. Saiz, D.K. Sato, K. Rostasy, F. Paul, S.J. Pittock, K. Fujihara, J. Palace, Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD panel proposed criteria, Lancet Neurol. 22 (3) (2023) 268–282.
[27] B.P. Trewin, F. Brilot, S.W. Reddel, R.C. Dale, S. Ramanathan, MOGAD: a comprehensive review of clinicoradiological features, therapy and outcomes in 4699 patients globally, Autoimmun. Rev. 24 (1) (2025) 103693.
[28] K. O'Connell, A. Hamilton-Shield, M. Woodhall, S. Messina, R. Mariano, P. Waters, S. Ramdas, M.I. Leite, J. Palace, Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire, UK, J. Neurol. Neurosurg. Psychiatry 91 (10) (2020) 1126–1128.
[29] C.L. de Mol, Y. Wong, E.D. van Pelt, B. Wokke, T. Siepman, R.F. Neuteboom, D. Hamann, R.Q. Hintzen, The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults, Mult. Scler. 26 (7) (2020) 806–814.
[30] R.R.R. Nagireddy, A. Kumar, V.K. Singh, R. Prasad, A. Pathak, R.N. Chaurasia, V. N. Mishra, D. Joshi, Clinicoradiological comparative study of Aquaporin-4-IgG seropositive neuromyelitis optica spectrum disorder (NMOSD) and MOG antibody associated disease (MOGAD): a prospective observational study and review of literature, J. Neuroimmunol. 361 (2021) 577742.
[31] A. Cobo-Calvo, A. Ruiz, E. Maillart, B. Audoin, H. Zephir, B. Bourre, J. Citron, N. Collongues, D. Brassat, F. Cotton, C. Papeix, F. Durand-Dubief, D. Lapiani, R. Deschamps, M. Cohen, D. Biotti, X. Ayrignac, C. Tilikete, E. Thouvenot, B. Brochet, C. Dulau, T. Moreau, A. Tourbah, P. Labauge, L. Michel, C. Lebrun-Frenay, A. Montcuquet, G. Mathey, M. Debouverie, J. Pelletier, P. Labauge, N. Deracke, M. Coustans, F. Rollot, J. De Seze, S. Vukusic, R. Marignier, Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: the MOGADOR study, Neurology 90 (21) (2018) e1858–e1869.
[32] M. Juryaczyk, S. Messina, M.R. Woodhall, N. Raza, R. Everett, A. Roca-Fernandez, G. Tackley, S. Hamid, A. Sheard, G. Reynolds, S. Chandratre, C. Herringway, A. Jacob, A. Vincent, M.I. Leite, P. Waters, J. Palace, Clinical presentation and prognosis in MOG-antibody disease: a UK study, Brain 140 (12) (2017) 3128–3138.
[33] S. Huda, D. Whittam, R. Jackson, V. Karthikeayan, P. Kelly, S. Linaker, K. Mutch, R. Kneen, M. Woodhall, K. Murray, D. Hunt, P. Waters, A. Jacob, Predictors of relapse in MOG antibody associated disease: a cohort study, Benj Open 11 (11) (2021) e055392.
[34] E.D. van Pelt, Y.Y.M. Wong, L.A. Ketelslegers, D. Hamann, R.Q. Hintzen, Neuromyelitis optica spectrum disorders: comparison of clinical and magnetic resonance imaging characteristics of AQP4-IgG versus MOG-IgG seropositive cases in the Netherlands, Eur. J. Neurol. 23 (3) (2016) 580–587.
[35] J. Jitprapaikulsan, J.J. Chen, E.P. Flanagan, W.O. Tobin, J.P. Fryer, B. G. Weinshenker, A. McKeon, V.A. Lennon, J.A. Leavitt, J.-M. Tillema, C. Lucchinetti, B.M. Keegan, O. Kantarci, C. Khanna, S.M. Jenkins, G.M. Spears, J. Sagan, S.J. Pittock, Aquaporin-4 and myelin oligodendrocyte glycoprotein autoantibody status predict outcome of recurrent optic neuritis, Ophthalmology 125 (10) (2018) 1628–1637.
[36] G. Zhao, Q. Chen, Y. Huang, Z. Li, X. Sun, P. Lu, S. Yan, M. Wang, G. Tian, Clinical characteristics of myelin oligodendrocyte glycoprotein seropositive optic neuritis: a cohort study in Shanghai, China, J. Neurol. 265 (1) (2018) 33–40.
[37] M. Spatola, O. Chuquisana, W. Jung, J.A. Lopez, E.M. Wendel, S. Ramanathan, C. W. Keller, T. Hahn, F. Meinl, M. Reindl, R.C. Dale, H. Wiendl, D.A. Lauffenburger, K. Rostásy, F. Brilot, G. Alter, J.D. Lünemann, Humoral signatures of MOG-antibody-associated disease track with age and disease activity, Cell Rep. Med. 4 (2) (2023) 100913.
[38] S. Ramanathan, S. Mohammad, E. Tantsis, T. Nguyen, V. Merheb, V. Fung, O. White, S. Broadley, J. Lechner-Scott, S. Vucic, A. Henderson, M. Barnett, S. Reddel, F. Brilot, R. Dale, The clinical course, therapeutic responses, and outcomes in relapsing MOG antibody-associated demyelination, Mult. Scler. 23 (13) (2017) NP1.
[39] S. Mariotto, S. Ferrari, S. Monaco, M.D. Benedetti, K. Schanda, D. Alberti, A. Farinazzo, R. Capra, C. Mancinelli, N. De Rossi, R. Bombardi, L. Zuliani, M. Zoccarato, R. Tanel, A. Bonora, M. Turatti, M. Calabrese, A. Polo, A. Pavone, L. Grazian, G. Sechi, E. Serchi, D. Urso, R. Delogu, F. James, L. Deotto, M. Cadaldini, M.R. Bianchi, G. Cantalupo, M. Reindl, A. Gajofatto, Clinical spectrum and IgG subclass analysis of anti-myelin oligodendrocyte glycoprotein antibody-associated syndromes: a multicenter study, J. Neurol. 264 (12) (2017) 2420–2430.
[40] D. Dubey, S.J. Pittock, K.N. Krecke, P.P. Morris, E. Sechi, N.L. Zalewski, B. G. Weinshenker, E. Shosha, C.F. Lucchinetti, J.P. Fryer, A.S. Lopez-Chiriboga, J. C. Chen, J. Jitprapaikulsan, A. McKeon, A. Gadoth, B.M. Keegan, J. M. Tillema, E. Naddaf, M.C. Patterson, K. Mesaroli, K.L. Tyler, E.P. Flanagan, Clinical, radiologic, and prognostic features of myelitis associated with myelin oligodendrocyte glycoprotein autoantibody, JAMA Neurol. 76 (3) (2019) 301–309.
[41] V.A. Lennon, D.M. Wingerchuk, T.J. Kryzer, S.J. Pittock, C.F. Lucchinetti, K. Fujihara, I. Nakashima, B.G. Weinshenker, A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis, Lancet 364 (9451) (2004) 2106–2112.
[42] V.A. Lennon, T.J. Kryzer, S.J. Pittock, A.S. Verkman, S.R. Hinson, IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel, J. Exp. Med. 202 (4) (2005) 473–477.
[43] J.A. Lopez, M. Denkova, S. Ramanathan, R.C. Dale, F. Brilot, Pathogenesis of autoimmune demyelination: from multiple sclerosis to neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody-associated disease, Clin. Transl. Immunol. 10 (7) (2021) e1316.
[44] C. Brunner, H. Lassmann, T.V. Waehneldt, J.-M. Matthieu, C. Linington, Differential ultrastructural localization of myelin basic protein, myelin/oligodendroglial glycoprotein, and 2',3'-cyclic nucleotide 3'-phosphodiesterase in the CNS of adult rats, J. Neurochem. 52 (1) (1989) 296–304.
[45] A.A. Hilton, A.J. Slavin, D.J. Hilton, C.C. Bernard, Characterization of cDNA and genomic clones encoding human myelin oligodendrocyte glycoprotein, J. Neurochem. 65 (1) (1995) 309–318.
[46] N.J. Scolding, S. Frith, C. Linington, B.P. Morgan, A.K. Campbell, D.A. Compston, Myelin-oligodendrocyte glycoprotein (MOG) is a surface marker of oligodendrocyte maturation, J. Neuroimmunol. 22 (3) (1989) 169–176.
[47] J.F. Kroepfl, L.R. Vlise, A.J. Charrua, C. Linington, M.V. Gardtner, Investigation of myelin/oligodendrocyte glycoprotein membrane topology, J. Neurochem. 67 (5) (1996) 2219–2222.
[48] A. Shetty, S.G. Gupta, M. Varrin-Doyer, M.S. Weber, T. Prod'homme, N. Molnarfi, N. Ji, P.A. Nelson, J.C. Patarroyo, U. Schulze-Topphoff, S.E. Fogal, T. Forsthuber, R.A. Sobel, C.C. Bernard, A.J. Slavin, S.S. Zamvil, Immunodominant T-cell epitopes of MOG reside in its transmembrane and cytoplasmic domains in EAE, Neurol. Neuroimmunol. Neuroinflamm. 1 (2) (2014) e22.
[49] C.R. Marta, C.M. Taylor, T. Coetzee, T. Kim, S. Winkler, R. Bansal, S.E. Pfeiffer, Antibody cross-linking of myelin oligodendrocyte glycoprotein leads to its rapid repartitioning into detergent-insoluble fractions, and altered protein phosphorylation and cell morphology, J. Neurosci. 23 (13) (2003) 5461–5471.
[50] H.-C. von Büdingen, F. Mei, A. Greenfield, S. Jahn, Y. A.A. Shen, H.H. Reid, D. D. McKemy, J.R. Chan, The myelin oligodendrocyte glycoprotein directly binds nerve growth factor to modulate central axon circuitry, J. Cell Biol. 210 (6) (2015) 891–898.
[51] K. Kohyama, H. Nishida, K. Kaneko, T. Mizu, I. Nakashima, H. Sakuma, Complement-dependent cytotoxicity of human autoantibodies against myelin oligodendrocyte glycoprotein, Front. Neurosci. 17 (2023).
[52] S. Jarius, M. Ringelstein, K. Schanda, K. Ruprecht, M. Korporal Kuhnke, A. Viehöver, M.W. Hümmert, P. Schindler, V. Endmayr, M. Gastaldi, C. Trebst, D. Franciotta, O. Aktas, R. Hoftberger, J. Haas, L. Komorowski, F. Paul, M. Reindl, B. Wildemann, Improving the sensitivity of myelin oligodendrocyte glycoprotein-antibody testing: exclusive or predominant MOG-IgG3 seropositivity—a potential diagnostic pitfall in patients with MOG EM/MOGAD, J. Neurol. 271 (7) (2024) 4660–4671.
[53] A.B. Ayrosa Galvão Ribeiro Gomes, L. Kuhlvehagen, P. Lippa, A. Cagol, N. Cerdá-Fuertes, T. Neziraj, J. Flammer, J. Lerner, A.-C. Lecourt, N. de Oliveira S. Siebenborn, R. Cortese, S. Schaedelin, V. Andreoli Schoeps, A. de Moura Brasil Matos, N. Trombini Mendes, C. dos Reis Pereira, M.L. Ribeiro Monteiro, S.L. dos Apóstolos-Pereira, P. Schindler, C. Chien, C. Schwake, R. Schneider, T. Pukenrathan, O. Aktas, U. Fischer, M. Mehling, T. Derfuss, L. Kappos, I. Ayzenberg, M. Ringelstein, F. Paul, D. Callegaro, J. Kuhle, A. Papadopoulou, C. Granziera, A.-K. Pröbstel, Immunoglobulin A antibodies against myelin oligodendrocyte glycoprotein in a subgroup of patients with central nervous system demyelination, JAMA Neurol. 80 (9) (2023) 989–996.
[54] S.T. Proulx, B. Engelhardt, Central nervous system zoning: how brain barriers establish subdivisions for CNS immune privilege and immune surveillance, J. Intern. Med. 292 (1) (2022) 47–67.
[55] C.E. Moseley, A. Virupakshaiah, T.G. Forsthuber, L. Steinman, E. Waubant, S. S. Zamvil, MOG CNS Autoimmunity and MOGAD, Neurol. Neuroimmunol. amp; Neuroinflamm. 11 (5) (2024) e200275.
[56] K. Karell, A.S. Louka, S.J. Moodie, H. Ascher, F. Clot, L. Green, P.J. Ciclitira, L. M. Sollid, J. Partanen, HLA types in celiac disease patients not carrying the DQA1* 05-DQB1* 02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease, Hum. Immunol. 64 (4) (2003) 469–477.
[57] G. Thomson, A.M. Valdes, J.A. Noble, I. Kockum, M.N. Grote, J. Najman, H. A. Erlich, F. Cocca, A. Pugliese, A. Steenkiste, J.S. Doxiadis, S. Caillat Zucman, R. Hermann, J. Ilonen, A.P. Lambert, P.J. Bingley, K.M. Gillespie, A. Lernmark, C. B. Sanjeevi, K.S. Ronningen, D.E. Undlien, E. Thorsby, A. Petrone, R. Buzzetti, B. P. Koeleman, B.O. Roep, G. Saruhan-Direskeneli, F.A. Uyar, H. Günoz, C. Gorodezky, C. Alaez, B.O. Boehm, W. Mlynarski, H. Ikegami, M. Berrino, M. E. Fasano, E. Dorrello, S. Israel, C. Brautbar, A. Santiago-Cortes, T. Frazer de Llado, J.K. She, T.L. Bugawan, J.I. Rotter, L. Raffel, A. Zeidler, F. Leyva-Cobian, B. R. Hawkins, S.H. Chan, L. Gaziano, F. Pociot, J. Nerup, Relative predispositional effects of HLA class II DRB1-DQB1 haplotypes and genotypes on type 1 diabetes: a meta-analysis, Tissue Antigens 70 (2) (2007) 110–127.
[58] L. Moutsianas, L. Jostins, A.H. Beecham, A.T. Dilthey, D.K. Xifara, M. Ban, T. S. Shah, N.A. Patsopoulos, L. Alfredsson, C.A. Anderson, K.E. Attfield, S. E. Baranzini, J. Barrett, T.M.C. Binder, D. Booth, D. Buck, E.G. Celius, C. Cotsapas, S. D'Alfonso, C.A. Dendrou, P. Donnelly, B. Dubois, B. Fontaine, L. Fugger, A. Goris, P.-A. Gourraud, C. Graetz, B. Hemmer, J. Hillert, I.B.D.G. C. International, I. Kockum, S. Leslie, C.M. Lill, F. Martinelli-Boneschi, J. R. Oksenberg, T. Olsson, A. Oturai, J. Saarela, H.B. Sondergaard, A. Sparkland, B. Taylor, J. Winkelmann, F. Zipp, J.L. Haines, M.A. Pericak-Vance, C.C.

A. Spencer, G. Stewart, D.A. Hafler, A.J. Ivinson, H.F. Harbo, S.L. Hauser, P.L. De Jager, A. Compston, J.L. McCauley, S. Sawcer, G. McVean, C. the International Multiple Sclerosis Genetics, Class II HLA interactions modulate genetic risk for multiple sclerosis, Nat. Genet. 47 (10) (2015) 1107–1113.
[59] X. Sun, W. Qiu, J. Wang, S. Wang, Y. Wang, X. Zhang, C. Liu, C. Cui, H. Hong, H. Hong, H. Yang, X.J. Li, Z. Lu, X. Hu, A.G. Kermode, A.G. Kermode, L. Peng, Myelin oligodendrocyte glycoprotein-associated disorders are associated with HLA subtypes in a Chinese paediatric-onset cohort, J. Neurol., Neurosurg. Psychiatry 91 (7) (2020) 733–739.
[60] A.L. Bruijstens, Y.Y.M. Wong, D.E. van Pelt, P.J.E. van der Linden, G. W. Hoogmoet, R.Q. Hintzen, F.H.J. Claas, R.F. Neuteboom, B.H.A. Wokke, HLA association in MOG IgG- and AQP4 IgG-related disorders of the CNS in the Dutch population, Neurol. Neuroimmunol. Neuroinflamm. 7 (3) (2020).
[61] M. Grant-Peters, G.R.D. Passos, H.-Y. Yeung, A. Jacob, S. Huda, M.I. Leite, C. A. Dendrou, J. Palace, No strong HLA association with MOG antibody disease in the UK population, Ann. Clin. Transl. Neurol. 8 (7) (2021) 1502–1507.
[62] M. Varrin-Doyer, A. Shetty, C.M. Spencer, U. Schulze-Topphoff, M.S. Weber, C. C. Bernard, T. Forsthuber, B.A. Cree, A.J. Slavin, S.S. Zamvil, MOG transmembrane and cytoplasmic domains contain highly stimulatory T-cell epitopes in MS, Neurol. Neuroimmunol. Neuroinflamm. 1 (2) (2014) e20.
[63] L.S. Hofer, M. Ramberger, V. Gredler, A.S. Pescoller, K. Rostásy, M. Suspedra, H. Hegen, T. Berger, A. Lutterotti, M. Reindl, Comparative Analysis of T-Cell Responses to Aquaporin-4 and myelin oligodendrocyte glycoprotein in inflammatory demyelinating central nervous system diseases, Front. Immunol. 11 (2020).
[64] G. Saggau, P. Bacher, D. Esser, M. Rasa, S. Meise, N. Mohr, N. Kohlstedt, A. Hutloff, S.-S. Schacht, J. Dargvainiene, G.R. Martini, K.H. Stürner, I. Schröder, R. Markewitz, J. Hartl, M. Hastermann, A. Duchow, P. Schindler, M. Becker, C. Bautista, J. Gottfreund, J. Walter, J.K. Pulansky, M. Yang, R. Naghavian, M. Wendorff, E.-M. Schuster, A. Dahl, A. Petzold, S. Reinhardt, A. Franke, M. Wieczorek, L. Henschel, D. Berger, G. Heine, M. Holtsche, V. Häußler, C. Peters, E. Schmidt, S. Fillatreau, D.H. Busch, K.-P. Wandinger, K. Schober, R. Martin, F. Paul, F. Leypoldt, A. Scheffold, Autoantigen-specific CD4+ T cells acquire an exhausted phenotype and persist in human antigen-specific autoimmune diseases, Immun. (Camb., Mass.) 57 (10) (2024) 2416–2432.e8.
[65] S. Winklmeier, M. Schlüter, M. Spadaro, F.S. Thaler, A. Vural, R. Gerhards, C. Macrini, S. Mader, A. Kurne, B. Inan, R. Karabudak, F.G. Özbay, G. Esendagli, R. Hohlfeld, T. Kümpfel, E. Meinl, Identification of circulating MOG-specific B cells in patients with MOG antibodies, Neurol. - Neuroimmunol. Neuroinflamm. 6 (6) (2019) 625.
[66] R. Hoftberger, Y. Guo, E.P. Flanagan, A.S. Lopez-Chiriboga, V. Endmayr, S. Hochmeister, D. Joldic, S.J. Pittock, J.M. Tillema, M. Gorman, H. Lassmann, C. F. Lucchinetti, The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody, Acta Neuropathol. 139 (5) (2020) 875–892.
[67] S. Jarius, K. Ruprecht, I. Kleiter, N. Borisow, N. Asgari, K. Pitarokoili, F. Pache, O. Stich, L.A. Beume, M.W. Hümmert, C. Trebst, M. Ringelstein, O. Aktas, A. Winkelmann, M. Buttmann, A. Schwarz, H. Zimmermann, A.U. Brandt, D. Franciotta, M. Capobianco, J. Kuchling, J. Haas, M. Korporal-Kuhnke, S. T. Lillevang, K. Fechner, K. Schanda, F. Paul, B. Wildemann, M. Reindl, MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin, J. Neuroinflamm. 13 (1) (2016) 279.
[68] R.C. Dale, E.M. Tantsis, V. Merheb, R.-Y.A. Kumaran, N. Sinmaz, K. Pathmanandavel, S. Ramanathan, D.R. Booth, L.A. Wienholt, K. Prelog, D. R. Clark, G.J. Guillemin, C.K. Lim, F.K. Mathey, F. Brilot, Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton, Neurol. (R.) Neuroimmunol. Neuroinflamm. 1 (1) (2014) e12.
[69] S. Carta, R. Hftberger, A. Bolzan, S. Bozzetti, B. Bonetti, M. Scarpelli, S. Ottaviani, Antibodies to MOG in CSF only: pathological findings support the diagnostic value, Acta Neuropathol. 141 (2021) 801 (+).
[70] P. Körtvélyessy, M. Breu, M. Pawlitzki, I. Metz, H.J. Hefrnae, M. Matzke, C. Mawrin, P. Rommer, G.G. Kovacs, C. Mitter, M. Reindl, W. Brück, K. P. Wandinger, H. Lassmann, R. Höftberger, F. Leypoldt, ADEM-like presentation, anti-MOG antibodies, and MS pathology: TWO case reports, Neurol. Neuroimmunol. Neuroinflamm. 4 (3) (2017) e335.
[71] V. Redenbaugh, J.P. Fryer, L. Cacciaguerra, J.J. Chen, T.M. Greenwood, M. Gilligan, S. Thakolwiboon, M. Majed, N.H. Chia, A. McKeon, J.R. Mills, A. S. Lopez Chiriboga, J.M. Tillema, B. Yang, Y. Abdulrahman, K. Guo, N. Voresaoc, C. Valencia Sanchez, D.A. Taffinoc, M. Toledano, A. Zekeridou, D. Dubey, G. Y. Gombolay, C. Caparó-Zarrallos, I. Kister, S.J. Pittock, E.P. Flanagan, Diagnostic utility of MOG antibody testing in cerebrospinal fluid, Ann. Neurol. 96 (1) (2024) 34–45.
[72] M. Reynolds, I. Tan, K. Nguyen, V. Merheb, F.X.Z. Lee, B.P. Trewin, M. Lerch, S. Shah, N. Wolfe, K. Buzzard, J. Lechner Scott, M. Fabis Pedrini, A. Fok, N. John, C. Kneebone, C. Yiannikas, D.A. Brown, A.G. Kermode, S. Reddel, R.C. Dale, F. Brilot, S. Ramanathan, The clinical relevance of MOG antibody testing in cerebrospinal fluid, Ann. Clin. Transl. Neurol. 11 (9) (2024) 2514–2519.
[73] E. Sechi, M. Buciuc, S.J. Pittock, J.J. Chen, J.P. Fryer, S.M. Jenkins, A. Budhram, B.G. Weinshenker, A.S. Lopez-Chiriboga, J.M. Tillema, A. McKeon, J.R. Mills, W. O. Tobin, E.P. Flanagan, Positive predictive value of myelin oligodendrocyte glycoprotein autoantibody testing, JAMA Neurol. 78 (6) (2021) 741–746.
[74] S.J. Piddlesden, H. Lassmann, F. Zimprich, B.P. Morgan, C. Linington, The demyelinating potential of antibodies to myelin oligodendrocyte glycoprotein is related to their ability to fix complement, Am. J. Pathol. 143 (2) (1993) 555–564.
[75] B.G. Xiao, C. Linington, H. Link, Antibodies to myelin-oligodendrocyte glycoprotein in cerebrospinal fluid from patients with multiple sclerosis and controls, J. Neuroimmunol. 31 (2) (1991) 91–96.
[76] T. Litzenburger, R. Fässler, J. Bauer, H. Lassmann, C. Linington, H. Wekerle, A. Iglesias, B lymphocytes producing demyelinating autoantibodies: development and function in gene-targeted transgenic mice, J. Exp. Med. 188 (1) (1998) 169–180.
[77] M. Spadaro, S. Winklmeier, E. Beltran, C. Macrini, R. Höftberger, E. Schuh, F. S. Thaler, L.A. Gerdes, S. Laurent, R. Gerhards, S. Brandle, K. Doemnair, C. Breithaupt, M. Krumbholz, M. Moser, G. Krishnamoorthy, F. Kamp, D. Jenne, R. Hohlfeld, T. Kumpfel, H. Lassmann, N. Kawakami, E. Meinl, Pathogenicity of human antibodies against myelin oligodendrocyte glycoprotein, Ann. Neurol. 84 (2) (2018) 315–328.
[78] M. Lerch, K. Schanda, E. Lafon, R. Wurzner, S. Mariotto, A. Dinoto, E.M. Wendel, C. Lechner, H. Hegen, K. Rostasy, T. Berger, D. Wilflingseder, R. Hoftberger, M. Reindl, More efficient complement activation by anti-aquaporin-4 compared with anti-myelin oligodendrocyte glycoprotein antibodies, Neurol.: Neuroimmunol. Neuroinflamm. 10 (1) (2023) e200059.
[79] S.S. Yandamuri, B. Filipek, A.H. Obaid, N. Lele, J.M. Thurman, N. Makhani, R. J. Nowak, Y. Guo, C.F. Lucchinetti, E.P. Flanagan, E.E. Longbrake, K.C. O'Connor, MOGAD patient autoantibodies induce complement, phagocytosis, and cellular cytotoxicity, JCI Insight 8 (11) (2023) e165373.
[80] S. Mader, S. Ho, H.K. Wong, S. Baier, S. Winklmeier, C. Riemer, H. Ribbenen, I. M. Fernandez, R. Gerhards, C. Du, O. Chuquisana, J.D. Lünemann, A. Lux, F. Nimmerjahn, M. Bradl, N. Kawakami, E. Meinl, Dissection of complement and Fc-receptor-mediated pathomechanisms of autoantibodies to myelin oligodendrocyte glycoprotein, Proc. Natl. Acad. Sci. USA 120 (13) (2023) e2300648120.
[81] G. Vidarsson, G. Dekkers, T. Rispens, IgG Subclasses and Allotypes: From Structure to Effector Functions, Front. Immunol. 5 (2014).
[82] P. Waters, S. Jarius, E. Littleton, M.I. Leite, S. Jacob, B. Gray, R. Geraldes, T. Vale, A. Jacob, J. Palace, S. Maxwell, D. Bosson, A. Vincent, Aquaporin-4 antibodies in neuromyelitis optica and longitudinally extensive transverse myelitis, Arch. Neurol. 65 (7) (2008) 913–919.
[83] J.M. Crane, C. Lam, A. Rossi, T. Gupta, J.L. Bennett, A.S. Verkman, Binding affinity and specificity of neuromyelitis optica autoantibodies to aquaporin-4 M1/M23 isoforms and orthogonal arrays, J. Biol. Chem. 286 (18) (2011) 16516–16524.
[84] K. Kaneko, H. Kuroda, Y. Matsumoto, N. Sakamoto, N. Yamazaki, N. Yamamoto, S. Umezawa, C. Narutame, H. Ono, Y. Takei, T. Takahashi, J. Fujimori, T. Nakashima, Y. Harigaya, H. Lassmann, K. Fujihara, T. Misu, M. Aoki, Different complement activation patterns following C5 cleavage in MOGAD and AQP4-IgG+NMOSD, Neurol. Neuroimmunol. amp; Neuroinflamm. 11 (5) (2024) e200293.
[85] F. Pache, M. Ringelstein, O. Aktas, I. Kleiter, S. Jarius, N. Siebert, J. Bellmann-Strobl, F. Paul, K. Ruprecht, C3 and C4 complement levels in AQP4-IgG-positive NMOSD and in MOGAD, J. Neuroimmunol. 360 (2021) 577699.
[86] C.W. Keller, J.A. Lopez, E.-M. Wendel, S. Ramanathan, C.C. Gross, L. Klotz, M. Reindl, R.C. Dale, H. Wiendl, K. Rostasy, F. Brilot, J.D. Lunemann, Complement activation is a prominent feature of MOGAD, Ann. Neurol. 90 (6) (2021) 976–982.
[87] S. Hakobyan, S. Luppe, D.R. Evans, K. Harding, S. Loveless, N.P. Robertson, B. P. Morgan, Plasma complement biomarkers distinguish multiple sclerosis and neuromyelitis optica spectrum disorder, Mult. Scler. J. 23 (7) (2017) 946–955.
[88] P. Horellou, M. Wang, V. Keo, P. Chretien, C. Serguera, P. Waters, K. Deiva, Increased interleukin-6 correlates with myelin oligodendrocyte glycoprotein antibodies in pediatric monophasic demyelinating diseases and multiple sclerosis, J. Neuroimmunol. 289 (2015) 1–7.
[89] M. Spadaro, L.A. Gerdes, M.C. Mayer, B. Ertl-Wagner, S. Laurent, M. Krumbholz, C. Breithaupt, T. Hogen, A. Straube, A. Giese, R. Hohlfeld, H. Lassmann, E. Meinl, T. Kumpfel, Histopathology and clinical course of MOG-antibody-associated encephalomyelitis, Ann. Clin. Transl. Neurol. 2 (3) (2015) 295–301.
[90] S. Jarius, I. Metz, F.B. König, K. Ruprecht, M. Reindl, F. Paul, W. Brück, B. Wildemann, Screening for MOG-IgG and 27 other anti-glial and anti-neuronal autoantibodies in 'pattern II multiple sclerosis' and brain biopsy findings in a MOG-IgG-positive case, Mult. Scler. 22 (12) (2016) 1541–1549.
[91] Y. Takai, T. Misu, K. Kaneko, N. Chihara, K. Narikawa, S. Tsuchida, H. Nishida, T. Komori, M. Seki, T. Komatsu, K. Nakamague, T. Ikeda, M. Yoshida, T. Takahashi, H. Ono, S. Nishiyama, H. Kuroda, I. Nakashima, H. Suzuki, M. Bradl, H. Lassmann, K. Fujihara, M. Aoki, Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study, Brain 143 (5) (2020) 1431–1446.
[92] P. Horellou, A. de Chaisy, L. Giorgi, C. Levy, P. Chretien, S. Hacein-Bey-Abina, C. Bourgeois, X. Mariette, C. Serguera, R. Le Grand, K. Deiva, Regulatory T cells increase after rh-MOG stimulation in non-relapsing but decrease in relapsing MOG antibody-associated disease at onset in children, Front. Immunol. 12 (2021) 679770.
[93] X. Chang, K. Jiao, D. Wang, Y. Zhou, Z. Zhao, Y. Xing, J. Zhanghao, C. Lu, J. Wang, C. Quan, The immune imbalance between follicular regulatory and helper T cells in myelin oligodendrocyte glycoprotein IgG-associated disease, Clin. Immunol. 255 (2023) 109734.
[94] K. Kothur, L. Wienholt, E.M. Tantsis, J. Earl, S. Bandodkar, K. Prelog, F. Teu, S. Ramanathan, F. Brilot, R.C. Dale, B Cell, Th17, and neutrophil related cerebrospinal fluid cytokine/chemokines are elevated in MOG antibody associated demyelination, PloS One 11 (2) (2016) e0149411.
[95] K. Kaneko, D.K. Sato, I. Nakashima, R. Ogawa, T. Akaishi, Y. Takai, S. Nishiyama, T. Takahashi, T. Misu, H. Kuroda, S. Tanaka, K. Nomura, Y. Hashimoto,

D. Callegaro, L. Steinman, K. Fujihara, M. Aoki, CSF cytokine profile in MOG-IgG + neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications, J. Neurol., Neurosurg. amp;amp; Psychiatry 89 (9) (2018) 927.
[96] K. Yoshizaki, T. Nakagawa, K. Fukunaga, L.T. Tsang, Y. Yamamura, T. Kishimoto, Isolation and characterization of B cell differentiation factor (BCDF) secreted from a human B lymphoblastoid cell line, J. Immunol. 132 (6) (1984) 2948–2954.
[97] M. Kopf, H. Baumann, G. Freer, M. Freudenberg, M. Lamers, T. Kishimoto, R. Zinkernagel, H. Bluethmann, G. Köhler, Impaired immune and acute-phase responses in interleukin-6-deficient mice, Nature 368 (6469) (1994) 339–342.
[98] E. Bettelli, Y. Carrier, W. Gao, T. Korn, T.B. Strom, M. Oukka, H.L. Weiner, V. K. Kuchroo, Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells, Nature 441 (7090) (2006) 235–238.
[99] P.A. Guerne, B.L. Zuraw, J.H. Vaughan, D.A. Carson, M. Lotz, Synovium as a source of interleukin 6 in vitro. Contribution to local and systemic manifestations of arthritis, J. Clin. Invest 83 (2) (1989) 585–592.
[100] M. Noris, F. Daina, S. Gamba, S. Bonazzola, G. Bernazzi, Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions? Circulation 100 (1) (1999) 55–60.
[101] J.A. SINGH, S. BEG, M.A. LOPEZ-OLIVO, Tocilizumab for rheumatoid arthritis: a cochrane systematic review, J. Rheumatol. 38 (1) (2011) 10–20.
[102] D.P. Misra, K. Singh, U. Rathore, P. Patro, A. Tomeferi, C. Campochiaro, V. Agarwal, A. Sharma, The effectiveness of tocilizumab and its comparison with tumor necrosis factor alpha inhibitors for Takayasu Arteritis: a systematic review and meta-analysis, Autoimmun. Rev. 22 (3) (2023) 103275.
[103] L. Sonderegger, G. Iezzi, R. Maier, N. Schmitz, M. Kurrer, M. Kopf, GM-CSF mediates autoimmunity by enhancing IL-6-dependent Th17 cell development and survival, J. Exp. Med. 205 (10) (2008) 2281–2294.
[104] L. Codarri, G. Gyülvészi, V. Tosevski, L. Hesske, A. Fontana, L. Magnenat, T. Suter, B. Becher, RORγt drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation, Nat. Immunol. 12 (6) (2011) 560–567.
[105] S. Kunwar, K. Dahal, S. Sharma, Anti-IL-17 therapy in treatment of rheumatoid arthritis: a systematic literature review and meta-analysis of randomized controlled trials, Rheumatol. Int. 36 (8) (2016) 1065–1075.
[106] M. Jurynczyk, S. Messina, M. Woodhall, N. Raza, R. Everett, A. Roca-Fernandez, G. Tackley, S. Hamid, A. Sheard, G. Reynolds, S. Chandratre, C. Hemingway, A. Jacob, A. Vincent, M.I. Leite, P. Waters, J. Palace, Disease course and disability outcomes in MOG-antibody disease in the UK, Mult. Scler. J. 23 (3 ement 1) (2017) 82.
[107] B.P. Trewin, R.C. Dale, J. Qiu, M. Cho, N. Jeyakumar, F. Dela Cruz, J. Andersen, P. Sirirattanam, K.K.M. Ma, T.A. Hardy, A. van der Walt, J. Lechner-Scott, H. Butzkueven, S.A. Broadley, M.H. Barnett, S.W. Reddel, F. Brilot, T. Kalincik, S. Ramanathan, Oral corticosteroid dosage and taper duration at onset in myelin oligodendrocyte glycoprotein antibody-associated disease influences time to first relapse, J. Neurol. Neurosurg. Psychiatry 95 (11) (2024) 1054–1063.
[108] A.S. Lopez-Chiriboga, M. Majed, J. Fryer, D. Dubey, A. McKeon, E.P. Flanagan, J. Jitprapaikulsan, N. Kothapalli, J.-M. Tillema, J. Chen, B. Weinshenker, D. Wingerchuk, J. Sagen, A. Gadoth, V.A. Lennon, B.M. Keegan, C. Lucchinetti, S. J. Pittock, Association of MOG-IgG serostatus with relapse after acute disseminated encephalomyelitis and proposed diagnostic criteria for MOG-IgG-associated disorders, JAMA Neurol. 75 (11) (2018) 1355–1363.
[109] E.-M. Hennes, M. Baumann, K. Schanda, B. Anlar, B. Bajer-Kornek, A. Blaschek, S. Brantner-Inthaler, K. Diepold, A. Eisenkölbl, T. Gotwald, Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome, Neurology 89 (9) (2017) 900–908.
[110] M. Baumann, E.-M. Hennes, K. Schanda, M. Karenfort, B. Kornek, R. Seidl, K. Diepold, H. Lauffer, I. Marquardt, J. Strautmanis, S. Syrbe, S. Vieker, R. Hoftberger, M. Reindl, K. Rostasy, Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): Extending the spectrum of MOG antibody positive diseases, Mult. Scler. (Houndmills, Basingstoke, Engl.) 22 (14) (2016) 1821–1829.
[111] M. Gastaldi, T. Foiadelli, G. Greco, S. Scaranzin, E. Riguzi, S. Mascolochi, S. Ferrari, C. Mancinelli, L. Beatrillia, M. Mancardi, T. Giacomini, D. Ferraro, M. Della Corte, A. Gallo, M. Di Filippo, L. Benedetti, G. Novi, M. Versino, P. Barzi, R. Iorio, L. Moiola, F. Turco, S. Sartori, M. Nosadini, M. Ruggieri, S. Savasta, E. Colombo, E. Ballante, S. Jarius, S. Mariotto, D. Franciotta, Prognostic relevance of quantitative and longitudinal MOG antibody testing in patients with MOGAD: a multicentre retrospective study, J. Neurol., Neurosurg., Psychiatry (2022).
[112] G. Liyanage, B.P. Trewin, J.A. Lopez, J. Andersen, F. Tea, V. Merheb, K. Nguyen, F.X.Z. Lee, M.J. Fabis-Pedrini, A. Zou, A. Buckland, A. Fok, M.H. Barnett, S. W. Reddel, R. Marignier, A. El Hajj, M. Morif, A. van der Walt, J. Lechner-Scott, A.G. Kermode, T. Kalincik, S.A. Broadley, R.C. Dale, S. Ramanathan, F. Brilot, The MOG antibody non-P42 epitope is predictive of a relapsing course in MOG antibody associated disease, J. Neurol., Neurosurg., Psychiatry (2024).
[113] J.M. Seok, M.Y. Jeon, Y.H. Chung, H. Ju, H.L. Lee, S. Kwon, J.-H. Min, E.S. Kang, B.J. Kim, Clinical characteristics of myelin oligodendrocyte glycoprotein antibody-associated disease according to their epitopes, Front. Neurol. 14 (2023) 1200861.
[114] M.C. Mayer, C. Breithaupt, M. Reindl, K. Schanda, K. Rostasy, T. Berger, R. C. Dale, F. Brilot, T. Olsson, D. Jenne, A.-K. Probstel, K. Dornmair, H. Wekerle, R. Hohlfeld, B. Banwell, A. Bar-Or, E. Meinl, Distinction and temporal stability of conformational epitopes on myelin oligodendrocyte glycoprotein recognized by patients with different inflammatory central nervous system diseases, J. Immunol. (Baltim., Md.: 1950) 191 (7) (2013) 3594–3604.
[115] A.R. Assel El Hajj, Antoine Gavoille, Justine Couturier, Pascale Giraudon, Lakhdar Benyahya, Lisa Malaise, Maxime Bigotte, Claire Benetollo, Gaetan Amorim, Kumaran Deiva, Anne-Kathrin Kogel, Ilya Ayzenberg, Friedemann Paul, Sudarshini Ramanathan, Fabienne Brilot, Romain Marignier, The MOG antibody non-P42 epitope is associated with a higher risk of relapse in paediatric MOGAD, J. Neurol., Neurosurg., Psychiatry (2025). Accepted for publication on February 13 2025.
[116] L. Lin, M. Ji, Y. Wu, H. Hang, J. Lu, Neutrophil to lymphocyte ratio may be a useful marker in distinguishing MOGAD and MS and platelet to lymphocyte ratio associated with MOGAD activity, Mult. Scler. Relat. Disord. 71 (2023) 104570.
[117] A. Lui, J. Cheng, E. Flanagan, A.W. Ahrens, K.M. Krysko, B. Arikan, C. Francisco, A. Runatangwa, E. Waubant, A. Zisel, High titers of myelin oligodendrocyte glycoprotein antibody are only observed close to clinical events in pediatrics, Mult. Scler. Relat. Disord. 56 (2021) 103253.
[118] J. Liu, M. Mori, K. Sugimoto, A. Uzawa, H. Masuda, T. Uchida, R. Ohtani, S. Kuwabara, Peripheral blood helper T cell profiles and their clinical relevance in MOG-IgG-associated and AQP4-IgG-associated disorders and MS, J. Neurol., Neurosurg., Psychiatry 91 (2) (2020) 132–139.
[119] S. Tanaka, B. Hashimoto, S. Izaki, S. Oji, H. Fukazawa, K. Nomura, Clinical and immunological differences between MOG associated disease and anti AQP4 antibody-positive neuromyelitis optica spectrum disorders: blood-brain barrier breakdown and peripheral plasmablasts, Mult. Scler. Relat. Disord. 41 (2020) 102005.
[120] S.-I. Baek, S. Ro, Y.H. Chung, H. Ju, S. Kwon, K.-A. Park, J.-H. Min, Novel index, neutrophil percentage (%) is a useful marker for disease activity in MOG antibody-associated disease, Mult. Scler. Relat. Disord. 76 (2023) 104796.
[121] T. Akaishi, T. Misu, K. Fujihara, K. Nakaya, N. Nakaya, T. Nakamura, M. Kogure, R. Hatanaka, F. Itabashi, I. Kanno, K. Kaneko, T. Takahashi, J. Fujimori, Y. Takai, S. Nishiyama, T. Ishii, M. Aoki, I. Nakashima, A. Uzawa, White blood cell count profiles in anti-aquaporin 4 antibody seropositive neuromyelitis optica spectrum disorder and anti-myelin oligodendrocyte glycoprotein antibody-associated disease, Sci. Rep. -uk 13 (1) (2023) 6481.
[122] C. Benetou, F. Berti, C. Hemingway, Y. Hacohen, M. Lim, Neutrophil-to-lymphocyte ratio correlates with disease activity in myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) in children, Mult. Scler. Relat. Disord. 45 (2020) 102345.
[123] Y. Park, N. Ke, A. Paneque, P.D. Cole, Tau, Glial fibrillary acidic protein, and neurofilament light chain as brain protein biomarkers in cerebrospinal fluid and blood for diagnosis of neurobiological diseases, Int. J. Mol. Sci. 25 (12) (2024).
[124] X. Chang, W. Huang, L. Wang, J. ZhangBao, L. Zhou, C. Lu, M. Wang, J. Yu, H. Li, Y. Li, C. Zhao, J. Lu, C. Quan, Serum neurofilament light and GFAP are associated with disease severity in inflammatory disorders with aquaporin-4 or myelin oligodendrocyte glycoprotein antibodies, Front. Immunol. 12 (2021) 647618.
[125] W. Luo, Y. Chen, S. Mao, J. Jin, C. Liu, X. Zhong, X. Sun, A.G. Kermode, W. Qiu, Serum neurofilament light chain in adult and pediatric patients with myelin oligodendrocyte glycoprotein antibody associated disease: correlation with relapses and seizures, J. Neurochem. (2021).
[126] E.-M. Wendel, A. Bertolini, L. Kousoulos, M. Rauchenzauner, K. Schanda, A. Wegener-Panzer, M. Baumann, M. Reindl, M. Otto, K. Rostasy, Serum neurofilament light-chain levels in children with monophasic myelin oligodendrocyte glycoprotein-associated disease, multiple sclerosis, and other acquired demyelinating syndrome, Mult. Scler. 28 (10) (2022) 1553–1561.
[127] J.-W. Hyun, S.Y. Kim, Y. Kim, N.Y. Park, K.H. Kim, S.-H. Kim, H.J. Kim, Absence of attack-independent neuroaxonal injury in MOG antibody-associated disease: Longitudinal assessment of serum neurofilament light chain, Mult. Scler. (2021) 13524585211063756.
[128] S. Mariotto, M. Gastaldi, L. Grazian, C. Mancinelli, R. Capra, R. Marignier, D. Alberti, S. Zanzoni, K. Schanda, D. Franciotta, F. Calabria, S. Munoco, M. Reindl, S. Ferrari, A. Gajofatto, Nfl. levels predominantly increase at disease onset in MOG-Abs-associated disorders, Mult. Scler. Relat. Disord. 50 (2021) 102833.
[129] H. Kim, E.-J. Lee, S. Kim, L.-K. Choi, K. Kim, H.W. Kim, K.-K. Kim, Y.-M. Lim, Serum biomarkers in myelin oligodendrocyte glycoprotein antibody-associated disease, Neurol. (R.) Neuroimmunol. Neuroinflamm. 7 (3) (2020).
[130] Y.N. Kwon, B. Kim, S. Ahn, J. Seo, S.B. Kim, S.S. Yoon, J.J. Sung, Y.S. Choi, S. M. Kim, Serum level of IL-1β in patients with inflammatory demyelinating disease: Marked upregulation in the early acute phase of MOG antibody associated disease (MOGAD), J. Neuroimmunol. 348 (2020).
[131] S. Saraladadeh, M.N. Olesen, M. Wirenfeldt, S. Moller, T. Misu, K. Soelberg, J. L. Frederiksen, S. Hoegaard, S. Mariotto, K. Fujihara, K. Ruprecht, T.L. Andersen, R. Marignier, S.T. Lillevang, E.P. Flanagan, S.J. Pittock, H.J. Kim, J.L. Bennett, F. Paul, G.L. Sorensen, B.G. Weinshenker, H. Lassmann, N. Asgari, Microfibrillar-associated protein 4 as a potential marker of acute relapse in inflammatory demyelinating diseases of the central nervous system: pathological and clinical aspects, Mult. Scler. J. 29 (14) (2023) 1721–1735.
[132] A. Zhou, W. Zhang, C. Ren, J. Zhou, H. Chang, X. Ren, High levels of cerebrospinal fluid soluble triggering receptor expressed on myeloid cells 2 might be a biomarker of activity in pediatric patients with MOG-AD, Front. Pediatr. 10 (2022) 908527.
[133] S. Saxena, H. Lokhande, G. Gomboley, R. Raheja, T. Koorey, T. Chitnis, Identification of TNFAIP3 as relapse biomarker and potential therapeutic target for MOG antibody associated diseases, Sci. Rep. -uk 10 (1) (2020) 12403.
[134] B. Arslan, G.A. Arslan, A. Tuncer, R. Karabudak, A.S. Dincel, Evaluation of thiol homeostasis in multiple sclerosis and neuromyelitis optica spectrum disorders, Front. Neurol. 12 (2021) 716195.

[135] H. Liu, X. Zhang, W. Chen, Y. Xu, X. Lin, A. Lin, The relationship between plasma prolactin levels and clinical manifestations with neuromyelitis optica spectrum disorders, Neurol. Sci. 45 (2) (2024) 699–707.

[136] O. Aktas, H.-P. Hartung, M.A. Smith, W.A. Rees, K. Fujihara, F. Paul, B. Marignier, J.L. Bennett, H.J. Kim, B.G. Weinshenker, S.J. Pittock, D.M. Wingerchuk, G. Cutter, D. Shu, M. Gunsior, D. Cimbora, E. Katz, B.A. Cree, Serum neurofilament light chain levels at attack predict post-attack disability worsening and are mitigated by inebilizumab: analysis of four potential biomarkers in neuromyelitis optica spectrum disorder, J. Neurol., Neurosurg., Psychiatry 94 (9) (2023) 757–768.

[137] D.H. Whittam, V. Karthikeayan, E. Gibbons, R. Kneen, S. Chandratre, O. Ciccarelli, Y. Hacohen, J. de Seze, K. Deiva, R.Q. Hintzen, B. Wildemann, S. Jarius, L. Kleiter, K. Rostasy, P. Huppke, B. Hemmer, F. Paul, O. Aktas, A. K. Pröbstel, G. Arrambide, M. Tintore, M.P. Amato, M. Nosadini, M.M. Mancardi, M. Capobianco, Z. Illes, A. Siva, A. Altintas, G. Akman-Demir, L. Pandit, M. Apiwattanakul, J.Y. Hur, S. Viswanathan, W. Qiu, H.J. Kim, I. Nakashima, K. Fujihara, S. Ramanathan, R.C. Dale, M. Boggild, S. Broadley, M.A. Lana-Peixoto, D.K. Sato, S. Tenembaum, P. Cabre, D.M. Wingerchuk, B. G. Weinshenker, B. Greenberg, M. Matiello, E.C. Klawiter, J.L. Bennett, A. L. Wallach, I. Kister, B.L. Banwell, A. Traboulsee, D. Pohl, J. Palace, M.I. Leite, M. Levy, B. Marignier, T. Solomon, M. Lim, S. Huda, A. Jacob, Treatment of MOG antibody associated disorders: results of an international survey, J. Neurol. 267 (12) (2020) 3565–3577.

[138] Y.Y.M. Wong, Y. Hacohen, T. Armangue, E. Wassmer, H. Verhelst, C. Hemingway, E.D. van Pelt, C.E. Catsman-Berrevoets, R.Q. Hintzen, K. Deiva, M.J. Lim, K. Rostásy, R.F. Neuteboom, Paediatric acute disseminated encephalomyelitis followed by optic neuritis: disease course, treatment response and outcome, Eur. J. Neurol. 25 (3) (2018) 782–788.

[139] S. Ramanathan, S. Mohammad, E. Tantsis, T.K. Nguyen, V. Merheb, V.S.C. Fung, O.B. White, S. Broadley, J. Lechner-Scott, S. Vucic, A.P.D. Henderson, M. H. Barnett, S.W. Reddel, F. Brilot, R.C. Dale, Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination, J. Neurol., Neurosurg. amp;amp; Psychiatry 89 (2) (2018) 127.

[140] B. Marignier, Y. Hacohen, A. Cobo-Calvo, A.K. Pröbstel, O. Aktas, H. Alexopoulos, M.P. Amato, N. Asgari, B. Banwell, J. Bennett, F. Brilot, M. Capobianco, T. Chitnis, O. Ciccarelli, K. Deiva, J. De Sèze, K. Fujihara, A. Jacob, H.J. Kim, I. Kleiter, H. Lassmann, M.I. Leite, C. Linington, E. Meini, J. Palace, F. Paul, A. Petzold, S. Pittock, M. Reindl, D.K. Sato, K. Selmaj, A. Siva, B. Stankoff, M. Tintoru, A. Traboulsee, P. Waters, E. Wuerfurt, B. Weinshenker, T. Derfuss, S. Vukusic, B. Hemmer, Myelin-oligodendrocyte glycoprotein antibody-associated disease, Lancet Neurol. 20 (9) (2021) 762–772.

[141] S. Ramanathan, R.C. Dale, F. Brilot, Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination, Autoimmun. Rev. 15 (4) (2016) 307–324.

[142] Y. Hacohen, B. Banwell, Treatment approaches for MOG-Ab-associated demyelination in children, Curr. Treat. Options Neurol. 21 (1) (2019) 2.

[143] C. Schwake, T. Ladopoulos, V. Häußler, L. Kleiter, M. Ringelstein, O. Aktas, T. Klimpfel, D. Engels, J. Havla, M.W. Hümmert, J.R. Kretschmer, D. Tkachenko, C. Trebst, A.B. Ayrosa Galvão Ribeiro Gomes, A. K. Pröbstel, M. Koerpel-Kuhnke, B. Wildemann, S. Jarius, R. Pul, M. Pompsch, M. Krämer, F. Then Bergh, C. Gödel, P. Schwarz, M.C. Kowarik, P.S. Rommer, I. Vardakas, M. Senel, A. Winkelmann, N. Retzlaff, M.S. Weber, L. Husseini, A. Walter, P. Schindler, J. Bellmann-Strobl, F. Paul, R. Gold, I. Ayzenberg, Apheresis therapies in MOGAD: a retrospective study of 117 therapeutic interventions in 571 attacks, J. Neurol., Neurosurg. amp; Psychiatry (2024) jnnp-2024-334863.

[144] A.B. Wolf, J. Palace, J.L. Bennett, Emerging principles for treating myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), Curr. Treat. Options Neurol. 25 (11) (2023) 437–453.

[145] P. Barreras, F.S. Vasileiou, A.G. Filippatou, K.C. Fitzgerald, M. Levy, C.A. Pardo, S.D. Newsome, E.M. Mowry, P.A. Calabresi, F.S. Sotirchos, Long-term effectiveness and safety of rituximab in neuromyelitis optica spectrum disorder and MOG antibody disease, Neurology 99 (23) (2022) E2504–E2516.

[146] F. Flieverd, W. Hoffmann, D. Wingerchuk, J. Carter, Interleukin-6 inhibition with tocilizumab for relapsing MOG-IgG associated disorder, Neurology 96 (15 1) (2021).

[147] M. Ringelstein, I. Ayzenberg, G. Lindenblatt, K. Fischer, A. Gahlen, G. Novi, H. Hayward-Koennecke, S. Schippling, P.S. Rommer, B. Kornek, T. Zrzavy, D. Biotti, J. Giron, B. Audoin, A. Berthele, K. Glighuber, H. Zephir, T. Kumpfel, R. Berger, J. Rother, V. Hatzler, J.-P. Stellmann, D. Whittam, A. Jacob, M. Kraemer, A. Guegnen, R. Deschamps, A. Bayas, M.W. Hummert, C. Trebst, A. Haarmann, S. Jarius, B. Wildemann, M. Gesche, N. Siebert, K. Ripprecht, F. Paul, N. Collongues, B. Marignier, M. Levy, M. Karenfort, M. Deppe, P. Albrecht, K. Hellwig, R. Gold, H.-P. Hartung, S.G. Meuth, I. Kleiter, O. Aktas, Neuromyelitis optica study, G., interleukin-6 receptor blockade in treatment refractory MOG-IgG-associated disease and neuromyelitis optica spectrum disorders, Neurol. (R.) Neuroimmunol. Neuroinflamm. 9 (1) (2022).

Chapter 2 | Laboratory Biomarkers for the Prediction of Relapse in MOGAD: A Systematic Review and Meta-Analysis

This chapter is a thorough synthesis of the current literature with quantitative and qualitative assessment of a multitude of laboratory biomarkers through the lens of predicting relapsing disease course and attack disease activity in MOGAD.

The contents of Chapter 2 are presented as a manuscript that has been accepted for publication on 1 September 2025 in the Journal of Neurology, Neurosurgery & Psychiatry:

Andersen J, Trewin B, Dale R, Ramanathan S, Brilot F. Laboratory biomarkers for the prediction of relapse in myelin oligodendrocyte glycoprotein antibody-associated disease: a systematic review and meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry.

Laboratory biomarkers for the prediction of relapse in myelin oligodendrocyte glycoprotein antibody-associated disease: a systematic review and meta-analysis

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Word count of the manuscript text (not including abstract, references, Tables, or Figure legends)**:** 4115

Word count of Abstract: 243

Word count of Introduction: 348

Number of Figures: 4

Number of Tables: 4

Number of Supplementary Figures: 2

Number of Supplementary Tables: 9

Abstract

Objectives

Detection of immunoglobulin G targeting myelin oligodendrocyte glycoprotein (MOG-IgG) is the mainstay of laboratory diagnosis of MOG antibody-associated disease (MOGAD). Laboratory biomarkers have the potential to predict disease course and activity, thus, informing prompt therapeutic decisions to minimise relapse-associated disability accrual.

Methods

This systematic review with meta-analysis was registered in PROSPERO (CRD42024554429). MEDLINE, Embase, and Scopus databases were searched. Random-effects or mixed-effects modellings were performed, and odds or hazard ratio with 95% confidence intervals reported.

Results

106 studies with ≥1710 individuals were included. Relapsing course was associated with persistent seropositivity (OR 2.7 (95%CI 1.8–4.0), p<0.0001), lower likelihood of seroreversion to negative status (HR 0.19 (95%CI 0.14–0.26), p<0.0001), and delayed seroreversion compared to monophasic participants (median 19 years versus 2.5 years, p<0.0001). ADEM was not associated with relapsing course (OR 0.049 (95%CI 0.0029–0.84), p=0.037). Serum MOG-IgG titre – negative, low positive, or clear positive – discriminated disease state. Attack was associated with clear positive titre (OR 3.6 (95%CI 2.6–5.0), p<0.0001), but not negative titre (OR 0.073 (95%CI 0.028–0.19), p<0.0001). CSF leukocytosis (≥5 cells/μL) was associated with attack (OR 3.1 (95%CI 1.7-5.9), p=0.0004). Neither serum GFAP nor NfL correlated with disease activity. Novel biomarkers of disease course and activity have also been assessed qualitatively.

Interpretation

MOG-IgG serostatus and titre, and CSF leukocytosis are biomarkers of disease course and activity. The findings provide rationale for serial serum MOG-IgG testing at 3-6 month intervals in the first 12 months of disease to assist in relapse risk stratification.

Keywords

MOGAD, MOG-IgG, anti-MOG antibody, biomarker, relapse prediction, disease activity

Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is an inflammatory demyelinating disease of the central nervous system (CNS), characterised by the presence of anti-MOG autoantibodies (MOG-IgG).[1] MOGAD is typically associated with the clinical phenotypes acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), or transverse myelitis (TM), and is less commonly associated with cerebral cortical encephalitis (CCE), brainstem presentations, or cerebellar presentations.[1] MOGAD affects both children and adults; however, there is a distinct divergence of phenotype – ADEM is the most frequent paediatric phenotype compared to ON as the primary manifestation in adults.[2] The disease course is either monophasic or relapsing, with a recent review reporting that relapsing disease course occurs in 72% of individuals when follow-up is extended beyond 5-years, suggesting that this is a predominantly relapsing disorder in the context of current diagnostic and therapeutic approaches.[3] The morbidity burden associated with MOGAD is significant, with residual neurological disability manifesting as visual acuity loss, motor deficits, sensory deficits, cognitive impairment, and sphincter dysfunction.[4-6] Moreover, disability may accumulate with relapses.[4] Thus, disease course prediction is a paramount yet elusive goal, which has the potential to facilitate early institution of maintenance immunotherapy to limit the accrual of disability that occurs with relapse while simultaneously avoiding unnecessary immunosuppression in monophasic individuals. Laboratory biomarkers offer an attractive avenue to address this conundrum. To date, temporal dynamics of serum MOG-IgG have been the most thoroughly investigated potential biomarker, with some studies reporting a significant association between persistent seropositive measurements and relapsing disease course;[7-9] however, the literature has lacked consensus regarding this relationship.[6, 10] Additionally, biomarkers of disease activity, rather than of disease course, may be diagnostically useful in settings of clinical uncertainty to discriminate whether symptoms represent a MOGAD attack as opposed to an alternate pathology. A widespread challenge of MOGAD research has been the rarity of its incidence – estimated at 1.6-3.4 per 1,000,000 person-years – which often translates to limited sample sizes.[11, 12] For these reasons, we aimed to conduct a systematic review with meta-analysis to investigate the capability of laboratory biomarkers to predict disease course, as well as differentiate remission compared to attack disease activity.

Methods

Search Strategy

This systematic review with meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[13] The PRISMA flowchart is presented (Figure 1). The study was registered with PROSPERO (registration number CRD42024554429). A systematic search of the databases MEDLINE, Embase, and Scopus was performed of all studies from inception to 21/2/2024, with English language restriction. The complete search strategy is presented in Supplementary Table 1. The literature search was performed by one author (JA) and reviewed by the senior author (FB).

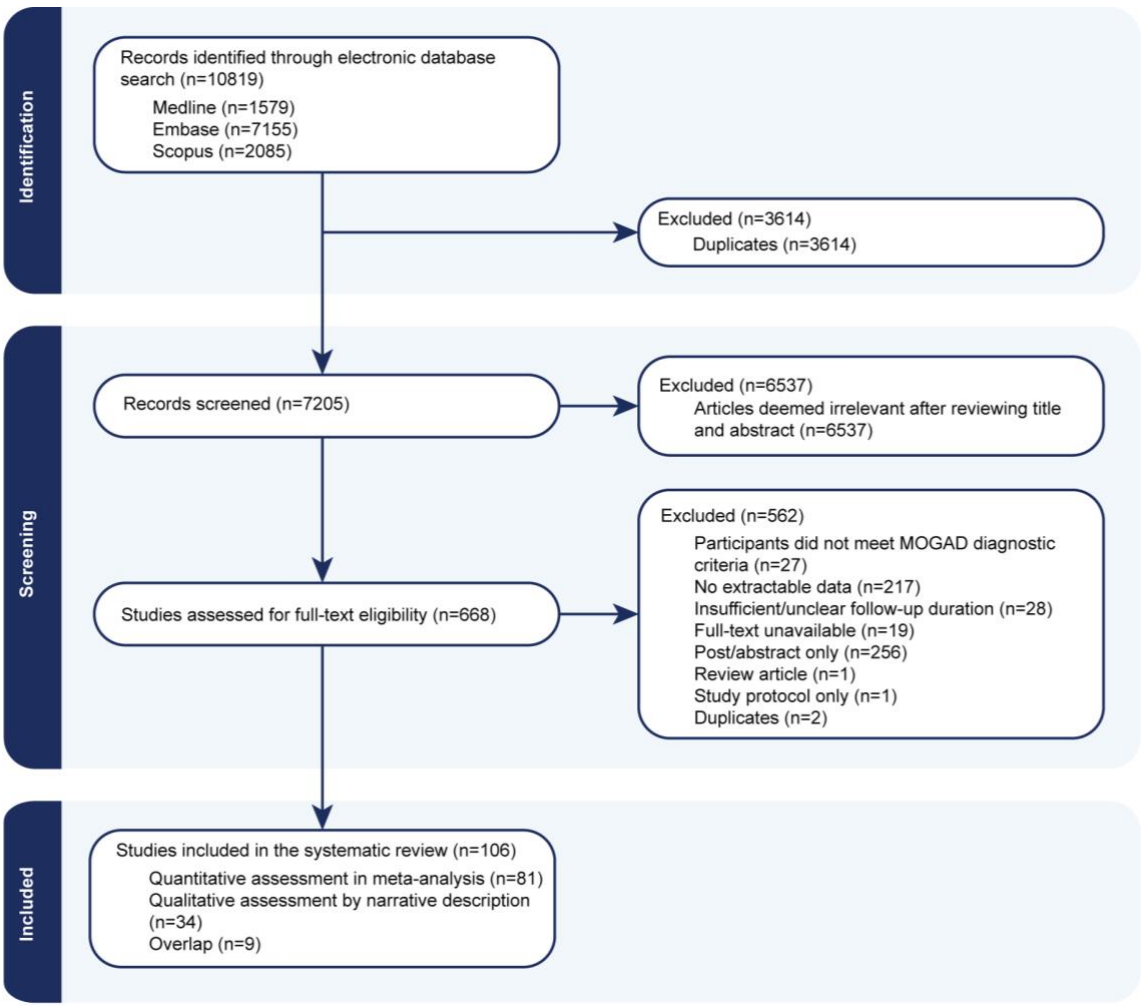

Figure 1: PRISMA Flow Diagram for the Systematic Review with Meta-Analysis.

Key Definitions

Key definitions are presented in Supplementary Method 1 and Supplementary Tables 2 and 3.

Study Selection

Study eligibility was assessed based on the following inclusion criteria: (i) published, full-text original research articles in English, (ii) measured laboratory biomarker(s) in terms of disease course and/or disease activity, (iii) participants met the 2023 International MOGAD Panel proposed diagnostic criteria, broadly defined by positive serum MOG-IgG measurement on cell-based assay (CBA) and characteristic clinical phenotype as per definitions outlined in Supplementary Tables 2 and 3, (iv) studies that measured disease course clearly reported follow-up duration as ≥1 year either in a direct statement or able to be inferred from descriptive statistics such as minimum-maximum range (reporting of only interquartile range (IQR) or standard deviation (SD) was insufficient), and (v) extractable data for ≥2 individuals, with data only being extracted for individuals meeting the inclusion criteria. There were no restrictions on follow-up duration for studies assessing disease activity. There were no restrictions on the types of study design eligible for inclusion. There were no restrictions based on individuals' age, sex, or comorbidity. All disagreements were resolved by consensus.

Data Extraction, Study Risk of Bias Assessment, and Certainty of Evidence Assessment

One author (JA) independently extracted data from all included studies with a standardized data extraction form hosted on Microsoft Excel software (v16.97.2). Data was sought for the following outcomes of interest: (i) laboratory biomarker(s) sampled at onset or any time during disease that were associated with disease course, and (ii) laboratory biomarker(s) that were associated with disease activity. Data were extracted as reported in the text, tables, and figures of the original papers and their published supplementary/appendix material. In the event of missing or incomplete data, the data or study (if there was no other extractable data for inclusion) was excluded; study investigators were not contacted. One author (JA) independently assessed the risk of bias of included studies using the Newcastle-Ottawa Quality Assessment Scale. Risk of bias scores were categorized into 'low' (7–9), 'medium' (4–6), and 'high' (0–3). One author (JA) assessed outcomes in terms of association, of any magnitude, with disease course and/or disease activity using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[14] The certainty of the

evidence was rated as ‘high’, ‘moderate’, ‘low’, or ‘very low’ (Table 4). This study assessed association rather than causation questions, thus, the most appropriate study design to answer these questions were observational studies.[14] Accordingly, the assessment of certainty started at ‘high’ and was downgraded one level for serious (or by two levels for very serious) limitations in the study design, inconsistency, imprecision, indirectness, and publication bias.[14] The senior author (FB) reviewed the extracted data, and risk of bias and certainty of evidence assessments. All disagreements were resolved by consensus.

Statistical Analysis

All analyses were performed using R software (v4.2.2) with the metafor, forestplot, lme4, coxme, dplyr, and estmeansd packages. Individual participant data (IPD) were extracted where available, otherwise aggregate data (AD) were extracted. Missing or incomplete data were excluded. For studies that reported median (range or IQR) summary statistics, the method for unknown non-normal distributions approach was used to estimate mean ± SD. Biomarker(s) were analysed quantitatively if there were extractable data from ≥3 studies, otherwise analysis was qualitative with tabulated and in-text description. A minimum subgroup sample size criterion (n ≥5) was applied to optimise model performance. Effect measures were: (i) ordinal outcome data were described with odds ratios (OR) with 95% confidence intervals (CI), with univariable analyses using a two-stage approach, whereby IPD was reduced to study-level effect estimates then combined with random-effects meta-analysis, and multivariable analyses using a one-stage IPD meta-analysis with logistic mixed-effects regression model, to account for clustering of participants within studies, (ii) time-to-event outcome data were described with hazard ratios (HR) with 95% CI, with univariable and multivariable analyses using a one-stage IPD meta-analysis with mixed-effects Cox regression model, to account for clustering of participants within studies, and using Kaplan-Meier survival curve for visualisation, and (iii) continuous outcome data were described with mean differences with 95% CI, where AD were combined in a random-effects meta-analysis of mean differences. The measurement scales and collection methodologies of continuous outcome data did not differ across studies; thus, standardisation was not required. All random-effects meta-analyses employed restricted maximum likelihood (REML) estimation, apart from one model which failed to converge and, thus, employed DerSimonian-Laird (DL) method.

In univariable random-effects meta-analyses, the degree of variability or inconsistency across different studies, termed 'heterogeneity', was assessed using the I^2 statistic.[15] For mixed-effects meta-analyses, an R statistic was estimated, which compared the impact of heterogeneity in the fixed-effect and random-effects models as previously described.[15] The R statistic was used to calculate an estimated I^2 statistic with the equation: $I^2 = (R^2 - 1)/R^2$.[16] The following interpretation for I^2 was applied[17, 18]; 0% to 40%: might not be important; 30% to 60%: may represent moderate between-study heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.

Potential publication bias was evaluated using the Egger regression test, with $p<0.05$ defined as statistically significant, and funnel plots for visualisation. Subgroup analyses were conducted to explore potential sources of heterogeneity after it was identified.

Results

The database search identified 10819 articles. Following exclusion of duplicates, 7205 articles were screened by title and abstract, of which 668 were deemed relevant and screened by full text. 106 articles, all observational studies, met the inclusion criteria and were included in the systematic review. 81 studies had extractable data sets able to be assessed quantitatively in the meta-analysis (Supplementary Table 4). This amounted to at least 1710 individuals from 77 studies; however, 6 studies specified sample numbers not participant numbers for part or all of their dataset. 34 included studies were assessed in a qualitative capacity by narrative description (Supplementary Table 4). 9 studies overlapped and were assessed in both a qualitative and quantitative capacity (Supplementary Table 4).

Characteristics of included studies are outlined (Supplementary Table 4). 72% (76/106) of studies had a low risk of bias, 28% (30/106) had a medium risk, and 0 studies had a high risk (Supplementary Table 4).

48 studies had extractable data for follow-up duration of both monophasic and relapsing groups, which allowed pairwise comparison at the level of the individual study (Supplementary Table 5). 25% (12/48) of studies were found to have statistically significant longer follow-up duration for individuals with a relapsing course compared to monophasic course (Supplementary Table 5).

Biomarkers of Disease Course

Biomarkers were assessed for capability to predict disease course. The most frequently reported biomarkers for disease course prediction, in descending order, were: (1) serial serum MOG Ig-G status, (2) serum MOG-IgG titre, (3) cerebrospinal fluid (CSF) oligoclonal bands (OCB) status, (4) CSF white cell count (WCC), and (5) CSF protein. Importantly, treatment status at time of sample collection was incompletely available and, thus, was not included in any proceeding analyses. Persistent seropositivity on serial serum MOG-IgG measurement collected ≥3 months apart conferred statistically significant increased odds of relapsing course compared to transient seropositivity (OR 2.7 (95% CI 1.8–4.0), $p<0.0001$) (Figure 2 and Supplementary Figure 1). No significant heterogeneity was detected ($I^2=0\%$) and Egger's test did not indicate significant publication bias ($p=0.28$). Persistent seropositivity remained associated with increased odds of relapsing course compared to transient seropositivity when

the sample collection interval was lengthened to ≥6 months apart (OR 2.3 (95% CI 1.5–3.4), p<0.0001), as well as ≥12 months apart (OR 2.8 (95% CI 1.8–4. 5), p<0.0001) (Supplementary Table 6). None of the other variables were significantly associated with relapsing course either in the first collected or onset samples (Figure 2). No significant heterogeneity was observed (I^2=0% for all analyses) nor was any significant publication bias detected (p>0.05 for all analyses).

Predictor of Relapsing Disease Course		Studies (n)	Total Individuals (n)	Monophasic Individuals (n)	Relapsing Individuals (n)	OR (95% CI) of Relapsing Disease Course	Univariable Random-Effects Meta-Analysis P value	I²	Egger's Test P value
Serum MOG-IgG Titre									
First collected	Low positive	43	607	108	111	1.0 (reference)	0.46	0%	0.66
	Clear positive			179	207	1.2 (0.78-1.8)			
Onset	Low positive	23	152	16	15	1.0 (reference)	0.56	0%	0.95
	Clear positive			68	53	0.79 (0.35-1.8)			
Serial Serum MOG-IgG Status									
	Transient seropositivity*	48	777	178	72	1.0 (reference)	**<0.0001**	0%	0.28
	Persistent seropositivity^			245	282	2.7 (1.8-4.0)			
CSF WCC									
First collected	Normal	32	391	63	60	1.0 (reference)	0.33	0%	0.82
	Elevated			165	103	0.76 (0.44-1.3)			
Onset	Normal	22	269	40	42	1.0 (reference)	0.38	0%	0.75
	Elevated			108	79	0.75 (0.39-1.4)			
CSF Protein									
First collected	Normal	25	288	109	80	1.0 (reference)	1.0	0%	0.57
	Elevated			50	49	1.0 (0.52-1.9)			
Onset	Normal	17	231	89	68	1.0 (reference)	0.60	0%	0.50
	Elevated			37	37	0.81 (0.37-1.8)			
CSF OCB									
First collected	Absent	38	569	234	269	1.0 (reference)	0.84	0%	0.13
	Present			31	35	0.95 (0.57-1.6)			
Onset	Absent	21	250	108	116	1.0 (reference)	0.64	0%	0.51
	Present			14	12	0.83 (0.37-1.8)			

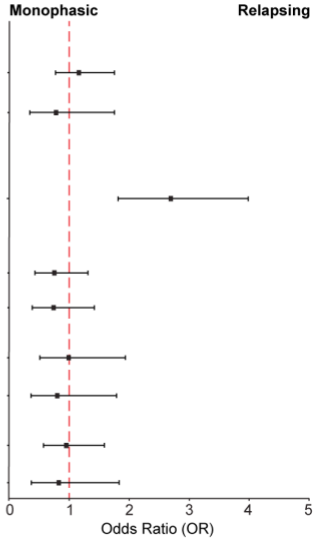

Figure 2: **Investigating the association of biomarkers and relapsing disease course**. 'First collected' analyses included the first collected serum or CSF specimen for an individual including, but not limited to, all samples collected at onset. 'Onset' analyses only included serum or CSF specimens collected <30 days following first clinical symptoms of MOGAD. *Transient seropositivity was defined as <2 positive serum MOG-IgG results on serial measurement ≥3 months apart. ^Persistent seropositivity was defined as ≥2 positive serum MOG-IgG results on serial measurement ≥3 months apart; individuals whose MOG-IgG measurements fluctuated between positive and negative were categorized as persistent seropositive if there were ≥2 positive results ≥3 months apart.

The association between persistent seropositivity and relapsing course was further explored in terms of individual-level covariables, including sex, age, and clinical phenotype (Table 1). Individuals who had serial serum MOG-IgG samples collected ≥3 months apart were examined for complete demographic data, which was only extractable for 131 individuals from 52% (25/48) of studies that reported serial serum MOG-IgG status. Data for 3 individuals with

'Other' phenotype were excluded due to insufficient subgroup sample size. The final analysis included 128 individuals. Persistent seropositivity remained significantly associated with increased odds of relapsing disease course in the multivariable analysis (OR 15, 95% CI 2.2–98, p=0.0059) (Table 1). There was substantial heterogeneity (I^2=77%), likely due to limited participant numbers. In addition, ADEM phenotype was found to be significantly associated with reduced risk of relapsing disease course (OR 0.049 (0.0029–0.84, p=0.037) (Table 1). Individual follow-up duration was available for 117/128 individuals. No statistically significant difference in follow-up duration between phenotype subgroups was identified with Kruskal-Wallis test (results not shown). Complete demographic data was available for 110 individuals with serial serum MOG-IgG samples collected ≥6 months apart and for 96 individuals with serial serum MOG-IgG samples collected ≥12 months apart. Interestingly, persistent seropositivity was not significantly associated with relapsing course in both of these multivariable analyses (Supplementary Table 7). There was substantial heterogeneity with both analyses (I^2=94% and I^2=83%, respectively)

Table 1: Investigating the multivariable association of persistent seropositivity and relapsing disease course alongside individual-level demographics.

Predictor of Relapsing Disease Course*		Total Participants (n)	Monophasic Participants (n)	Relapsing Participants (n)	OR (95% CI) of Relapsing Disease Course	P value^
Serial MOG-IgG status						
	Transient seropositivity	32	23	9	1.0 (reference)	
	Persistent seropositivity	96	18	78	15 (2.2-98)	**0.0059**
Sex						
	Male	59	25	34	1.0 (reference)	
	Female	69	16	53	1.1 (0.27-4.2)	0.93
Age						
	Paediatric (<18)	77	27	50	1.0 (reference)	
	Adult (≥18)	51	14	37	1.5 (0.17-14)	0.71
Phenotype						
	Brain/Brainstem	23	7	16	1.0 (reference)	—
	ADEM	26	18	8	0.049 (0.0029–0.84)	**0.037**
	ON	20	8	12	0.99 (0.072–14)	1.0
	TM	5	3	2	0.20 (0.0059–6.4)	0.36
	ADEM+ON	16	1	15	5.6 (0.15–205)	0.35
	ON+TM	10	2	8	6. 7 (0.12–360)	0.35
	Mixed	28	2	26	11 (0.61–193)	0.10

^Analysis was with a one-stage IPD meta-analysis with multivariable logistic mixed-effects regression. There was substantial heterogeneity (I^2=77%).

*Minimum subgroup sample size criterion (n ≥5); phenotype 'Other' was excluded due to insufficient participant numbers (n=3).

Next, we analysed whether any clinical predictors were associated with seroreversion to MOG-IgG negative status (Table 2). In the univariable analysis, relapsing disease course, female sex, and ON+TM phenotype all had significantly decreased likelihood of seroreversion to negative status while ADEM phenotype conferred significantly increased likelihood of seroreversion to negative status (Table 2). In the multivariable analysis, only the association between relapsing course and reduced likelihood of seroreversion to negative status remained statistically significant (Table 2). Expanded age categories (<18, 18-49, ≥50 years) were assessed; however, there was marked instability in estimates for the ≥50 years group due to limited data (n=6) (results not shown), thus, age groups were condensed to <18 and ≥18 years to improve model stability (Table 2).

Table 2: Investigating the association of clinical predictors and seroreversion to MOG-IgG negative status^.

Predictor of Seroreversion to MOG-IgG Negative Status*		Univariable					Multivariable				
		Studies (n)	Participants (n)	HR (95% CI) of seroreversion to MOG-IgG negative status	P value	I^2	Studies (n)	Participants (n)	HR (95% CI) of seroreversion to MOG-IgG negative status	P value	I^2
Disease course	Monophasic	45	382	1.0 (reference)	**<0.0001**	52 %	28	135	1.0 (reference)	—	73 %
	Relapsing		369	0.19 (0.14–0.26)					0.11 (0.034–0.39)	**0.0004**	
Sex	Male	29	64	1.0 (reference)	**0.03**	71 %			1.0 (reference)	—	
	Female		74	0.47 (0.29–0.92)					0.80 (0.36–1.8)	0.57	
Age	Paediatric (<18)	38	400	1.0 (reference)	0.53	68 %			1.00 (reference)	—	
	Adult (≥18)		55	0.75 (0.31–1.8)					0.92 (0.28–3.1)	0.89	
Phenotype	Not Brain/Brainstem	32	159	1.0 (reference)	0.46	75 %			—	—	
	Brain/Brainstem		24	1.5 (0.51–4.5)					1.0 (reference)	—	
	Not ADEM		129	1.0 (reference)	**0.040**	73 %			—	—	
	ADEM		54	2.6 (1.1–6.4)					1.2 (0.25–5.8)	0.83	
	Not ON		150	1.0 (reference)	0.47	77 %			—	—	
	ON		33	1.3 (0.63–2.7)					0.59 (0.11–3.1)	0.53	
	Not TM		177	1.0 (reference)	0.51	72 %			—	—	
	TM		6	1.5 (0.42–5.6)					0.50 (0.060–4.2)	0.53	
	Not ADEM+ON		164	1.0 (reference)	0.52	73 %			—	—	
	ADEM+ON		19	0.71 (0.25–2.1)					1.8 (0.27–12)	0.54	
	Not ON+TM		167	1.0 (reference)	**0.010**	75 %			—	—	
	ON+TM		16	0.22 (0.067–0.70)					0.16 (0.018–1.4)	0.091	
	Not Mixed		152	1.0 (reference)	0.56	74 %			—	—	
	Mixed		31	0.75 (0.28–2.0)					0.69 (0.19–2.5)	0.57	

^Analysis was with one-stage IPD meta-analysis with univariable and multivariable mixed-effects Cox regression models. *Minimum subgroup sample size criterion (n ≥5); phenotype 'Other' was excluded due to insufficient participant numbers (n=2 in univariable analysis and n=1 in multivariable analysis).

Individuals with relapsing disease course became MOG-IgG seronegative significantly later than their monophasic counterparts (median 19 years versus 2.5 years, respectively, p<0.0001) (Figure 3).

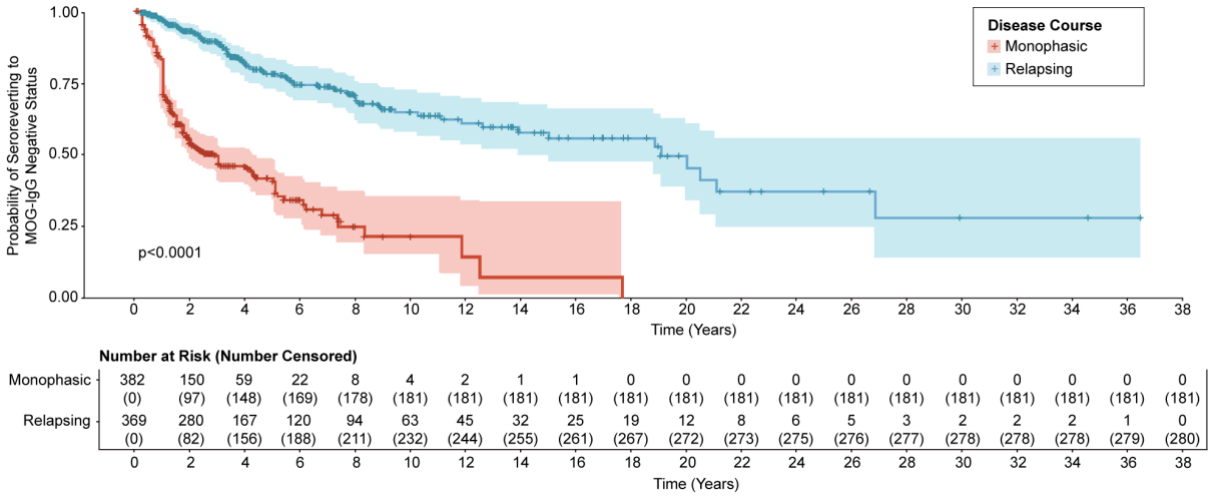

Figure 3: **Kaplan-Meier survival curve of time to seroreversion to MOG-IgG negative status**.

Biomarkers of Disease Activity

Biomarkers were next assessed for capability to differentiate between remission and attack. The most frequently reported biomarkers, in descending order, were: (1) serum MOG-IgG titre, (2) CSF WCC, (3) CSF protein, (4) CSF OCB, (5) serum neurofilament light chain (NfL), and (6) serum glial fibrillary acidic protein (GFAP) (Figure 4, Table 3, and Supplementary Table 8). It was common for individuals to have multiple serum MOG-IgG samples collected over the course of their disease and so titre was examined for its capability to correlate with disease activity. Serum MOG-IgG titre – categorised as 'negative', 'low positive', or 'clear positive' as per the latest international MOGAD diagnostic criteria[1] – was shown to effectively discriminate between remission (disease stability ≥30 days following symptoms) and attack (<30 days following symptoms). Low or clear positive titre was significantly associated with attack, while negative titre was significantly associated with remission (Figure 4). This relationship persisted even when parameters were relaxed, with attack samples defined as those collected <3 months following symptoms (Figure 4). No significant heterogeneity was observed (I^2=0% for both analyses). In addition, the presence of CSF leukocytosis, compared to a normal WCC, was significantly associated with attack (Figure 4). In contrast, the presence of CSF OCB, compared to the absence, was significantly associated with remission (Figure 4). Egger's test identified significant funnel plot asymmetry for CSF OCB analyses (Figure 4 and Supplementary Figure 2).

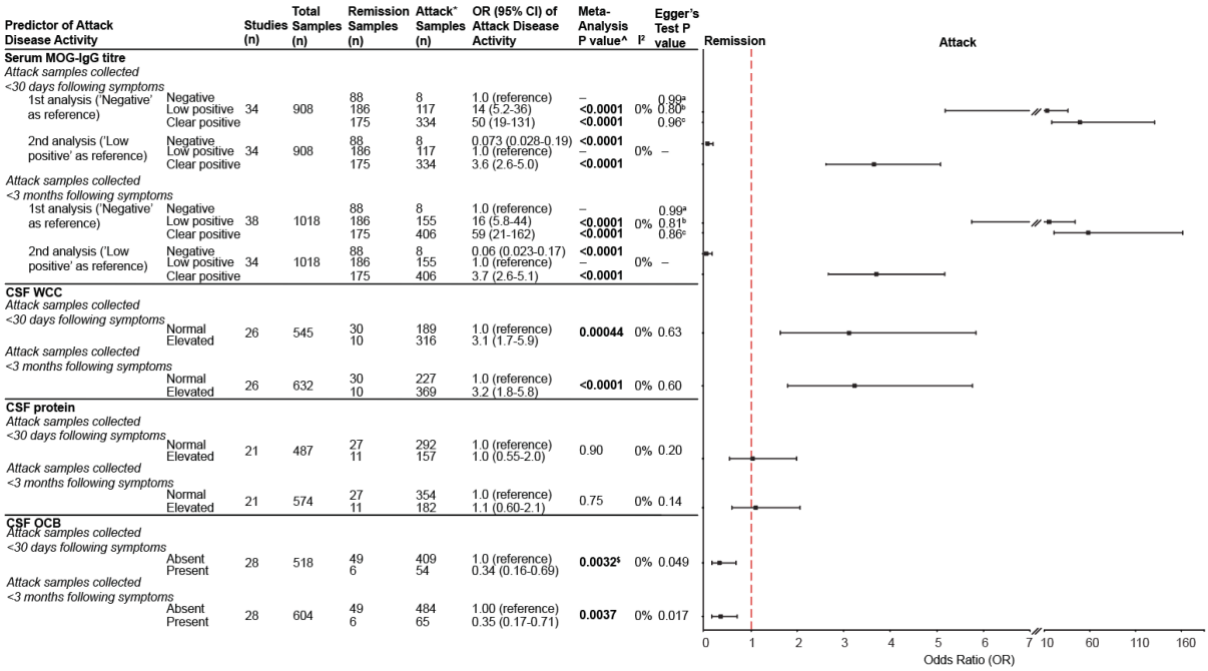

Figure 4: **Investigating the association of biomarkers and attack disease activity**. ^Analysis of serum MOG-IgG titre used one-stage IPD meta-analysis with mixed-effects logistic regression while analyses of CSF WCC, protein, and OCB used univariable random-effects meta-analysis. *Attack samples included serum collected at disease onset and during relapse. [a]Egger's test comparison 'Negative' versus 'Low positive'. [b]Egger's test comparison 'Negative' versus 'Clear positive'. [c]Egger's test comparison 'Low positive' versus 'Clear positive'. [$]Due to convergence failure of this model with REML, DL method was used for random-effects meta-analysis.

We did not observe a significant association with either serum GFAP or serum NfL and disease activity (Table 3). Both analyses were characterised by considerable heterogeneity (I^2=79% and I^2=89%, respectively). Notably, 66% (2/3) of studies reporting GFAP and 50% (2/4) of studies reporting NfL defined attack samples as those collected <3 months following symptoms but, due to limited data, were analysed alongside studies which collected samples <30 days following symptoms. Heterogeneity was explored with subgroup analyses stratified by attack sample collection time (<30 days versus <3 months following symptoms) and sample size (n<10 versus n≥10). Regarding GFAP, all observed heterogeneity was accounted for by sample size (I^2=0%, R^2=100%). Regarding NfL, attack sample collection time accounted for approximately one-third of the initially observed heterogeneity (I^2=73%, R^2=35%), while sample size was not impactful (I^2=81%, R^2=0%). There were additional studies that reported serum GFAP or serum NfL levels collected at a single disease state (either attack or remission)

and, thus, were not amenable for direct statistical comparison due to the lack of paired attack-remission data; however, random-effects meta-analysis of these means is presented (Supplementary Table 8).

Table 3: Investigating serum GFAP and NfL biomarker association with disease activity.

Predictor of Disease Activity	Study	Age Category	Disease Activity at Time of Sampling	Samples (n)	Mean	SD (±)	Mean difference (95% CI)	P value*	I^2
GFAP	Kim, et al., 2020 [19]	Adult	Remission	9	75pg/mL	20pg/mL	54 (-7.1–115) pg/mL higher at attack compared to remission	0.083	79%
			Attack^	7	90pg/mL	22pg/mL			
	Chang, et al., 2021 [20]	Combined	Remission	19	158pg/mL	232pg/mL			
			Attack^	23	310pg/mL	367pg/mL			
	Hyun, et al., 2021 [21]	Adult	Remission	54	107pg/mL	47pg/mL			
			Attack	17	186pg/mL	81pg/mL			
NfL	Kim, et al., 2020 [19]	Adult	Remission	9	11pg/mL	5.0 pg/mL	47 (-2.1–97) pg/mL higher at attack compared to remission	0.061	89%
			Attack^	7	19 pg/mL	23pg/mL			
	Chang, et al., 2021 [20]	Combined	Remission	19	44pg/mL	78pg/mL			
			Attack^	23	68pg/mL	85 pg/mL			
	Hyun, et al., 2021 [21]	Adult	Remission	55	22pg/mL	36pg/mL			
			Attack	17	165pg/mL	154 pg/mL			
	Luo, et al., 2021 [22]	Combined	Remission	47	13pg/mL	12 pg/mL			
			Attack	22	60 pg/mL	61pg/mL			

*Analysis was with random-effects meta-analysis of mean differences.
^Sample collected within 3 months of last clinical symptoms.

Novel Biomarkers of Disease Course and Activity

Multiple novel biomarkers were assessed qualitatively and are described in Supplementary Table 9. Serum NfL was most frequently reported (all relevant studies appear in Supplementary Table 9, including those that were assessed earlier quantitatively). There was no consensus whether serum NfL demonstrated a significant attack-related association. 3 studies were against (2 with Class I evidence and 1 with Class III evidence) and 3 studies were in favour (2 with Class I evidence and 1 with Class II evidence) (Supplementary Table 9). Numerous other biomarkers were reported to significantly correlate with disease activity, including serum interleukin-1β (IL-1β), CSF microfibrillar-associated protein 4 (MFAP4), CSF-secreted ectodomain of soluble triggering receptor expressed on myeloid cells 2 (sTREM2), tumour necrosis factor alpha-induced protein 3 (TNFAIP3), and serum total thiol and native thiol (Supplementary Table 9). Moreover, MOG epitope binding pattern, human leukocyte antigen

(HLA) genotype, and peripheral blood mononuclear cells (PBMCs) were highlighted as promising biomarkers for disease course prediction (Supplementary Table 9).

Key outcomes of the quantitative component of this review are presented in the Summary of Findings table (Table 4).

Table 4: Summary of Findings

Outcomes	Relative Effect (95% CI)	P-value	Studies (n)	Participants (n)	Quality of the Evidence (GRADE)[a]	Recommendations
Persistent seropositivity* on serial serum MOG-IgG measurement was associated with relapsing disease course	OR 2.7 (95% CI 1.8–4.0)	<0.0001	48	777	Moderate[b]	Serial measurement of serum MOG-IgG at 3-6 month intervals in the 12 months following disease onset may be considered to stratify risk of relapsing disease course; however, increased burden of sample collection and cost are important caveats
Relapsing disease course was associated with decreased likelihood of seroreverting to MOG-IgG negative status	HR 0.19 (95% CI 0.14–0.26)	<0.0001	43	751	Moderate[c]	
Serum MOG IgG titre – categorised as negative, low positive, or clear positive – effectively discriminated between remission and attack, with a positive correlation between titre and odds of attack	Odds of attack with titre: • Negative: OR 0.073 (0.028–0.19) • Low: OR 1.0 (reference) • Clear: OR 3.6 (2.6–5.0)	<0.0001	34	908	Moderate[d]	Measurement of serum MOG-IgG titre may be diagnostically useful in settings of clinical uncertainty whereby an individual, who has an existing diagnosis of MOGAD, has symptoms that are not clearly attributable to a relapse of MOGAD
CSF leukocytosis (≥5 cells/μL), compared to a normal WCC, was significantly associated with attack	OR 3.1 (1.7-5.9)	p=0.00044	26	545	Moderate[e]	Balancing the risk of lumbar puncture procedure, the presence of CSF leukocytosis may be a useful auxiliary finding to diagnose MOGAD attack; however, CNS infection must be effectively ruled out

[a]GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate. [b]Downgrade one point due to study design concerns as 38% (18/48) studies had 'medium' risk of bias, with the remaining having 'low' risk of bias. [c]Downgrade one point due to heterogeneity (I^2=56%). [d]Downgrade one point due to study design concerns as 34% (13/38) studies had 'medium' risk of bias, with the remaining having 'low' risk of bias. [e]Despite no significant heterogeneity (I^2=0%), downgraded one point due to study design concerns as 54% (14/26) studies had 'medium' risk of bias, with the remaining having 'low' risk of bias. *Persistent seropositivity was defined as ≥2 positive serum MOG-IgG results on serial measurement ≥3 months apart; individuals whose MOG-IgG measurements fluctuated between positive and negative were categorized as persistent seropositive if there were ≥2 positive results ≥3 months apart.

Discussion

This systematic review and meta-analysis assessed the capability of laboratory biomarkers to predict MOGAD disease course and activity. Continued detection of serum MOG-IgG was significantly associated with relapsing course. Furthermore, individuals with a relapsing course were significantly less likely to serorevert to MOG-IgG negative status. Categorization of serum MOG-IgG titres as negative, low positive, and clear positive per international MOGAD diagnostic criteria enabled comparison of measurements from various CBAs collected throughout the disease duration.[1] Serum MOG-IgG titre effectively discriminated between remission and attack; there was a positive correlation between titre (clear positive > low positive) and attack and a clear association of negative titre with remission. Elevated CSF WCC was similarly associated with MOGAD attack. The presence of CSF OCB favoured remission state; however, this is likely to reflect the overall scarcity of OCB positivity in MOGAD. Many novel biomarkers were reported, with NfL and GFAP being the most frequent; however, based on literature published within the timeframe of this systematic review, neither effectively correlated with disease activity. We have transparently reported the heterogeneity of the literature, especially with regards to timing of sample collection.

To date, serial serum MOG-IgG status has been the most thoroughly investigated biomarker candidate for disease course prediction, with some groups reporting a significant association between persistent seropositive measurements and relapsing disease course,[7-9] while others did not.[6, 10] It is likely that limited sample sizes contributed to this lack of consensus. With meta-analysis, we demonstrated that relapsing disease course was associated with persistent seropositivity, lower likelihood of seroreversion to negative status, and delayed seroreversion compared to monophasic individuals. Univariable analyses confirmed that relapsing course was significantly associated with persistent seropositivity on serial serum MOG-IgG measurements collected ≥3, ≥6, and ≥12 months apart, re-inforcing that relapsing individuals remained MOG-IgG seropositive for >7.5 times longer than monophasic individuals. Multivariable analyses that investigated this association alongside individual-level demographics (sex, age, and phenotype) yielded significance when the sample collection interval to determine persistent seropositivity was set at ≥3 months but were likely underpowered at ≥6 and ≥12 months. Overall, the data suggest that the highest rate of seroreversion to negative status occurred within 12 months following disease onset; hence, we

recommend that serial measurement of serum MOG-IgG at 3-6 month intervals in the 12 months following disease onset be considered to stratify risk of relapsing disease course; however, increased burden of sample collection and cost are important caveats.

The International MOGAD Panel proposed criteria outlines the low positive and clear positive CBA categories to standardize serum MOG-IgG titres and to strengthen diagnostic criteria as individuals with low positive tests require at least one supportive clinical and/or radiological criteria for MOGAD diagnosis.[1] Our meta-analysis observed a significant positive correlation between serum MOG-IgG titre and odds of attack (clear positive > low positive) as well as negative titre being significantly associated with remission. These findings highlight the value of serum MOG-IgG measurement in individuals with known diagnosis of MOGAD for settings of clinical uncertainty to discriminate whether symptoms are likely to represent a MOGAD attack as opposed to an alternate pathology. Pragmatically, the applicability of serum MOG-IgG titre as a biomarker of disease activity is limited by the following important caveats: (i) the range of titres within the clear positive category is extremely broad, (ii) further reference data to characterise additional thresholds appropriately sensitive and specific for prediction of attack or remission are currently lacking, (iii) longitudinal sampling has revealed that titres may fluctuate independently of attacks,[10] and (iv) international standardization of all CBAs is required.

Lumbar puncture is a common investigation in the workup of MOGAD. Elevated CSF WCC, compared to normal CSF WCC, was significantly associated with MOGAD attack. Crucially, the most common aetiology of CSF leukocytosis is CNS infection, which requires emergent investigation, while autoimmune and neoplastic culprits occur less commonly.[23] In addition, the presence of CSF OCB, compared to the absence, was significantly associated with remission. The overall positive rate of CSF OCB in all pooled samples was 14% (77/551). It is well-known that CSF OCB positivity occurs at a much lower rate in MOGAD than MS, in which it is a core component of diagnosis.[3, 24] Our observed association of CSF OCB positivity with remission is biologically challenging to reconcile; it is likely that this estimate has been considerably impacted by the overall scarcity of CSF OCB positivity in MOGAD alongside limited remission CSF samples due to the relatively invasive nature of lumbar puncture and need to rationalise this procedure only in the setting of active disease. Egger's test identified significant funnel plot asymmetry for CSF OCB analyses; visual inspection appeared to highlight potential sampling error with smaller studies. MOG-IgG synthesis appears to occur

primarily in the periphery; thus, serum was the primary biospecimen focus of this review; however, intrathecal synthesis has also been reported.[25-28] Individuals with intrathecal MOG-IgG synthesis may exhibit comparable clinical and pathological characteristics and, as such, the International MOGAD Panel proposed criteria supported CSF MOG-IgG testing in seronegative individuals whose pre-test assessment was suggestive of MOGAD.[1, 29-31] Nonetheless, caution is warranted when interpreting CSF-restricted MOG-IgG, with alternative diagnosis such as MS and CNS vasculitis, as opposed to MOGAD, identified in over half the cases.[32] MOG-IgG-specific antibody index, calculated using serum and CSF titres to assess MOG-IgG intrathecal synthesis, has been shown to be a useful prognostic biomarker and may enhance the clinical relevance of CSF MOG-IgG testing.[33]

Serum GFAP – an astrocyte-associated protein – has been identified as a useful candidate biomarker of disease activity in AQP4-IgG seropositive NMOSD – a primary astrocytopathy.[34] In contrast, astrocytes appear to be largely unaffected in multiple histopathological studies of MOGAD specimens.[25, 35-37] This aligns with our meta-analysis, which did not identify a significant association between serum GFAP and disease activity. Serum levels of NfL – an axon-associated protein – were also not found to be significantly associated with disease activity in this meta-analysis. Importantly, both analyses were weakened by considerable heterogeneity attributable to variable timing of sample collection and sample size. Since our literature search, a large retrospective cohort study has been published, which found that both serum GFAP and serum NfL were elevated in MOGAD at baseline with longitudinal decrement and that serum NfL values effectively predicted risk of relapse when samples were collected within 3 months of attack.[38] Given this study was published outside the timeframe of our database search, we only conducted an preliminary analysis. Incorporation of this GFAP data found that GFAP levels were significantly elevated at attack compared to remission. NfL data was unable to be assessed as raw values could not be calculated from the published age-adjusted Z-scores. While serum NfL and GFAP currently remain largely restricted to the research setting, their ease of testing with commercially available kits is favourable for a potential future in diagnostics.

At this stage, serum MOG-IgG itself is the strongest biomarker of MOGAD disease course and activity. This highlights MOG epitope binding pattern, capable of being tested at disease onset and highly stable over time, as a particularly promising biomarker candidate for disease course prediction; however, the current evidence is mixed. While some recent studies have observed

a significant association of non-P42 MOG binding pattern with relapsing disease course [39, 40], others have not.[41, 42] While MOG epitope binding pattern has been shown to be highly stable over time, which would enable the use of serum collected at onset or remission prior to first relapse, thorough validation in the clinical setting is needed.[39, 40, 42]

Our study, although providing a thorough synthesis of the current literature landscape, was limited by the degree of heterogeneity in some of the analysed outcomes, likely due to between-study methodological diversity including sample size, geographic location, sample collection timing, and treatment status. In particular, treatment status at time of sample collection was not accounted for due to limited reporting; this methodological decision aimed to capture maximal relevant published works. We hypothesize that steroid-sparing immunosuppressants that act via mechanisms of B- and T-cell depletion would likely reduce serum MOG-IgG titre and promote seroreversion to negative status. Omission of treatment status at time of sample collection may have underestimated serum MOG-IgG titres as well as the longitudinal trends of serial MOG-IgG measurements.

Conclusions

Our study recommends the use of serial sampling of serum MOG-IgG as well as serum MOG-IgG titre and CSF WCC as biomarkers to stratify risk of relapsing disease course and to diagnose MOGAD attacks, respectively. Multiple novel biomarkers of disease course and activity have been identified and require further investigation. Our study highlights the need for future research, for which we propose the adoption of similar definitions for disease course, disease activity, and sample collection timing to reduce the impact of between-study heterogeneity in future meta-analyses.

Acknowledgments

We thank all the patients and family members who have provide data for the studies reported in this study. We thank the Sydney Informatics Hub (The University of Sydney) for their assistance with statistical analyses.

Contributors

JA and FB had full access to all of the data in the study and FB is responsible for the overall content as guarantor. JA and FB contributed to the conception and design of the study. All authors contributed to acquisition and analysis of data. JA and FB contributed to drafting the text and preparing the Figures. All authors contributed to the critical review of the manuscript for important intellectual content. FB obtained funding and FB supervised JA.

Funding

This work was supported by research and investigators grants from the National Health Medical Research Council (Australia, FB GNT2016841, SR GNT2008339, RCD GNT1193648), MS Australia and Sydney Research Excellence Initiative 2020 (The University of Sydney, Australia).

Competing interest

JA and BT have no conflict of interest. RCD has received research funding from the Star Scientific Foundation, The Trish Multiple Sclerosis Research Foundation, Multiple Sclerosis Research Australia, the Petre Foundation and the NHMRC (Australia; Investigator Grant). He has also received honoraria from Biogen Idec as an invited speaker, and is on the IDMC for a Roche RCT in paediatric MS. He is on the medical advisory board (non-remunerated position). SR received research funding from the National Health and Medical Research Council (Australia), the Royal Australasian College of Physicians, and the University of Sydney. She serves as a consultant on an advisory board for UCB and Limbic Neurology, The MOG Project and the Sumaira Foundation, and has been an invited speaker for Biogen, Excemed, Alexxion, Limbic Neurology, and Novartis. FB has received research funding from investigator-initiated research grant from Novartis and MS Australia for this project. She also received funding form NSW Health, the National Health Medical Research Council (Australia), the Medical Research Future Fund (Australia). She was on advisory boards for Novartis, Merck, and The MOG Project and the Sumaira Foundation, and has been an invited speaker for Biogen, Novartis, and Limbic Neurology.

Ethics statements

Patient consent for publication

Not applicable

Ethics approval

Not applicable

Data availability statement

The data that support the findings can be available from the corresponding author upon reasonable request.

References

1. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. The Lancet Neurology. 2023;22(3):268-82.
2. Spatola M, Chuquisana O, Jung W, et al. Humoral signatures of MOG-antibody-associated disease track with age and disease activity. Cell Rep Med. 2023 Feb 21;4(2):100913.
3. Trewin BP, Brilot F, Reddel SW, Dale RC, Ramanathan S. MOGAD: A comprehensive review of clinicoradiological features, therapy and outcomes in 4699 patients globally. Autoimmunity Reviews. 2025 2025/01/03/;24(1):103693.
4. Ramanathan S, Mohammad S, Tantsis E, et al. The clinical course, therapeutic responses, and outcomes in relapsing MOG antibody-associated demyelination. Multiple Sclerosis. 2017;23(13):NP1.
5. Jurynczyk M, Messina S, Woodhall M, et al. Disease course and disability outcomes in MOG-antibody disease in the UK. Multiple Sclerosis Journal. 2017;23(3 Supplement 1):82.
6. Huda S, Whittam D, Jackson R, et al. Predictors of relapse in MOG antibody associated disease: a cohort study. BMJ Open. 2021;11(11):e055392.
7. Lopez-Chiriboga AS, Majed M, Fryer J, et al. Association of MOG-IgG Serostatus With Relapse After Acute Disseminated Encephalomyelitis and Proposed Diagnostic Criteria for MOG-IgG-Associated Disorders. JAMA neurology. 2018;75(11):1355-63.
8. Hennes E-M, Baumann M, Schanda K, et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. Neurology. 2017;89(9):900-8.
9. Baumann M, Hennes E-M, Schanda K, et al. Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): Extending the spectrum of MOG antibody positive diseases. Multiple sclerosis (Houndmills, Basingstoke, England). 2016;22(14):1821-9.
10. Gastaldi M, Foiadelli T, Greco G, et al. Prognostic relevance of quantitative and longitudinal MOG antibody testing in patients with MOGAD: a multicentre retrospective study. Journal of neurology, neurosurgery, and psychiatry. 2022.
11. O'Connell K, Hamilton-Shield A, Woodhall M, et al. Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire, UK. J Neurol Neurosurg Psychiatry. 2020 Oct;91(10):1126-8.
12. de Mol CL, Wong Y, van Pelt ED, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. Mult Scler. 2020 Jun;26(7):806-14.
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
14. Brignardello-Petersen R, Guyatt GH. Assessing the Certainty of the Evidence in Systematic Reviews: Importance, Process, and Use. American Journal of Epidemiology. 2024.
15. Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. Stat Med. 2012 Dec 20;31(29):3805-20.
16. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine. 2002;21(11):1539-58.
17. Deeks JJ HJ, Altman DG, McKenzie JE, Veroniki AA. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane; 2024.
18. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
19. Kim H, Lee E-J, Kim S, et al. Serum biomarkers in myelin oligodendrocyte glycoprotein antibody-associated disease. Neurology(R) neuroimmunology & neuroinflammation. 2020;7(3).

20. Chang X, Huang W, Wang L, et al. Serum Neurofilament Light and GFAP Are Associated With Disease Severity in Inflammatory Disorders With Aquaporin-4 or Myelin Oligodendrocyte Glycoprotein Antibodies. Frontiers in immunology. 2021;12:647618.
21. Hyun J-W, Kim SY, Kim Y, et al. Absence of attack-independent neuroaxonal injury in MOG antibody-associated disease: Longitudinal assessment of serum neurofilament light chain. Multiple sclerosis (Houndmills, Basingstoke, England). 2021:13524585211063756.
22. Luo W, Chen Y, Mao S, et al. Serum neurofilament light chain in adult and pediatric patients with myelin oligodendrocyte glycoprotein antibody-associated disease: Correlation with relapses and seizures. Journal of neurochemistry. 2021.
23. Dyckhoff-Shen S, Bewersdorf JP, Teske NC, et al. Characterization and diagnosis spectrum of patients with cerebrospinal fluid pleocytosis. Infection. 2024 2024/02/01;52(1):219-29.
24. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-73.
25. Hoftberger R, Guo Y, Flanagan EP, et al. The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody. Acta neuropathologica. 2020;139(5):875-92.
26. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation. 2016 Sep 26;13(1):279.
27. Brilot F, Dale RC, Selter RC, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. Annals of Neurology. 2009;66(6):833-42.
28. Dale RC, Tantsis EM, Merheb V, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurology(R) neuroimmunology & neuroinflammation. 2014;1(1):e12.
29. Carta S, Hˆftberger R, Bolzan A, et al. Antibodies to MOG in CSF only: pathological findings support the diagnostic value. Acta Neuropathologica. 2021 2021/05// //;141:801+.
30. Körtvélyessy P, Breu M, Pawlitzki M, et al. ADEM-like presentation, anti-MOG antibodies, and MS pathology: TWO case reports. Neurol Neuroimmunol Neuroinflamm. 2017 May;4(3):e335.
31. Redenbaugh V, Fryer JP, Cacciaguerra L, et al. Diagnostic Utility of MOG Antibody Testing in Cerebrospinal Fluid. Ann Neurol. 2024 Jul;96(1):34-45.
32. Reynolds M, Tan I, Nguyen K, et al. The clinical relevance of MOG antibody testing in cerebrospinal fluid. Ann Clin Transl Neurol. 2024 Sep;11(9):2514-9.
33. Greco G, Risi M, Masciocchi S, et al. Clinical, prognostic and pathophysiological implications of MOG-IgG detection in the CSF: the importance of intrathecal MOG-IgG synthesis. J Neurol Neurosurg Psychiatry. 2024 Nov 18;95(12):1176-86.
34. Aktas O, Hartung H-P, Smith MA, et al. Serum neurofilament light chain levels at attack predict post-attack disability worsening and are mitigated by inebilizumab: analysis of four potential biomarkers in neuromyelitis optica spectrum disorder. Journal of neurology, neurosurgery, and psychiatry. 2023;94(9):757-68.
35. Spadaro M, Gerdes LA, Mayer MC, et al. Histopathology and clinical course of MOG-antibody-associated encephalomyelitis. Annals of clinical and translational neurology. 2015;2(3):295-301.
36. Jarius S, Metz I, Konig FB, et al. Screening for MOG-IgG and 27 other anti-glial and anti-neuronal autoantibodies in 'pattern II multiple sclerosis' and brain biopsy findings in a MOG-IgG-positive case. Mult Scler. 2016 Oct;22(12):1541-9.

37. Takai Y, Misu T, Kaneko K, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: An immunopathological study. Brain. 2020;143(5):1431-46.
38. Marignier R, Villacieros-Álvarez J, Espejo C, et al. Assessment of neuronal and glial serum biomarkers in myelin oligodendrocyte glycoprotein antibody-associated disease: the MULTIMOGAD study. Journal of Neurology, Neurosurgery & Psychiatry. 2025:jnnp-2024-335137.
39. Liyanage G, Trewin BP, Lopez JA, et al. The MOG antibody non-P42 epitope is predictive of a relapsing course in MOG antibody-associated disease. Journal of neurology, neurosurgery, and psychiatry. 2024.
40. Aseel El Hajj AR, Antoine Gavoille, Justine Couturier, Pascale Giraudon, Lakhdar Benyahya, Lisa Malaise, Maxime Bigotte, Claire Benetollo, Gaetan Amorim, Kumaran Deiva, Anne-Kathrin Kogel, Ilya Ayzenberg, Friedemann Paul, Sudarshini Ramanathan, Fabienne Brilot, Romain Marignier. The MOG antibody non-P42 epitope is associated with a higher risk of relapse in paediatric MOGAD. Journal of Neurology, Neurosurgery and Psychiatry. 2025.
41. Seok JM, Jeon MY, Chung YH, et al. Clinical characteristics of myelin oligodendrocyte glycoprotein antibody-associated disease according to their epitopes. Frontiers in neurology. 2023;14:1200961.
42. Mayer MC, Breithaupt C, Reindl M, et al. Distinction and temporal stability of conformational epitopes on myelin oligodendrocyte glycoprotein recognized by patients with different inflammatory central nervous system diseases. Journal of immunology (Baltimore, Md : 1950). 2013;191(7):3594-604.

Laboratory biomarkers for the prediction of relapse in myelin oligodendrocyte glycoprotein antibody-associated disease: a systematic review and meta-analysis
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Supplementary Files

Supplementary Method 1

Supplementary Figure 1: Forest plot demonstrating that persistent seropositivity on serial serum MOG-IgG measurement ≥3 months apart is associated with relapsing disease course (OR 2.7 (95% CI 1.8–4.0), p<0.0001). TS = transient seropositivity; PS = persistent seropositivity.

Supplementary Figure 2: Funnel plot asymmetry identified when investigating the association of CSF OCB and disease activity; (A) attack samples were collected <30 days following clinical symptoms, (B) attack samples were collected <3 months following clinical symptoms.

Supplementary Table 1: Systematic search strategy as of February 21, 2024. All terms were searched as text words and as exploded medical subject headings where possible. All terms within a concept were combined with "OR" and concepts were combined with "AND".

Supplementary Table 2: Key definitions

Supplementary Table 3: Clinical phenotype categories

Supplementary Table 4: Characteristics of 106 studies included in systematic review

Supplementary Table 5: Comparison of follow-up duration between included monophasic and relapsing participants as reported by 48 studies. Statistical significance assessed with Mann-Whitney U Test.

Supplementary Table 6: Investigating the association of serial serum MOG-IgG measurement at various sample collection intervals and relapsing disease course.

Supplementary Table 7: Investigating the multivariable association of serial serum MOG-IgG measurement at various sample collection intervals and relapsing disease course alongside participant-level demographics.

Supplementary Table 8: Random-effects meta-analysis of means to investigate serum GFAP and NfL biomarker levels during different disease activity

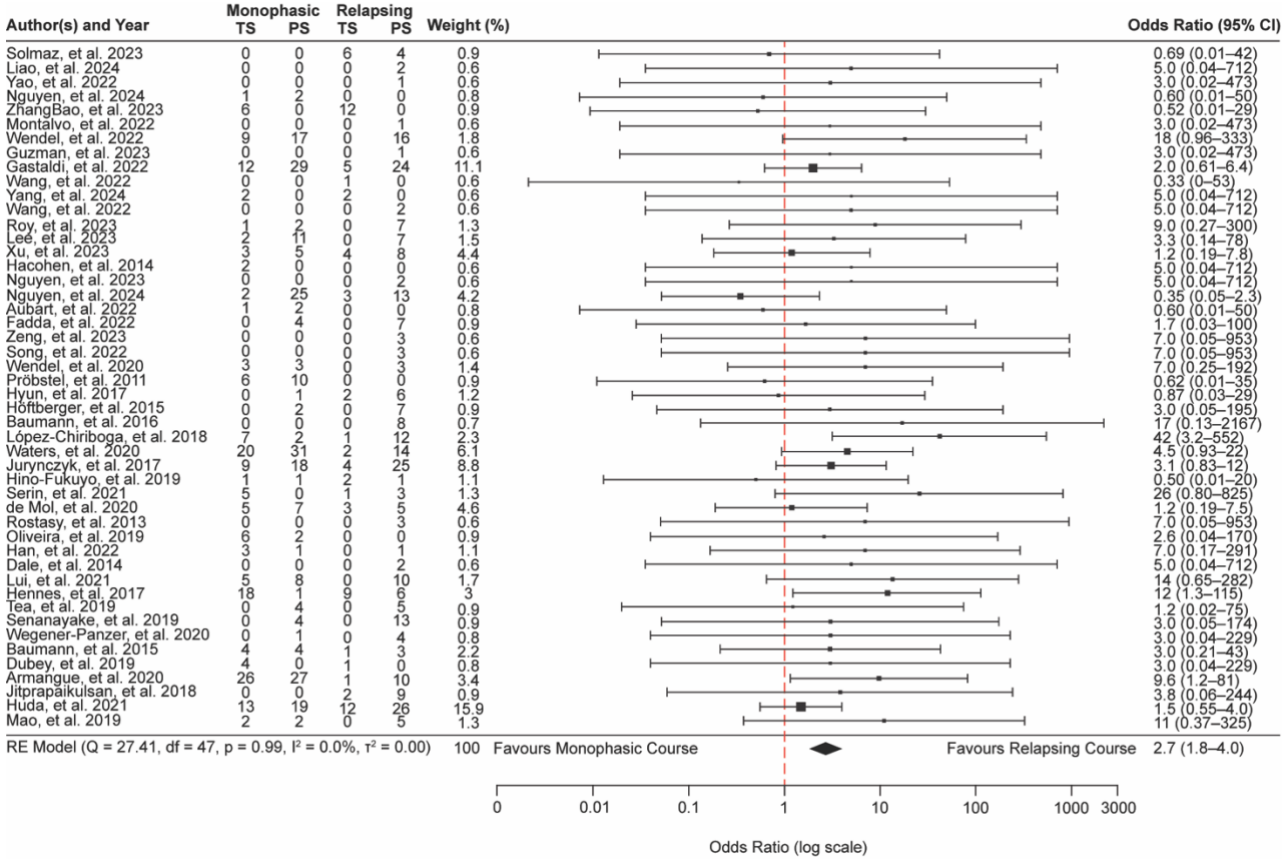
Supplementary Table 9: Qualitative assessment of studies reporting novel biomarkers.

Supplementary References

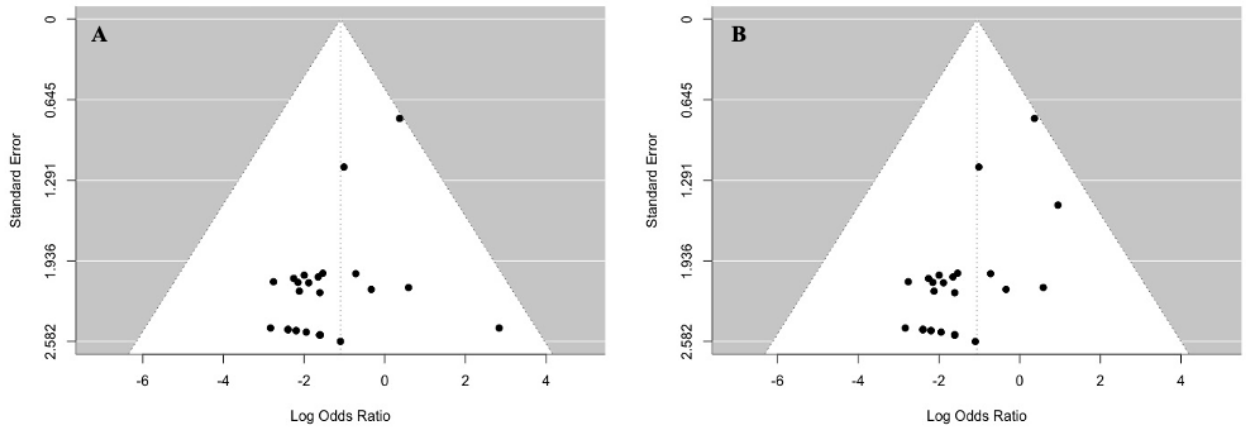
Supplementary method 1

Key definitions

Monophasic disease course was defined as 1 episode of new CNS symptoms or signs lasting >24 hours, in the absence of other causes, and clinically and/or radiologically compatible with a MOGAD episode in an individual with ≥1 year of follow-up. Relapsing disease course was defined as ≥2 episodes of new CNS symptoms or signs lasting >24 hours each and separated by ≥30 days, in the absence of other causes, and clinically and/or radiologically compatible with MOGAD episodes in an individual with ≥1 year of follow-up. Disease activity was categorised as attack or remission, with attack defined as <30 days following >24 hours of new CNS symptoms or signs, in the absence of other causes, and clinically and/or radiologically compatible with a MOGAD episode (including both onset and relapse events), whereas remission was defined as disease stability ≥30 days following >24 hours of new CNS symptoms or signs, in the absence of other causes, and clinically and/or radiologically compatible with a MOGAD episode (after onset or relapse event). Transient seropositivity was defined as <2 positive serum MOG-IgG results on serial measurement ≥3 months apart. Persistent seropositivity was defined as ≥2 positive serum MOG-IgG results on serial measurement ≥3 months apart. Individuals whose MOG-IgG measurements fluctuated between seropositive and seronegative were categorized as persistent seropositive if there were ≥2 positive results ≥3 months apart. ≥3 months was defined as the primary sample collection interval to maximise the number of included studies; however, additional analyses utilising ≥6- and ≥12-month sample collection intervals were also explored. Absolute MOG-IgG titres were semi-quantitatively categorised as 'negative', 'low positive', or 'clear positive' in accordance with Supplementary Table 5 of the international MOGAD diagnostic criteria.[1] Phenotypes were categorised as 'Brain/Brainstem' (CCE as well as brainstem and cerebellar presentations but excluded ADEM), 'ADEM', 'ON', 'TM', 'ON+TM' (simultaneous ON and TM as well as isolated ON or TM with sequential presentation of the other), 'ADEM+ON' (simultaneous ADEM and ON as well as isolated ADEM or ON with sequential presentation of the other), 'mixed' (simultaneous and/or sequential presentation of any combination of the above categories), and 'other' (demyelinating phenotypes with insufficient detail to be otherwise categorised). Further definitions are presented (Supplementary tables 2 and 3).



Supplementary Figure 1: Forest plot demonstrating that persistent seropositivity on serial serum MOG-IgG measurement ≥3 months apart is associated with relapsing disease course (OR 2.7 (95% CI 1.8–4.0), p<0.0001). TS = transient seropositivity; PS = persistent seropositivity.



Supplementary Figure 2: Funnel plot asymmetry identified when investigating the association of CSF OCB and disease activity; (A) attack samples were collected <30 days following clinical symptoms, (B) attack samples were collected <3 months following clinical symptoms.

Supplementary Table 1: Systematic search strategy as of February 21, 2024. All terms were searched as text words and as exploded medical subject headings where possible. All terms within a concept were combined with "OR" and concepts were combined with "AND".

Concept 1		Concept 2		Concept 3
"myelin oligodendrocyte glycoprotein" "myelin oligodendrocyte glycoprotein antibody associated disease" "MOG antibody associated disease" "MOGAD" "MOG-AAD" "myelin oligodendrocyte glycoprotein immunoglobulin" "myelin oligodendrocyte glycoprotein antibody" "MOG IgG" "MOG Ab" "acquired demyelinating syndrome" "ADS"	AND	"relaps*" "recur*" "monophasic" "prognosis" "disease progression" "disease course" "demyelinating attack" "demyelinating episode" "annualised relapse rate" "annualized relapse rate" "ARR"	AND	"cell-based assay" "CBA" "immunoglobulin G" "seropositive*" "antibod*" "IgG" "cerebrospinal fluid" "CSF" "cytokine" "chemokine" "complement" "neurofilament" "pleocytosis" "leukocytosis" "lymphocytosis" "monocytosis" "oligoclonal band" "OCB" "titre" "biomarker" "IgG index" "erythrocyte sedimentation rate" "ESR" "C reactive protein" "CRP" "inflammation" "intrathecal" "Epstein-Barr virus" "EBV" "Epstein-Barr virus nuclear antigen" "EBNA" "infectious mononucleosis"

Supplementary Table 2: Key definitions	
Term	Definition
Relapsing disease course	≥2 episodes of new CNS symptoms or signs lasting >24 hours each and separated by ≥30 days, in the absence of other causes, and clinically and/or radiologically compatible with MOGAD episodes.
Monophasic disease course	1 episode of new CNS symptoms or signs lasting >24 hours, in the absence of other causes, and clinically and/or radiologically compatible with a MOGAD episode.
Disease onset	<30 days following >24 hours of new CNS symptoms or signs, in the absence of other causes, and clinically and/or radiologically compatible with the first MOGAD episode.
Attack disease activity	<30 days following >24 hours of new CNS symptoms or signs, in the absence of other causes, and clinically and/or radiologically compatible with a MOGAD episode (including both onset and relapse events).
Near attack disease activity	<3 months following >24 hours of new CNS symptoms or signs, in the absence of other causes, and clinically and/or radiologically compatible with a MOGAD episode (including both onset and relapse events). A relaxed definition of attack disease activity used for subgroup analyses, with the aim of capturing further published works.

Remission disease activity	Disease stability ≥30 days following >24 hours of new CNS symptoms or signs, in the absence of other causes, and clinically and/or radiologically compatible with a MOGAD episode (after onset or relapse event).
Onset sample	Serum or CSF sample collected at disease onset.
First collected sample	The first collected serum or CSF sample for an individual, including but not limited to samples collected at disease onset and irrespective of disease activity at time of sampling.
Transient seropositivity	<2 positive serum MOG-IgG results on serial measurement ≥3 months apart.
Persistent seropositivity	≥2 positive serum MOG-IgG results on serial measurement ≥3 months apart. Individuals whose MOG-IgG measurements fluctuated between seropositive and seronegative were categorized as persistent seropositive if there were ≥2 positive results ≥3 months apart.

Supplementary Table 3: Clinical phenotype categories	
Phenotype	Comments
Brain/Brainstem	Included CCE as well as brainstem and cerebellar presentations but excluded ADEM.
ADEM	—
ON	—
TM	—
ON+TM	Included simultaneous ON and TM as well as isolated ON or TM with sequential presentation of the other.
ADEM+ON	Included simultaneous ADEM and ON as well as isolated ADEM or ON with sequential presentation of the other.
Mixed	Included simultaneous and/or sequential presentation of any combination of the above phenotype categories.
Other	Included demyelinating phenotypes with insufficient detail to be otherwise categorized e.g. ‘uncategorized relapsing MOGAD’ or ‘clinically isolated syndrome (CIS)’.

Supplementary Table 4: Characteristics of 106 studies included in systematic review

	MOG-IgG Seropositive Participants						Cell-Based Assay (CBA)				Contributed Biomarker(s)			
Source	*Participants (n)*	*Age at Onset, Median (range) (years)*	*Sex (n female [%])*	*Disease Course (n relapsing [%])*	*Clinical Phenotype (n)*	*Follow-up Duration, Median (range) (months)*	*Fixed or Live*	*Titre positivity threshold*	*Type of CBA*	*Centre*	*Disease Course Correlation*	*Disease Activity Correlation*	**Risk of Bias**	**Assessment**
Baumann et al, 2016 [9]											(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB		
Total	8	3 (1–7)	5 [62.5]	8 [100.0]	ADEM (8)	48 (12-96)								
Included	8	3 (1–7)	5 [62.5]	8 [100.0]	ADEM (8)	48 (12-96)	Live	≥1:160	In-house CBA at Medical University of Innsbruck, Innsbruck, Austria	Medical University of Innsbruck, Innsbruck, Austria			Medium	Quantitative
Kwon et al, 2020 [43]									In-house CBA at Seoul National University Hospital, Seoul, Republic of Korea	Seoul National University Hospital, Seoul, Republic of Korea				
Total	21	45.6 (17-70)	9 [42.9]	13 [61.9]	ON (7), CRION (10), AQP4-IgG negative NMOSD (2), ADEM (2)	NA								
Included	21	45.6 (17-70)	9 [42.9]	13 [61.9]	ON (7), CRION (10), AQP4-IgG negative NMOSD (2), ADEM (2)	NA	Live	Semi-quantitative			—	(i) Serum cytokines	Low	Qualitative
Kim et al., 2020 [19]									Commercially available Euroimmun, Lubeck, Germany	Asan Medical Centre, Seoul, Republic of Korea		(i) Serum NfL (ii) Serum GFAP (iii) Serum tau		
Total	16	40.5 (21-57)[$]	7 [43.8]	8 [50.0]	ON (7), TM (3), Brain (2), ON+Brain (2), ON+TM+Brain (2)	NA								Qualitative and quantitative
Included	16	40.5 (21-57)[$]	7 [43.8]	8 [50.0]	ON (7), TM (3), Brain (2), ON+Brain (2), ON+TM+Brain (2)	NA	Fixed	>1:40			—		Low	
Wendel et al, 2020 [44]									In-house CBA at Medical University of Innsbruck, Innsbruck, Austria	Medical University of Innsbruck, Innsbruck, Austria	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status	(i) Serum MOG-IgG titre		
Total	22	7.5 (2-15)^	10 [45.5]	4 [18.2]	bON (16), ADEM (1), recurrent ON (2), ON+LETM (3)	17 (4-141)								
Included	9	NA	NA	3 [33.3]	bON (6), bON+LETM (1), bON+uON (2)	36 (12-141)	Live	≥1:160					Medium	Quantitative
Pröbstel et al, 2011 [45]									In-house CBA at Ludwig-Maximilians-University, Munich, Germany	Max Planck Institute of Neurobiology, Martinsried, Germany	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status	(i) Serum MOG-IgG titre		
Total	31	7 (1-16)[%^]	146 [58.2]	11 [35.5]	ADEM (19), MS (10), CIS (2)	44 (12-75)[%]		MCF > mean+4 SD of control (>1.45)						
Included	16	NA	NA	0 [0]	ADEM (16)	≥12	Live						Low	Quantitative
Hyun, et al., 2017 [46]									Referred CBA at University of Oxford, UK	National Cancer Center, Republic of Korea	(i) Serum MOG-IgG titre	—		
Total	22	30 (4-50)	14 [63.6]	17 [77.3]	Brain (2), ON (2), bON (2), TM (1), LETM (3), Brain+ON (3), Brain+bON (1), Brain+TM (2), Brain+LETM (1), ON+LETM (2),	63 (7-200)								
Included	16	NA	NA	0 [0]	ADEM (16)	≥12	Live	≥1					Medium	Quantitative

					Brain+ON+LETM (1), Brain+ bON +TM (2)						(ii) Serial serum MOG-IgG status (iii) CSF OCB			
Included	19	30 (4-50)	12 [63.2]	15 [79.0]	Brain (2), ON (2), bON (2), TM (1), LETM (3), Brain+ON (3), Brain+bON (1), Brain+TM (1), Brain+LETM (1), Brain+ON+LETM (1), Brain+ bON +TM (2)	61 (23-200)								
Höftberger, et al., 2015 [47] *Total*	17	27 (18-59)	9 [52.9]	10 [58.8]	ON (7), LETM (6), ON+LETM (5), ADEM (1)	67 (11–415)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF OCB	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF OCB		
Included	15	27 (18-45)	8 [53.3]	10 [66.7]	ON (6), LETM (6), ADEM (1), ON+LETM (2)	87 (17-415)	Live	≥1:160	In-house CBA at IDIBAPS, University of Barcelona, Spain	IDIBAPS, University of Barcelona, Spain			Low	Quantitative
Horellou, et al., 2021 [48] *Total*	12	Monophasic: 10.2 ± 5.2; Relapsing: 9.9 ± 2.4*	7 [58.3]	7 [58.3]	ON (3), TM (6), ADEM (2), Brainstem (2)[#]	Not available								
Included	12	Monophasic: 10.2 ± 5.2; Relapsing: 9.9 ± 2.4*	7 [58.3]	7 [58.3]	ON (3), TM (6), ADEM (2), Brainstem (2)[#]	Monophasic: 22.8 ± 26.4; Relapsing: 58.8 ± 26.4[&]	Live and fixed	MFI > mean+6 SD of control (live) and ≥1:160 (fixed)	In-house CBA at Universite Paris-Saclay, Le Kremlin Bicetre, France	Universite Paris-Saclay, Le Kremlin Bicetre, France	(i) PBMCs	—	Low	Qualitative
Chang, et al., 2021 [20] *Total*	42	27 (17-38)[$]	22 [52.4]	NA	ON (14), TM (3), Brain (10), ON+TM (3), ON+Brain (4), Brain+TM (7), ON+Brain+TM (1)	NA								
Included	42	27 (17-38)[$]	22 [52.4]	NA	ON (14), TM (3), Brain (10), ON+TM (3), ON+Brain (4), Brain+TM (7), ON+Brain+TM (1)	NA	Fixed	≥1:32	Commercially available Euroimmun, Lubeck, Germany	Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China	—	(i) Serum NfL (ii) Serum GFAP	Low	Qualitative and quantitative
Jarius, et al., 2020 [49] *Total*	80	6 (0.6-17.7)[!]	45 [56.3]	38 [47.5]	Attack phenotype (n=94 samples): TM+/-other symptoms (30), uON (15), bON (12), ADEM (34), Brainstem/Cerebellar (3)	34.5 (0-229)[@]								
Included	80	6 (0.6-17.7)[!]	45 [56.3]	38 [47.5]	Attack phenotype (n=94 samples): TM+/-other symptoms (30), uON (15), bON (12), ADEM (34), Brainstem/Cerebellar (3)	34.5 (0-229)[@]	Live and fixed	NA	(i) Live CBA referred to Medical University Innsbruck, Austria, University of Vienna, Austria, and Ludwig Maximilian University Munich, Germany	University of Heidelberg, Heidelberg, Germany	—	(i) CSF WCC (ii) CSF protein (iii) CSF OCB	Medium	Quantitative

									(ii) Fixed CBA in-house at University of Heidelberg, Germany and commercially available Euroimmun, Lubeck, Germany					
Cobo-Calvo, et al., 2017 [50] *Total*	27	16.8 (6.8–33.7)[$]	14 [51.9]	11 [40.7]	ADEM (8), ON (8), TM (1), LETM (4), NMOSD (4), MS (2)	17.8 (11.5–68.3)[$]			In-house CBA at Université Hospital of Lyon, France	Université Hospital of Lyon, France	(i) CSF WCC (ii) CSF protein (iii) CSF OCB	(i) Serum MOG-IgG titre	Medium	Quantitative
Included	3	13 (3-16)^	1 [33.3]	0 [0.0]	ADEM (2), TM (1)	13 (12-24)	Live	≥1:640						
Hyun, et al., 2021 [21] *Total*	15	38 (27-41)[$!]	6 [40.0]	15 [100.0]	NA	24 (21–43)			In-house CBA at National Cancer Center, Republic of Korea	National Cancer Center, Republic of Korea	—	(i) Serum NfL (ii) Serum GFAP	Low	Qualitative and quantitative
Included	15	38 (27-41)[$!]	6 [40.0]	15 [100.0]	NA	24 (21–43)	Live	NA						
Ikeda, et al., 2019 [51] *Total*	4	8 (3-12)	2 [50.0]	3 [75.0]	Brain+TM (1), ON+Brain+TM (1), bON+Brain+TM (1), bON+uON+Brain+TM (1)	32.5 (18-87)					(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB	Low	Quantitative
Included	4	8 (3-12)	2 [50.0]	3 [75.0]	Brain+TM (1), ON+Brain+TM (1), bON+Brain+TM (1), bON+uON+Brain+TM (1)	32.5 (18-87)	Live	≥1:160	Referred CBA to Tohoku University, Japan	Yokohama City University Medical Centre, Japan				
López-Chiriboga, et al., 2018 [7] *Total*	25	(i) 4 (2-9) (ii) 6.5 (4-8) (iii) 26 (22-45) (iv) 22.5 (18-45) ~	15 [60.0]	16 [64.0]	ADEM (9), ADEM+ON (7), ADEM+Brain (3), ADEM+ON+TM (2), ADEM+Brain+ON (2)[a]	(i) 75 (15-236) (ii) 32 (24-114) (iii) 39 (10-161) (iv) 16 (13-27) ~								
Included	24	(i) 4 (2-9) (ii) 6.5 (4-8) (iii) 26 (22-45) (iv) 22.5 (18-45) ~	14 [58.3]	15 [62.5]	ADEM (9), ADEM+ON (7), ADEM+Brain (3), ADEM+ON+TM (2), ADEM+Brain+ON (2)[a]	(i) 75 (15-236) (ii) 32 (24-114) (iii) 57 (15-161) (iv) 16 (13-27) ~	Live	≥1:20	In-house CBA at Mayo Clinic, USA	Mayo Clinic, USA	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status	(i) Serum MOG-IgG titre	Low	Quantitative
Waters, et al., 2020 [52] *Total*	84	7.31 (4.93-10.57)[$]	46 [54.8]	16/82 [19.5]	ADEM (32), ADEM+ON (3), ADEM+TM (9), ADEM+ON+TM (1), ON (34), TM (12), ON+TM (3), Other (3)[c]	6.74 (4.77-8.75)[$]	Live	≥1:200	In-house CBA at University of Oxford, UK	University of Oxford, UK	(i) Serial serum MOG-IgG status	—	Low	Quantitative

Included	67	(i) 9.06 (6.60-13.36)[$] (ii) 6.95 (5.28-9.96)[$]	33 [53.2]	16 [23.9]	ADEM (22), ADEM+ON (2), ADEM+TM (4), ADEM+ON+TM (1), ON (24), TM (9), ON+TM (4), Other (3)	(i) 4.29 (3.00-5.96)[$] (ii) 4.04 (2.99-6.01)[$b] All ≥12-months								
Jurynczyk, et al., 2017 [53]														
Total	252	30.1 ± 18.3*	144 [57.1]	111 [44.1]	ON (44), TM (17), ADEM (32), ON+TM (26)[a]	NA			In-house CBA at University of Oxford, UK	University of Oxford, UK	(i) Serial serum MOG-IgG status	—	Low	Quantitative
Included	56	NA	NA	29 [51.8]	NA	27.5 (12-438)	Live	NA						
Hino-Fukuyo, et al., 2019 [54]														
Total	5	5 (2-10)	2 [40.0]	3 [60.0]	ADEM (2), uON (1), bON (1), ADEM+bON (1)	150 (68-322)			In-house CBA at Tohoku University, Japan	Tohoku University, Japan	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status	(i) Serum MOG-IgG titre	Low	Quantitative
Included	5	5 (2-10)	2 [40.0]	3 [60.0]	ADEM (2), uON (1), bON (1), ADEM+bON (1)	150 (68-322)	Live	NA						
Serin, et al., 2021 [55]														
Total	9	6 (3-13)	6 [66.7]	4 [44.4]	ADEM (3), ON (2), CIS (1), ADEM+ON (1), Uncategorized relapsing MOGAD (2)	28 (24-196)								
Included	9	6 (3-13)	6 [66.7]	4 [44.4]	ADEM (3), ON (2), CIS (1), ADEM+ON (1), Uncategorized relapsing MOGAD (2)	28 (24-196)	Fixed	≥1:10	Commercially available Euroimmun, Lubeck, Germany	Ege University Medical Faculty, Izmir, Turkey	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF OCB	(i) Serum MOG-IgG titre	Low	Quantitative
Jarius, et al., 2020 [56]														
Total	100	38 (18-78)[!]	58 [58.3]	NA	Attack phenotype (n=123 samples): TM+/-other symptoms (56), ON without TM (53), isolated brain or brainstem/cerebellar (11)[a]	29 (0-511)[@]								
Included	100	38 (18-78)[!]	58 [58.3]	NA	Attack phenotype (n=123 samples): TM+/-other symptoms (56), ON without TM (53), isolated brain or brainstem/cerebellar (11)[a]	29 (0-511)[@]	Live and fixed	NA	(i) Live CBA referred to Medical University Innsbruck, Austria, University of Vienna, Austria, and Ludwig Maximilian University Munich, Germany (ii) Fixed CBA in-house at University of Heidelberg, Germany and commercially available	University of Heidelberg, Heidelberg, Germany	—	(i) CSF WCC (ii) CSF protein (iii) CSF OCB	Medium	Quantitative

									Euroimmun, Lubeck, Germany					
Jarius, et al., 2016 [26]														
Total	50	39 (range not stated)	35 [70.0]	NA	ON (22), LETM (6), ON+TM (22)	NA			In-house CBA at University of Heidelberg, Germany	University of Heidelberg, Germany		(i) Serum MOG-IgG titre	Low	Quantitative
Included	75 samples; unclear participants	NA	NA	NA	NA	NA	Live	≥1:160			—			
Oliveira, et al., 2019 [57]														
Total	31	33 (8-52)	17 [54.8]	23 [74.2]	bON (10), ON (11), Brainstem (2), LETM (4), ON+LETM (1), ON+TM (1), bON+TM (1), Brainstem+LETM (1)	79 (38-104)[$] All ≥12 months					(i) Serum MOG-IgG titre			
Included	31	33 (8-52)	17 [54.8]	23 [74.2]	bON (10), ON (11), Brainstem (2), LETM (4), ON+LETM (1), ON+TM (1), bON+TM (1), Brainstem+LETM (1)	79 (38-104)[$] All ≥12 months	Live	≥1:128	In-house CBA at HC-FMUSP, São Paulo, Brazil	HC-FMUSP, São Paulo, Brazil	(ii) Serial serum MOG-IgG status	—	Low	Quantitative
Arslan, et al., 2021 [58]														
Total	8	32.1 ±10.0*	3 [37.5]	2 [25.0]	ON (6), TM (1), ON+TM (1)	NA			Commercially available Euroimmun, Lubeck, Germany	Gazi University Faculty of Medicine, Ankara, Turkey				
Included	8	32.1 ±10.0*	3 [37.5]	2 [25.0]	ON (6), TM (1), ON+TM (1)	NA	Fixed	≥1:10			—	(i) Serum thiol	Low	Qualitative
Liu, et al., 2020 [59]														
Total	26	(i) 48 ± 20.4* (ii) 46 ± 19.7*[d]	(i) 7 [58.3] (ii) 14 [63.6] [d]	NA	Attack phenotype: ON (5), TM (5), Brain (3)[a]	NA								
Included	26	(i) 48 ± 20.4* (ii) 46 ± 19.7*[d]	(i) 7 [58.3] (ii) 14 [63.6] [d]	NA	Attack phenotype: ON (5), TM (5), Brain (3)[a]	NA	Live	NA	In-house CBA at Chiba University, Chiba, Japan	Chiba University, Chiba, Japan	—	(i) PBMCs (ii) CSF OCB	Low	Qualitative and quantitative
de Mol, et al., 2020 [12]														
Total	61	16.6 (7.9–31.9)[$]	28 [45.9]	20 [32.8]	ON (7), bON (9), ADEM (14), Brainstem (1), TM (5), LETM (4), ON+ADEM (3), ON+Brain (1), ON+TM (13), ADEM+TM (1), CIS (1), RRMS (1)[a]	27.5 (1–329)								
Included	20	NA	NA	8 [40.0]	NA	30.5 (12-246)	Live	MFI > 10 SD of control	In-house CBA at MS Centre ErasMS, Erasmus MC, Rotterdam, The Netherlands	MS Centre ErasMS, Erasmus MC, Rotterdam, The Netherlands	(i) Serial serum MOG-IgG status	—	Medium	Quantitative
Rostásy, et al., 2012 [60]														
Total	17	10 (2-16)	10 [58.8]	12 [70.6]	uON (9), bON (3), uON+ADEM (2), MS (3)	30 (11-74)			In-house CBA at Medical University of Innsbruck, Innsbruck, Austria	Medical University of Innsbruck, Innsbruck, Austria	(i) Serum MOG-IgG titre (ii) CSF OCB	—	Low	Quantitative
Included	13	10 (2-16)	7 [53.9]	11 [84.6]	uON (9), bON (3), uON+ADEM (1)	35 (19-74)	Live	≥1:160						
Rostásy, et al., 2013 [61]														
Total	3	3 (3-14)	3 [100]	3 [100]	uON+TM (1), LETM+ON (2)	28 (18-48)	Live	≥1:160	In-house CBA at Medical University of Innsbruck,	Medical University of Innsbruck,	(i) Serum MOG-IgG titre	(i) Serum MOG-IgG titre	Low	Quantitative

Included	3	3 (3-14)	3 [100.0]	3 [100.0]	uON+TM (1), LETM+ON (2)	28 (18-48)			Innsbruck, Austria	Innsbruck, Austria	(ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB	(ii) CSF WCC (iii) CSF protein (iv) CSF OCB		
Saxena, et al., 2020 [62] *Total*	24	4.5–52[e^]	15 [62.5]	NA	ADEM (1), ON+TM (2) ADEM+ON (7), ADEM+TM (1), MS (7), CIS (1), demyelinating neurological disease (1)[a]	NA								
Included	24	4.5–52[e^]	15 [62.5]	NA	ADEM (1), ON+TM (2) ADEM+ON (7), ADEM+TM (1), MS (7), CIS (1), demyelinating neurological disease (1)[a]	NA	Live	NA	Referred CBA to Harvard University, USA and Mayo Clinic, USA	Brigham and Women's Hospital, Harvard Medical School, Boston, USA	—	(i) Serum TNFAIP3	Low	Qualitative
Luo, et al., 2021 [22] *Total*	49	25 (10-29.5)[$]	28 [57.1]	34 [69.4]	Most recent attack phenotype: ON (23), Brain (15), TM (6), ON+Brain (2), ON+TM (2), Brain+TM (1)	12[f]								
Included	49	25 (10-29.5)[$]	28 [57.1]	34 [69.4]	Most recent attack phenotype: ON (23), Brain (15), TM (6), ON+Brain (2), ON+TM (2), Brain+TM (1)	12[f]	Live	NA	In-house CBA at the Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China	The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China	—	(i) Serum NfL	Low	Qualitative and quantitative
Tanaka, et al., 2020 [63] *Total*	17	32 (8-76)	10 [58.8]	9 [52.9]	Onset attack: uON (10), bON (1), Brain (1), TM (4), ON+Brainstem (1)	NA								
Included	17	32 (8-76)	10 [58.8]	9 [52.9]	Onset attack: uON (10), bON (1), Brain (1), TM (4), ON+Brainstem (1)	NA	Live	NA	Referred CBA to Tohoku University School of Medicine, Sendai, Japan	Saitama Medical University, Kawagoe, Japan	—	(i) PBMCs	Low	Qualitative
Han, et al., 2022 [64] *Total*	8	11 (1-17)	3 [37.5]	1 [12.5]	Brain (7), Brain+TM (1)	15.5 (2-54)								
Included	6	8 (1-17)	3 [50.0]	1 [16.7]	Brain (5), Brain+TM (1)	18 (12-54)	Live	Borderline: >2.60–≤3.65; Positive: >3.65	In-house CBA at Seoul National University Children's Hospital, Seoul, Republic of Korea	Seoul National University Children's Hospital, Seoul, Republic of Korea	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB	—	Low	Quantitative
Mariotto, et al., 2021 [65] *Total*	18	34.5 (6-75)	8 [44.4]	7 [38.9]	ON (7), TM (3), Idiopathic demyelinating disorders (8)	19 (3-93)								
Included	18	34.5 (6-75)	8 [44.4]	7 [38.9]	ON (7), TM (3), Idiopathic demyelinating disorders (8)	19 (3-93)	Live	≥1:160	In-house CBA at the University of Verona, Verona, Italy	University of Verona, Verona, Italy	—	(i) Serum NfL	Medium	Qualitative
Sun, et al., 2020 [66]	95	13 (2–67)	NA	NA	Onset attack: ON (58), Brain (30), Brainstem (6), TM (11), Other (4)	12 (4–36)[&]	Live	NA	In-house CBA at the Third	The Third Affiliated	(i) HLA genotype	—	Low	Qualitative

Total									Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China	Hospital of Sun Yat-Sen University, Guangzhou, China				
Included	95	13 (2–67)	NA	NA	Onset attack: ON (58), Brain (30), Brainstem (6), TM (11), Other (4)	12 (4–36)[&]								
Mariotto, et al., 2019 [67]														
Total	38	35.5 (6–75)[!]	16 [42.1]	18 [47.4]	ON (14), ADEM (2), TM (4), ON+TM (4), Idiopathic demyelinating disorder (12), MS (2)	19.5 (2–266)								
Included	38	35.5 (6–75)[!]	16 [42.1]	18 [47.4]	ON (14), ADEM (2), TM (4), ON+TM (4), Idiopathic demyelinating disorder (12), MS (2)	19.5 (2–266)	Live	≥1:160	In-house CBA at the University of Verona, Verona, Italy	University of Verona, Verona, Italy	—	(i) Serum NfL	Low	Qualitative
Alshamrani, et al., 2021 [68]														
Total	9	35 (28-69)	7 [77.8]	6 [66.7]	ON (3), Brain (1), Brainstem (2), TM (1), LETM (2)	48 (1-132)								
Included	5	43 (28-58)	3 [60.0]	4 [80.0]	ON (2), Brain (1), Brainstem (2)	120 (13-132)	NA	NA	Referred CBA to London (Ontario) MS clinic	King Fahad University Hospital, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia	(i) CSF OCB	—	Medium	Quantitative
Dale, et al., 2014 [28]														
Total	31	6.7 (2.0-15.3)^	18 [58.1]	10 [32.3]	ON (9), ADEM (11), TM (4), MS (7)	48 (3-164)								
Included	2	9.5 (5-14)^	1 [50.0]	2 [100.0]	LETM+ON (1), ADEM+Brain (1)	17.5 (16-19)	Live	MFI > mean+6 SD of control	In-house CBA at the Kids Research Institute at the Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Australia	The Kids Research Institute at the Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Australia	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF OCB	(i) Serum MOG-IgG titre	Low	Quantitative
Lui, et al., 2021 [69]														
Total	65	7.6 (4.3-10.9)[$]	36 [55.4]	NA	ADEM (2), ON+TM (1), CIS (1), RRMS (7), Demyelinating disorder not otherwise specified (54)	42 (6-78)[$]								
Included	25	NA	NA	9 [36.0]	NA	60 (15-300)	Live	≥1:20	Referred CBA to Mayo Clinic, USA	University of California, USA	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status	(i) Serum MOG-IgG titre	Low	Quantitative
Dubey, et al., 2019 [70]														
Total	54	25 (3-73)	24 [44.4]	NA	TM (21), ON+TM (32), ADEM+TM (1)	24 (2-120)								
Included	5	NA	NA	1 [20.0]	NA	35 (15-120)	Live	≥1:20	Referred CBA to Mayo Clinic, USA	Mayo Clinic, USA	(i) Serial serum MOG-IgG status	—	Medium	Quantitative
Hennes, et al., 2017 [8]														
Total	65	(i) 9 (3–15) (ii) 5 (0–17)[g^]	35 [53.9]	25 [38.5]	ON (8), ADEM (22), ADEM+ON (11), ON+TM (9), CIS (12), MS (3)	24[f]	Live	≥1:160	Referred CBA to Medical University of Innsbruck,	Olga Hospital, Stuttgart, Germany	(i) Serum MOG-IgG titre	(i) Serum MOG-IgG titre	Low	Quantitative

Included	62	NA	NA	22 [35.5]	ON (8), ADEM (22), ADEM+ON (11), ON+TM (9), CIS (12)	24[f]			Innsbruck, Austria		(ii) Serial serum MOG-IgG status (iii) CSF OCB	(ii) CSF OCB		
Tea, et al., 2019 [71] *Total*	287	22 (8–43)[$]	165 [57.5][i]	105 [43.6][j]	uON (62), bON (58), mixed ON (9), ADEM (54), LETM (18), ADEM+ON (10), ADEM+LETM (1), Brainstem+LETM (1), Brainstem+ON+TM (1), ON+TM (9), uON+LETM (2), TM (6), bON+LETM (2), bON+LETM+ADEM (2), CIS (1), Other (12), Unknown (39)	NA			In-house CBA at the Kids Research Institute at the Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Australia	The Kids Research Institute at the Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Australia	(i) Serial serum MOG-IgG status (ii) CSF WCC (iii) CSF protein (iv) CSF OCB	(i) CSF WCC (ii) CSF protein (iii) CSF OCB		
Included	16	13 (3-45)[$h]	5 [71.4][i]	8 [50.0]	uON (1), bON (3), ADEM (6), ADEM+ON (2), ADEM+LETM (1), Brainstem+LETM (1), ON+LETM (2)	34 (17-99)	Live	MFI > mean+6 SD of control					Low	Quantitative
Senanayake, et al., 2019 [72] *Total*	126	26 (3–68)	70 [55.6]	43 [34.1]	ON (58), TM (24), ADEM (12), NMOSD (32)	48 (1–240)								
Included	17	NA	NA	13 [76.5]	NA	(i) Monophasic: 12 (12-24) (ii) Relapsing: 84 (36-204)	NA	NA	Clinical Laboratory Improvement Amendments approved flow cytometric assays	The National Hospital of Sri Lanka, Colombo, Sri Lanka	(i) Serial serum MOG-IgG status	—	Low	Quantitative
Wegener-Panzer, et al., 2020 [73] *Total*	10	8 (4–16)	4 [40.0]	5 [50.0]	Brain (9), Brain+ON (1)	18 (6-48)			(i) Live: referred CBA to Medical University of Innsbruck, Innsbruck, Austria (ii) Fixed: commercially available Euroimmun, Lubeck, Germany		(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF OCB	(i) Serum MOG-IgG titre (iii) CSF WCC (iv) CSF OCB		
Included	6	6.5 (3-16)	3 [50.0]	4 [66.7]	Brain (5), Brain+ON (1)	33 (12-48)	Live and fixed	(i) Live: ≥1:160 (ii) Fixed: NA		Children's Hospital Datteln, University Witten/Herdecke, Germany			Medium	Quantitative
Zhou, et al., 2019 [74] *Total*	23	5.38 (2.33–12.75)	13 [56.5]	23 [100.0]	ADEM (2), ADEM+ON (3), NMOSD (11), Uncategorized CNS demyelination (7)	≥12			Commercially available Euroimmun, Lubeck, Germany	Peking University First Hospital, Beijing, China	(i) CSF OCB	(i) CSF WCC (ii) CSF protein (iii) CSF OCB		
Included	23	5.38 (2.33–12.75)	13 [56.5]	23 [100.0]	ADEM (2), ADEM+ON (3), NMOSD (11), Uncategorized CNS demyelination (7)	≥12	Fixed	NA					Low	Quantitative

Keller, et al., 2021 [75] *Total*	109	(i) Paediatric: 9 (1-17) (ii) Adult: 38 (18–70	70 [64.2]	38 [34.9]	uON (36), bON (19), LETM (14), ADEM (40)	NA		(i) University of Sydney: MFI > mean + 3 SD of control (ii) Medical University of Innsbruck: ≥1:160	CBA referred to The Kids Research Institute at the Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Australia and Innsbruck Medical University, Innsbruck, Austria	University Hospital Münster, Münster, Germany	—	(i) Serum complement	Low	Qualitative
Included	109	(i) Paediatric: 9 (1-17) (ii) Adult: 38 (18–70	70 [64.2]	38 [34.9]	uON (36), bON (19), LETM (14), ADEM (40)	NA	Live							
Baumann, et al., 2015 [76] *Total*	19	4 (1-17)	9 [47.4]	4 [21.1]	ADEM (16), ADEM+ON (3)	27 (5-81)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF OCB	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF OCB	Low	Quantitative
Included	14	4 (1-17)	NA	4 [28.6]	ADEM (11), ADEM+ON (3)	33.5 (14-81)	Live	≥1:160	In-house CBA at Medical University of Innsbruck, Innsbruck, Austria	Medical University of Innsbruck, Innsbruck, Austria				
Ramanathan, et al., 2018 [77] *Total*	59	12 (1-74)	40 [67.8]	59 [100.0]	Brainstem/Cerebellar (1), bON (3), uON (8), uON+bON (6), ADEM+Brainstem (2), bON+Brain (2), ADEM+Brainstem/Cerebellar (1), ADEM+Cerebellar (1), ADEM+bON (2), ADEM+uON (3), ADEM+LETM (2), bON+LETM (3), uON+Brain (2), uON+LETM (2), Cerebellar+Sensory non-spinal (1), bON+Sensory non-spinal (2), TM+LETM (1), uON+Brainstem (1), uON+bON+Brain (1), uON+Brainstem+TM (2), uON+Brainstem/Cerebellar+LETM (1), ADEM+Cerebellar+uON (2), uON+TM+Sensory non-spinal (1), ADEM+LETM+nonencephalitic ADS (1), bON+uON+TM (2), ADEM+uON+bON+LETM (1), ADEM+Brain+uON+bON (1), ADEM+Brainstem/Cerebellar+uON+LETM (1), bON+uON+LETM+Brainstem (1),	45 (12–288)	Live	MFI > mean + 3 SD of control	In-house CBA at the Kids Research Institute at the Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Australia	The Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Australia	(i) CSF WCC (ii) CSF protein (iii) CSF OCB	(i) CSF WCC (ii) CSF protein (iii) CSF OCB	Low	Quantitative

					ADEM+Brainstem/Cerebellar+bON+ uON (1), bON+uON+TM+LETM (1)									
Included	51	10 (1-74)	35 [68.6]	51 [100.0]	Brainstem/Cerebellar (1), bON (3), uON (1), uON+bON (6), ADEM+Brainstem (2), bON+Brain (2), ADEM+Brainstem/Cerebellar (1), ADEM+Cerebellar (1), ADEM+bON (2), ADEM+uON (3), ADEM+LETM (2), bON+LETM (3), uON+Brain (2), uON+LETM (2), Cerebellar+Sensory non-spinal (1), bON+Sensory non-spinal (1), TM+LETM (1), uON+Brainstem (1), uON+bON+Brain (1), uON+Brainstem+TM (2), uON+Brainstem/Cerebellar+LETM (1), ADEM+Cerebellar+uON (2), uON+TM+Sensory non-spinal (1), ADEM+LETM+nonencephalitic ADS (1), bON+uON+TM (2), ADEM+uON+bON+LETM (1), ADEM+Brain+uON+bON (1), ADEM+Brainstem/Cerebellar+uON+ LETM (1), bON+uON+LETM+Brainstem (1), ADEM+Brainstem/Cerebellar+bON+ uON (1), bON+uON+TM+LETM (1)	49 (12-288)								
Benetou, et al., 2020 [78]										Evelina London Children's Hospital, Guys and St. Thomas' Hospital NHS Foundation Trust, Kings Health Partners, London, UK				
Total	17	6.3 (4.1–9.6)[$^]	9 [52.9]	NA	NA	NA								
Included	17	6.3 (4.1–9.6)[$^]	9 [52.9]	NA	NA	NA	NA	NA	NA		—	(i) Peripheral blood count index ratios	Low	Qualitative
Armangue, et al., 2020 [79]					ADEM (42), ON (5), uON (8), bON (6), Brain (18), LETM (9), ADEM+ON (4), Brain+ON (3), ON+Other (1), NMOSD (11), MS (5), Other (4)					IDIBAPS, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain				
Total	116	6·2 (3·7–10·0)[$^]	57 [49.1]	33 [28.5]		42 (8–197)					(i) Serial serum MOG-IgG status			
Included	64	NA	NA	11 [17.2]	NA	24 (12-24)	Live	≥1:160	In-house CBA at IDIBAPS, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain			—	Low	Quantitative
Nakajima, et al., 2015 [80]														
Total	8	31 (16-65)[^]	6 [75.0]	3 [37.5]	ON (8)	26.5 (3-53)								
Included	7	25 (15-55)[k^]	5 [71.4]	3 [42.9]	ON (7)	30 (15-53)	Fixed	≥1:10	In-house CBA at Nagasaki University Hospital, Nagasaki, Japan	Nagasaki University Hospital, Nagasaki, Japan	(i) CSF WCC (ii) CSF protein (iii) CSF OCB	—	Low	Quantitative

Mao, et al., 2019 [81] *Total*	25	6.6 (3–12.4)	13 [52.0]	10 [40.0]	ADEM (9), ON (1), bON (5), Brain (4), TM (1), LETM (1), CIS (1), ADEM+ON (1), ADEM+uON (1), ADEM+TM (1)	15 (7–63)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB		
Included	20	6 (3-12)	10 [50.0]	10 [50.0]	ADEM (8), ON (1), bON (3), Brain (2), TM (1), LETM (1), CIS (1), ADEM+ON (1), ADEM+uON (1), ADEM+TM (1)	15.5 (12-63)	Fixed	NA	Commercially available Euroimmun, Lubeck, Germany	Xiangya Hospital, Central South University, Changsha, China			Medium	Quantitative
Siritho, et al., 2016 [82] *Total*	6	33 (18-57)	5 [83.3]	5 [83.3]	bON (2), uON (2), bON+TM (1), uON+Brain+LETM (1)	NA								
Included	4	33.5 (19-57)	3 [75.0]	4 [100.0]	bON (1), uON (1), bON+TM (1), uON+Brain+LETM (1)	18 (13-34)	NA	NA	Referred CBA to Tohoku University, Japan	MS and Related Disorders Clinic, Siriraj Hospital, Mahidol University, Bangkok, Thailand	(i) Serum MOG-IgG titre (ii) CSF OCB	—	Medium	Quantitative
Zhang, et al., 2021 [83] *Total*	34	6 (1-14)	16 [47.1]	8 [23.5]	ADEM (18), ON (7), NMOSD (4), LETM (2), CIS (1), Brain (2)	34.5 (14–63)								
Included	31	(i) Monophasic: median 5.8 (1.6–13.6) (ii) Relapsing: 6.7 (2.9–14.2)	NA	6 [19.4]	NA	(i) Monophasic: 33 (14–57) (ii) Relapsing: 42.5 (16–63)	Fixed	≥1:10	Commercially available Euroimmun, Lubeck, Germany	Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China	(i) CSF WCC (ii) CSF protein	(i) CSF WCC (ii) CSF protein	Low	Quantitative
Jitprapaikulsan, et al., 2018 [84] *Total*	31	32 (7-66)	15 [48.4]	31 [100.0]	ON (27), ON+other CNS demyelination (3)	(i) 44.6 (19.7-64.8)[$] (ii) 75.4 (41.3-183.1)[$l]					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status	(i) Serum MOG-IgG titre		
Included	11	NA	NA	11 [100.0]	ON (11)	27 (12-237)	Live	≥1:20	In-house CBA at Mayo Clinic, USA	Mayo Clinic, USA			Low	Quantitative
Huda, et al., 2021 [6] *Total*	76	27 (19–45)[$]	41 [54.0]	42 [55.3]	Onset attack phenotype by site: ADEM (5), ON (46), bON (27), TM (32), LETM (21), ON+TM (14), Brain (19)	49 (28–113)[$]								
Included	75	NA	NA	41 [54.7]	NA	51 (12-400)	Live	NA	Referred CBA to University of Oxford, UK	The Walton Centre NHS Foundation Trust, Liverpool, UK	(i) Serial serum MOG-IgG status (ii) CSF OCB	—	Low	Quantitative
Dauby, et al., 2021 [85] *Total*	8	27.7 (9.8–39.5)	4 [50.0]	5 [62.5]	ON (7), ON+TM (1)	90 (16.8-394.8)[m]	Live	NA	Referred CBA to University of Oxford, UK	University Hospital of Liège, Liège, Belgium	(i) CSF OCB	—	Low	Quantitative

Included	8	27.7 (9.8–39.5)	4 [50.0]	5 [62.5]	ON (7), ON+TM (1)	90 (16.8-394.8)[m]								
Solmaz, et al., 2023 [86] *Total*	10	7.5 (2–16.5)	8 [80.0]	10 [100.0]	Onset attack: bON (1), TM (6), ADEM (3)	78 (30–216)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB			
Included	10	7.5 (2–16.5)	8 [80.0]	10 [100.0]	Onset attack: bON (1), TM (6), ADEM (3)	78 (30–216)	Live and fixed	NA	NA	Etlik City Hospital, Ankara, Turkey		(i) Serum MOG-IgG titre	Low	Quantitative
Seok, et al., 2023 [41] *Total*	55	39.7 ± 17.2*	29 [52.7]	37/47 [78.7]	Onset attack: ON (38), TM (5), Brainstem (7), Brain or ADEM (4), Poly-regional (1)	NA			In-house CBA at Soonchunhyang University Hospital Cheonan, Cheonan, Republic of Korea					
Included	47	NA	NA	37 [78.7]	NA	≥12	Live	≥1		Soonchunhyang University Hospital Cheonan, Cheonan, Republic of Korea	(i) Serum MOG-IgG epitope	—	Low	Qualitative
Martin, et al., 2024 [87] *Total*	58	24.3 (1.2–77.3)	26 [44.8]	36 [62.1]	Onset attack: ON (35), TM (4), ADEM (10), Brain (3), NMOSD (1), Brainstem/Cerebellar (1), Other (4)	(i) 32.8 (31.0-38.5)[$] (ii) 50.8 (17.5-206.4)[$] (iii) 29.3 (22.6–44.3)[$] (iv) 47.0 (29.8–90.1)[$]						(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB		
Included	104 serum and 56 CSF samples; unclear participants	NA	NA	NA	NA	NA	NA	NA	NA	Oregon Health & Science University, Portland, OR, USA	—		Low	Quantitative
Liao, et al., 2024 [88] *Total*	12	8.5 (2-12)	8 [72.7]	9 [75.0]	Brain+uON (1), Brain (8), Brain+bON (2), Brain+bON+uON (1)	NA					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF OCB			
Included	6	9 (7-12)	5 [83.3]	6 [100.0]	Brain+uON (1), Brain (3), Brain+bON (2)	32 (range 25.5-68.9)	Fixed	NA	Commercially available Euroimmun, Lubeck, Germany	Xiangya Hospital of Central South University, Changsha, China		(i) Serum MOG-IgG titre (ii) CSF OCB	Medium	Quantitative
Nosadini, et al., 2023 [89]	75	7 (1.8–18.6)	40 [53.3]	26/65 [40.0]	ADEM (30), ON ± CNS lesions (27), CNS demyelination (6), ADEM+ON	30 (1–130)	Live and fixed	NA	NA	University Hospital of Padova, Italy	(i) CSF WCC	(i) CSF WCC	Medium	Quantitative

Total					(4), NMOSD (3), CIS (2), Brain (2), LETM (1)						(ii) CSF protein (iii) CSF OCB	(ii) CSF protein (iii) CSF OCB		
Included	51	NA	NA	18 [35.3]	NA	≥12								
Kang, et al., 2023 [90]					ADEM (24), NMOSD (4), Autoimmune Encephalitis Overlap Syndrome (8), ON (5), Cranial neuritis (2), Brain (2), Meningitis (2), Demyelinating pseudotumor (1)				Referred CBA to Guangzhou Medical Laboratory Center and Kindstar Medical Laboratory, China					
Total	48	6.57 ± 3.02*	30 [62.5]	11 [22.9]		≥12								
Included	48	6.57 ± 3.02*	30 [62.5]	11 [22.9]	ADEM (24), NMOSD (4), Autoimmune Encephalitis Overlap Syndrome (8), ON (5), Cranial neuritis (2), Brain (2), Meningitis (2), Demyelinating pseudotumor (1)	≥12	NA	≥1:10		Hunan Children's Hospital, Changsha, China	(i) Serum MOG-IgG titre (ii) CSF WCC	—	Low	Quantitative
Yao, et al., 2022 [91]														
Total	11	27 (16–32)	4 [36.4]	2 [18.2]	Brain (11)	10 (3-23)			Commercially available Euroimmun, Lubeck, Germany	Xiangya Hospital, Central South University, Changsha, China	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein	—	Medium	Quantitative
Included	4	24.5 (18-31)	1 [25.0]	1 [25.0]	Brain (4)	21 (12-23)	Fixed	≥1:10						
Bauer, et al., 2022 [92]									In-house CBA at Medical University of Innsbruck, Innsbruck, Austria	Medical University of Innsbruck, Innsbruck, Austria	(i) Serum cytokines and chemokines	(i) Serum cytokines and chemokines	Low	Qualitative
Total	40	23.7 (3.3-72.0)^	22 [55.0]	16/32 [50.0]	NA	12 (6-38)								
Included	40	23.7 (3.3-72.0)^	22 [55.0]	16/32 [50.0]	NA	12 (6-38)	Live	≥1:160						
Rechtman, et al., 2024 [93]														
Total	26	29.91 ± 15.62*	18 [69.2]	NA	NA	NA								
Included	26	29.91 ± 15.62*	18 [69.2]	NA	NA	NA	NA	NA	NA	Hadassah-Hebrew University Medical Center, Ein–Kerem, Hebrew University of Jerusalem. Jerusalem, Israel	(i) Serum thyroid function profile	—	Low	Qualitative
Nguyen, et al., 2024 [94]														
Total	43	(i) 10.7 (5.8-13.2)[$] (ii) 5.0 (4.3-12.2)[$o]	20 [46.5]	10 [23.3]	ADEM (14), ON (22), TM (3), Other (4)	(i) 13.7 (5.1-30.4)[$] (ii) 52.1 (28.5-105.2)[$o]								
Included	5	4 (3-6)	2 [40.0]	2 [40.0]	ADEM (5)	86 (21-151)	Live and fixed	NA	NA	University of Texas Southwestern Medical Center, Dallas	(i) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein	Medium	Quantitative
ZhangBao, et al., 2023 [95]														
Total	186	25 (2–65)	100 [53.8]	112 [60.2]	Onset attack: ON (94), TM (29), Brain (20), ADEM (19), Brainstem (5), Other brain syndrome (3), Mixed (16)	51 (9–326)	Fixed	NA	NA	Shanghai Medical College, Fudan	(i) Serial serum MOG-IgG status	—	Medium	Quantitative

Included	44	NA	NA	38 [86.4]	NA	108.5 (60-326)				University, Shanghai, People's Republic of China				
Montalvo, et al., 2022 [96] *Total*	23	9 (2-47)	12 [52.2]	16 [69.6]	ADEM (2), Brain (3), ADEM+ON (3), ADEM+Brain (1), Brain+ON (2), Brain+TM (1), Brain+ON+TM (4), ADEM+Brain+ON (2), ADEM+ON+TM (3), ADEM+Brain+ON+TM (2)	NA			Referred CBA to Mayo Clinic, USA	Mayo Clinic, USA	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status	—	Medium	Quantitative
Included	2	13 (6-20)	1 [50.0]	2 [100.0]	ADEM+Brain (1), ADEM+Brain+ON (1)	156 (108-204)	Live	NA						
Aktas, et al., 2023 [34] *Total*	7	NA	NA	NA	NA	≥24				Heinrich Heine University Düsseldorf, Düsseldorf, Germany		(i) Serum GFAP (ii) Serum NfL (iii) Serum tau (iv) Serum UCHL1	Low	Qualitative and quantitative
Included	8 serum samples; unclear participants	NA	NA	NA	NA	≥24	NA	NA	NA		—			
Akaishi, et al., 2023 [97] *Total*	26	43 (34.5–56)[$!]	18 [69.2]	NA	NA	NA			In-house CBA at Tohoku University School of Medicine, Sendai, Japan	Tohoku University School of Medicine, Sendai, Japan		(i) Peripheral blood count index ratios	Low	Qualitative
Included	26	43 (34.5–56)[$!]	18 [69.2]	NA	NA	NA	Live	NA			—			
Wang, et al., 2022 [98] *Total*	4	21 (20–51)	1 [25.0]	2 [50.0]	Brain (3), Brainstem (1)	14 (6-72)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB			
Included	3	20 (20-22)	0 [0.0]	2 [66.7]	Brain (3)	16 (12-72)	NA	NA	NA	Affiliated Hospital Xingtai People's Hospital, Hebei Medical University, Xingtai, China		(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB	Medium	Quantitative
Wendel, et al., 2022 [99] *Total*	116	7 (4–12)[$]	57 [49.1]	44 [37.9]	Onset attack: ADEM (59), uON (21), bON (16), TM (6), NMOSD (8), Brain (6)	43 (27-69)[$] ; all ≥24					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF OCB			
Included	107 participants for CSF analysis and 70 participants for serum analysis;	NA	NA	44 [40.4]	NA	≥24	Live	≥1:160	In-house CBA at Medical University of Innsbruck, Innsbruck, Austria	Olga Hospital, Klinikum Stuttgart, Germany		(i) Serum MOG-IgG titre	Low	Quantitative

	unclear overlap													
Guzman, et al., 2023 [100]					Onset attack: ON (12), TM (8), ADEM (5), Brain (4), ON+TM (3), Brainstem (1), Area Postrema Syndrome (1)				Commercially available Euroimmun, Lubeck, Germany	Pontifical Catholic University of Chile, Santiago, Chile	(i) Serial serum MOG-IgG status (ii) CSF WCC			
Total	35	30 (1–64)	25 [71.4]	12 [34.3]		24 (12–348)[p]						(i) CSF WCC	Medium	Quantitative
Included	3	NA	NA	2 [66.7]	NA	30 (12-36)	Fixed	≥1:10						
Gastaldi, et al., 2022 [10]					uON (20), bON (18), TM (7), LETM (4), ADEM (28), NMOSD (16), Other (9)									
Total	102	17 (6-33)[$]	59 [57.8]	44 [43.1]		29 (3-320)								
Included	162 samples for MOG-IgG titre analysis and 80 participants for serial MOG-IgG status analysis; unclear overlap	NA	NA	36 [45.0]	NA	30.5 (14-320)	Live	≥1:160	In-house CBA at IRCCS Mondino Foundation, Pavia, Lombardia, Italy following protocol from Medical University of Innsbruck, Innsbruck, Austria	IRCCS Mondino Foundation, Pavia, Lombardia, Italy	(i) Serial serum MOG-IgG status	(i) Serum MOG-IgG titre	Medium	Quantitative
Wu, et al., 2023 [101]											(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB		
Total	9	29 (15–57)	4 [44.4]	2 [22.2]	Brain (9)	9 (2-36)			Referred CBA to Omeng Weiyi Medical Laboratory, Hangzhou, China	The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China				
Included	4	23.5 (15-29)	1 [25.0]	1 [25.0]	Brain (4)	25 (13-36)	NA	≥1:10					Medium	Quantitative
Liu, et al., 2024 [102]														
Total	15	29.20 ± 11.87*	3 [20.0]	NA	NA	NA			Commercially available Euroimmun, Lubeck, Germany	Fujian Medical University, Fujian, China	—	(i) Serum prolactin	Low	Qualitative
Included	15	29.20 ± 11.87*	3 [20.0]	NA	NA	NA	Fixed	≥1:10						
Zhou, et al., 2022 [103]														
Total	19	6 ± 3*^	9 [47.4]	NA	ON (2), ADEM (15), Other (2)	NA				Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China	—	(i) Serum sTREM2	Low	Qualitative
Included	19	6 ± 3*^	9 [47.4]	NA	ON (2), ADEM (15), Other (2)	NA	NA	NA	NA					

Zhou, et al., 2022 [104] *Total*	30	7.05 (2.50–12.75)	17 [56.7]	30 [100.0]	NMOSD (10), MDEM (3), ADEM+ON (2), RON (2), Unclassified (13)	45 (19.9-105.9)								
Included	30	7.05 (2.50–12.75)	17 [56.7]	30 [100.0]	NMOSD (10), MDEM (3), ADEM+ON (2), RON (2), Unclassified (13)	45 (19.9-105.9)	Fixed	≥1:10	Commercially available Euroimmun, Lubeck, Germany	Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China	(i) Serum MOG-IgG titre	—	Low	Quantitative
Yang, et al., 2024 [105] *Total*	6	31.5 (29–40)^	1 [16.7]	2 [33.3]	Brain (6)	37.5 (6-62)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB			
Included	2	32 (30-34)^	1 [50.0]	0 [0]	Brain (2)	47 (39-55)	NA	NA	NA	Tianjin Huanhu Hospital, Tianjin, People's Republic of China		(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB	Medium	Quantitative
Wang, et al., 2023 [106] *Total*	2	1.75 (0.5-3)	0 [0]	2 [100.0]	Brain (2)	42 (36-48)					i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB			
Included	2	1.75 (0.5-3)	0 [0]	2 [100.0]	Brain (2)	42 (36-48)	Live	NA	NA	Hebei Children's Hospital, Shijiazhuang, China		(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB	Low	Quantitative
Roy, et al., 2023 [107] *Total*	10	9 (1-58)	6 [60.0]	7 [70.0]	ON (3), ADEM (3), ADEM+ON (3), ON+TM (1)	33 (16-98)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status			
Included	10	9 (1-58)	6 [60.0]	7 [70.0]	ON (3), ADEM (3), ADEM+ON (3), ON+TM (1)	33 (16-98)	Live	≥1:20	Referred CBA at Mayo Clinic, USA	Johns Hopkins University, Baltimore, MD, USA		(i) Serum MOG-IgG titre	Low	Quantitative
Lee, et al., 2023 [108] *Total*	40	32 (22.5–44.5)[$]	11 [27.5]	16 [40.0]	ADEM (12), Brain (21), ADEM+Brain (5), ADEM+ON (2)	29.5 (18.5–36.5)[$]; all ≥12								
Included	40	32 (22.5–44.5)[$]	11 [27.5]	16 [40.0]	ADEM (12), Brain (21), ADEM+Brain (5), ADEM+ON (2)	29.5 (18.5–36.5)[$]; all ≥12	Live	MFI ≥2.60	In-house CBA at Seoul National University Hospital, Seoul National University College of Medicine,	Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC	—	Low	Quantitative

									Seoul, South Korea		(iv) CSF protein (v) CSF OCB			
Xu, et al., 2023 [109]											(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF OCB			
Total	35	30 (15–73)	22 [62.9]	14 [40.0]	Brainstem involvement (35)	38 (4–64)								
Included	22	NA	NA	13 [59.1]	Brainstem involvement (22)	34 (13-58)	Live	≥1:10	In-house CBA at Xuanwu Hospital Neuroimmunology Laboratory	Xuanwu Hospital, Capital Medical University, Beijing, China		(i) Serum MOG-IgG titre (ii) CSF OCB	Low	Quantitative
Lin, et al., 2023 [110]														
Total	31	31.94 ± 18.03*	13 [41.9]	14 [45.2]	Overall phenotype not available; clinical symptoms at onset: ON (9), TM (9)	≥12								
Included	31	31.94 ± 18.03*	13 [41.9]	14 [45.2]	Overall phenotype not available; clinical symptoms at onset: ON (9), TM (9)	≥12	Fixed	≥1:10	Commercially available Euroimmun, Lubeck, Germany	Affiliated Nanjing Brain Hospital, Nanjing Medical University, Nanjing, Jiangsu, China	(i) Peripheral blood count index ratios	—	Low	Qualitative
Horellou, et al., 2023 [111]														
Total	15	(i) Monophasic: 6.8 ± 3.8* (ii) Relapsing: 5.8 ± 3.5*	9 [60.0]	8 [53.3]	Overall phenotype not available; onset phenotype: ON (2), ADEM (5), Brain (4), NMOSD (4)	(i) Monophasic: 4.5 ± 2.7*& (ii) Relapsing: 8.6 ± 4.8*&								
Included	15	(i) Monophasic: 6.8 ± 3.8* (ii) Relapsing: 5.8 ± 3.5*	9 [60.0]	8 [53.3]	Overall phenotype not available; onset phenotype: ON (2), ADEM (5), Brain (4), NMOSD (4)	(i) Monophasic: 4.5 ± 2.7* (ii) Relapsing: 8.6 ± 4.8*	Live	≥1:160	In-house CBA at Center for Immunology of Viral, Auto-Immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), Université Paris- Saclay, CEA, INSERM, Le Kremlin Bicêtre, France	Center for Immunology of Viral, Auto-Immune, Hematological and Bacterial diseases (IMVA-HB/IDMIT), Université Paris- Saclay, CEA, INSERM, Le Kremlin Bicêtre, France	—	(i) Serum NfL	Low	Qualitative and quantitative
Hacohen, et al., 2014 [112]											(i) Serial serum MOG-IgG status (ii) CSF WCC (iii) CSF OCB			
Total	7	12 (3-15)	5 [71.4]	2 [28.6]	ADEM (2), ON (2), TM (1), MS (2)	12								
Included	4	6 (3-12)	2 [50.0]	0 [0]	ADEM (2), ON (2)	12	Live	≥1:20	In-house CBA at University of Oxford, UK	John Radcliffe Hospital, Oxford University Hospital, Oxford, UK		—	Low	Quantitative
Salunkhe, et al., 2023 [113]														
Total	64	(i) Encephalitis group: 14.5 (11.75–18)^ (ii) Non-encephaliti	33 [51.6]	36 [56.3]	Encephalitis group: Brain (4), Brain+Brainstem/Cerebellar (2), Brain+ON (4), Brain+TM (3), Brain+ON+TM (3) Non-encephalitis group: NA	NA	Fixed	NA	NA	All India Institute of Medical Sciences, New Delhi, India	(i) CSF WCC (ii) CSF protein	—	Medium	Quantitative

		s group: 28 (19.75–42)^												
Included	3	13 (11-15)	1 [33.3]	2 [66.7]	Brain+ON (1), Brain+ON+TM (2)	36 (12-36)								
Huang, et al., 2024 [114] *Total*	110	(i) Paediatric onset: 6 (3-13) (ii) Adult onset: 26.5 (14-49) (iii) Late onset: 58 (50-78)	59 [53.6]	44 [40.0]	MS (12), NMOSD (24), ADEM (17), ON (28), TM (6), IIDDs (23)	≥12								
Included	(i) Homocysteine level: 20 (ii) MOG-IgG titre: 131 samples; unclear participants	NA	NA	NA	NA	≥12	Fixed	≥1:10	NA	The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China	(i) Serum homocysteine	(i) Serum MOG-IgG titre	Low	Qualitative and quantitative
Samadzadeh, et al., 2023 [115] *Total*	22	48.6 (33.3-56.5)[$!]	8 [36.3]	NA	Overall phenotype not available; Most recent attack phenotype prior to sampling: ON (7), TM (3), Brain (4), Unknown (8)	NA			In-house CBA at University of Southern Denmark, Odense, Denmark	University of Southern Denmark, Odense, Denmark				
Included	22	48.6 (33.3-56.5)[$!]	8 [36.3]	NA	Overall phenotype not available; Most recent attack phenotype prior to sampling: ON (7), TM (3), Brain (4), Unknown (8)	NA	Live	NA			—	(i) CSF MFAP4	Low	Qualitative
Liyanage, et al., 2024 [39] *Total*	202	39.89 (30.85–51.24)[$]	121 [59.9]	137 [67.8]	uON (62), bON (31), ON NOS (2), uON+bON (24), ON+TM (23), TM (25), Brain (9), Mixed (26)	48 (26.4-86.4)[$]; all ≥12			In-house CBA at Kids Neuroscience Centre, Kids Research at the Children's Hospital at Westmead, Australia	Kids Neuroscience Centre, Kids Research at the Children's Hospital at Westmead, Australia				
Included	202	39.89 (30.85–51.24)[$]	121 [59.9]	137 [67.8]	uON (62), bON (31), ON NOS (2), uON+bON (24), ON+TM (23), TM (25), Brain (9), Mixed (26)	48 (26.4-86.4)[$]; all ≥12	Live	MFI > mean + 3 SD of control			(i) Serum MOG epitope recognition pattern	—	Low	Qualitative
Wang, et al., 2023 [116] *Total*	11	20^[q]	6 [54.6]	NA	ON (1), TM (6), ON+TM (2), Brainstem (2)	NA			Commercially available Euroimmun, Lubeck, Germany	The Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai, China				
Included	11	20^[q]	6 [54.6]	NA	ON (1), TM (6), ON+TM (2), Brainstem (2)	NA	Fixed	NA			—	(i) Serum cytokines	Low	Qualitative
Yandamuri, et al., 2023 [117]	25	Number in Age Range: 0-9	17 [68.0]	NA	NA	NA	Live	NA	In-house CBA at Yale School of Medicine,	Yale School of Medicine, New Haven,	—	(i) Serum MOG-IgG	Low	Qualitative

Total		(1), 10-19 (2), 20-29 (5), 30-39 (5), 40-49 (3), 50-59 (8), Unknown (1)^							New Haven, Connecticut, USA	Connecticut, USA		effector functions (CDC and ADCP)		
Included	25	Number in Age Range: 0-9 (1), 10-19 (2), 20-29 (5), 30-39 (5), 40-49 (3), 50-59 (8), Unknown (1)^	17 [68.0]	NA	NA	NA								
Nguyen, et al., 2023 [118] *Total*	67	(i) 9.99 ± 4.15*[r] (ii) 6.06 ± 3.56*[r]	36 [53.7]	NA	Overall phenotype not available; onset phenotype: ADEM (23), ON (27), TM (5), Other (12)	(i) 45.09 ± 41.05*[r] (ii) 73.12 ± 55.55*[r]					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status			
Included	10	7 (3-14)^	8 [80.0]	5 [50.0]	ADEM (3), ON (1), ADEM+Brain (1), ADEM+Brainstem/Cerebellar (2), ADEM+ON (1), Brainstem/Cerebellar+ON (1), ON+Other (1)	57 (16-192)	Live	NA	Referred CBA at Mayo Clinic, USA and University of Oxford, Oxford, UK	University of Texas Southwestern Medical Center, Dallas, TX, USA		(i) Serum MOG-IgG titre	Low	Quantitative
Wendel, et al., 2022 [119] *Total*	19	5 (4-7)[$]	6 [31.6]	0 [0]	ADEM (14), ON (3), LETM (1), NMOSD (1)	24 (24-36)[$]			Referred CBA at Innsbruck Medical University, Innsbruck, Austria	Olgahospital, Klinikum Stuttgart, Stuttgart, Germany				Qualitative and quantitative
Included	19	5 (4-7)[$]	6 [31.6]	0 [0]	ADEM (14), ON (3), LETM (1), NMOSD (1)	24 (24-36)[$]	Live	≥1:160			—	(i) Serum NfL	Low	
Zhang, et al., 2022 [120] *Total*	12	8 (6–14.5)	3 [37.5]	4 [33.3]	Overall phenotype NA; onset phenotype: Brain/Brainstem (5), ON+TM (4), Brain/Brainstem+ON (3)	12				Jinan Central Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China				
Included	12	8 (6–14.5)	3 [37.5]	4 [33.3]	Overall phenotype NA; onset phenotype: Brain/Brainstem (5), ON+TM (4), Brain/Brainstem+ON (3)	12	Fixed	NA	NA		(i) CSF OCB	—	Low	Quantitative
Aubart, et al., 2022 [121] *Total*	3	4 (1-10)	1 [33.3]	0 [0]	ADEM (2), ADEM+ON (1)	12-18[e]					(i) Serial serum MOG-IgG status (ii) CSF WCC (iii) CSF protein (iv) CSF OCB	(i) CSF WCC (ii) CSF protein (iii) CSF OCB		
Included	3	4 (1-10)	1 [33.3]	0 [0]	ADEM (2), ADEM+ON (1)	12-18[e]	Fixed	NA	Commercially available Euroimmun, Lubeck, Germany	University of Paris Cite, Paris, France			Low	Quantitative

Tzanetakos, et al., 2022 [122] *Total*	11	37 (3-75)[!]	8 [72.7]	4 [36.4]	uON (3), bON (3), Brainstem (1), NMO (1), Brain+uON (1), ADEM (1), TM (1)	18 (1-49)			In-house CBA at Eginition Hospital, National and Kapodistrian University of Athens, Athens, Greece	Eginition Hospital, National and Kapodistrian University of Athens, Athens, Greece	(i) Serum MOG-IgG titre (ii) CSF OCB			
Included	7	56 (19-75)!	5 [71.4]	3 [42.9]	uON (3), bON (2), Brainstem (1), ADEM (1)	20 (13-49)	Live	≥1:20				—	Medium	Quantitative
Kim, et al., 2022 [123] *Total*	6	27.2 ± 18.2*^	5 [83.3]	3 [50.0]	ON (6)	25.2 (12-48)[%]			In-house CBA at Kyungpook National University, Daegu, Korea	Kyungpook National University, Daegu, Korea				
Included	6	27.2 ± 18.2*^	5 [83.3]	3 [50.0]	ON (6)	25.2 (12-48)[%]	Live	≥2.5			(i) Serum LCN2	—	Low	Qualitative
Nguyen, et al., 2024 [124] *Total*	87	8.3 (4.8-12.2)[$]	44 [50.6]	27/61 [44.3]	Overall phenotype NA; onset phenotype: ADEM (32), ON (33), TM (6), Other (16)	29.5 (8.7–55.0)[$] (85/87)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein (v) CSF OCB	(i) Serum MOG-IgG titre (ii) CSF WCC (iii) CSF protein (iv) CSF OCB		
Included	52	NA	NA	20 [38.5]	NA	NA	Live and unknown	≥1:20 (live)	Referred CBA at Mayo Clinic, USA, University of Oxford, Oxford, UK, and unknown	University of Texas Southwestern Medical Center, Dallas, TX, USA			Medium	Quantitative
Fadda, et al., 2022 [125] *Total*	12	9.04 (6.50-10.36)[$]	8 [66.7]	7 [58.3]	ON (4), TM (1), ON+TM (4), ADEM+TM (1), ADEM+ON+Other (1), Other (1)	77.5 (12-132)			In-house CBA at Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA	Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA				
Included	11	NA	NA	7 [63.6]	ON (3), TM (1), ON+TM (4), ADEM+TM (1), ADEM+ON+Other (1), Other (1)	81 (12-132)	Live	≥1			(i) Serial serum MOG-IgG status	(i) Serum MOG-IgG titre	Low	Quantitative
Vosoughi, et al., 2023 [126] *Total*	4	37 (18-45)	2 [50.0]	2 [50.0]	uON (3), uON+TM+LETM (1)	54 (12-108)				Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status			
Included	4	37 (18-45)	2 [50.0]	2 [50.0]	uON (3), uON+TM+LETM (1)	54 (12-108)	Live and fixed	NA	NA			(i) Serum MOG-IgG titre	Low	Quantitative
Jiang, et al., 2023 [127] *Total*	4	2.5 (2-5)	2 [50.0]	0 [0]	Brain (1), ADEM (3)	13.5 (11-47)				Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders,				
Included	4	2.5 (2-5)	2 [50.0]	0 [0]	Brain (1), ADEM (3)	13.5 (11-47)	NA	NA	NA		(i) CSF WCC (ii) CSF protein (iii) CSF OCB	(i) CSF WCC (ii) CSF protein (iii) CSF OCB	Medium	Quantitative

										Ministry of Education Key Laboratory of Child Development and Disorders, China				
Zeng, et al., 2023 [128] *Total*	15	29 (4-65)	7 [46.7]	6 [40.0]	ON (7), TM (1), Brain (2), Brainstem (1), Brain+Brainstem/Cerebellar (1), Brain+ON (1), Brain+Brainstem/Cerebellar+ON (1)	33 (24-64)								
Included	15	29 (4-65)	7 [46.7]	6 [40.0]	ON (7), TM (1), Brain (2), Brainstem (1), Brain+Brainstem/Cerebellar (1), Brain+ON (1), Brain+Brainstem/Cerebellar+ON (1)	33 (24-64)	Fixed	≥1:10	Referred CBA at Guangzhou Jinyu Medical Laboratory, Guangzhou, China	Liuzhou People's Hospital, Liuzhou, China	(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF WCC (iv) CSF protein	(i) Serum MOG-IgG titre	Medium	Quantitative
Baek, et al., 2023 [129] *Total*	39	37.4 ± 12*	20 [51.3]	NA	NA	NA				Sungkyunkwan University School of Medicine, Seoul, South Korea		(i) Peripheral blood count index ratios		
Included	39	37.4 ± 12*	20 [51.3]	NA	NA	NA	NA	NA	NA		—		Low	Qualitative
Singh, et al., 2022 [130] *Total*	2	10 (5-15)	2 [100]	2 [100]	uON+Brain (2)	126 (36-216)					(i) Serum MOG-IgG titre (ii) Serial serum MOG-IgG status (iii) CSF OCB			
Included	2	10 (5-15)	2 [100]	2 [100]	uON+Brain (2)	126 (36-216)	Live	NA	NA	Texas Tech University Health Sciences Center, El Paso, USA		(i) Serum MOG-IgG titre (ii) CSF OCB	Low	Quantitative
Wang, et al., 2023 [131] *Total*	25	27 (15-35)[$^]	10 [40.0]	8 [32.0]	Overall phenotype NA; regions affected at NOS time: Brain (18), Brainstem (6), ON (4), ADEM (3), Cerebellar (2)	12								
Included	25	27 (15-35)[$^]	10 [40.0]	8 [32.0]	Overall phenotype NA; regions affected at NOS time: Brain (18), Brainstem (6), ON (4), ADEM (3), Cerebellar (2)	12	Fixed	NA	Commercially available Euroimmun, Lubeck, Germany	Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China	(i) Peripheral blood count index ratios	—	Low	Qualitative
Song, et al., 2022 [132] *Total*	18	9.5 (3-13)^	12 [66.7]	3 [16.7]	Brain (13), Cerebellar (1), Brain+Brainstem (1), Brain+Cerebellar (2), Brain+Brainstem+Cerebellar (1)	17 (8-39)								
Included	17	9 (3-13)^	12 [70.6]	3 [17.7]	Brain (12), Cerebellar (1), Brain+Brainstem (1), Brain+Cerebellar (2), Brain+Brainstem+Cerebellar (1)	17 (13-39)	Fixed	NA	NA	Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders,	(i) Serial serum MOG-IgG status (ii) CSF WCC (iii) CSF protein	(i) CSF WCC (ii) CSF protein	Medium	Quantitative

										Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing Key Laboratory of Pediatrics, Chongqing, China				
Masuda, et al., 2023 [133] *Total*	18	45 (26.25-63.75)[$!]	12 [66.7]	NA	NA	NA				Graduate School of Medicine, Chiba University, Inohana, Chuo-Ku, Chiba-Shi, Japan	—	(i) Serum and CSF cytokines	Low	Qualitative
Included	18	45 (26.25-63.75)[$!]	12 [66.7]	NA	NA	NA	NA	NA	NA					

NA, not available. Phenotypes were directly reported as they appeared in the original manuscript
[$]Median (IQR)
[%]Mean (range)
*Mean ± SD
^Age not otherwise specified
[#]Original study reports phenotypes for n=13; discrepancy with total participants n=12
[@]Original study defines as "disease duration at last follow-up"
[!]Age at sampling
[~]Original study reported characteristic by following subgroups: (i) paediatric persistent MOG-IgG seropositivity, (ii) paediatric transient MOG-IgG seropositivity, (iii) adult persistent MOG-IgG seropositivity, and (iv) adult transient MOG-IgG seropositivity
[a]Phenotype partially available
[b]Original study reported characteristic by following subgroups: (i) persistent MOG-IgG seropositivity and (ii) transient MOG-IgG seropositivity
[c]Original study reported phenotypes for n=97; discrepancy with total participants n=84
[d]Original study reported characteristic by following subgroups: (i) attack and (ii) remission
[e]Range only
[f]All included participants had the same follow-up duration
[g]Original study reported characteristic by following subgroups: (i) MOG-IgG titre 1:160-1:640 and (ii) MOG-IgG titre ≥1:1280
[h]Age partially available
[i]Sex partially available
[j]Disease course partially available
[k]Only age decade specified, therefore, estimated as mid-decade
[l]Original study reported characteristic by following subgroups: (i) isolated recurrent ON (rON only) and (ii) recurrent ON with subsequent central nervous system demyelinating attack beyond the optic nerve (rON-plus)
[m]Follow-up duration for participants with MOGAD, AQP4-IgG positive NMOSD, and double seronegative NMOSD
[n]Original study reported characteristic by following subgroups: (i) paediatric monophasic, (ii) paediatric relapsing, (iii) adult monophasic, (iv) adult relapsing
[o]Original study reported characteristic by following subgroups: lumbar puncture opening pressure (i) ≤28cm H_2O and (ii) >28cm H_2O
[p]Unclear if median (IQR) or median (range) from original study
[q]Mean only; no SD reported
[r]Original study reported characteristic by following subgroups: (i) no subclinical disease activity on OCT and (ii) subclinical disease activity on OCT

Supplementary Table 5: Comparison of follow-up duration between included monophasic and relapsing participants as reported by 48 studies. Statistical significance assessed with Mann-Whitney U Test.

Source	Monophasic		Relapsing		Follow-up Data Format	P-value
	Participants (n)	Follow-up Duration, Median (range) (months)	Participants (n)	Follow-up Duration, Median (range) (months)		
Wendel, et al., 2020 [44]	6	31.5 (12-36)	3	36 (18-141)	IPD	0.590
Hyun, et al., 2017 [46]	4	39 (23-113)	15	65 (23-200)	IPD	0.368
Höftberger, et al., 2015 [47]	5	43 (18-127)	10	108 (17-415)	IPD	0.371
Horellou, et al., 2021 [48]	5	22.8 ± 26.4*	7	58.8 ± 26.4*	AD	0.106
Jarius, et al., 2020 [49]	42	21 (0-65)^	38	63 (1-229)^	AD	**<0.0001**
Ikeda,et al., 2019 [51]	1	19[&]	3	46 (18-87)	IPD	1
Jurynczyk, et al., 2017 [53]	27	20 (12-131)	29	50 (12-438)	IPD	**<0.0001**
Hino-Fukuyo, et al., 2019 [54]	2	140 (68-212)	3	150 (87-322)	IPD	0.800
Serin, et al., 2021 [55]	5	25 (24-34)	4	41 (28-196)	IPD	0.174
Oliveira, et al., 2019 [57]	8	49 (34-77)[$]	23	80 (38-105)[$]	AD	0.133
de Mol, et al., 2020 [12]	12	23 (12-88)	8	41 (24-246)	IPD	0.141
Rostasy, et al., 2012 [60]	2	37.5 (35-40)	11	31 (19-74)	IPD	0.923
Han, et al., 2022 [64]	5	19 (12-54)	1	17[&]	IPD	1
Alshamrani, et al., 2020 [68]	1	13[&]	4	126 (48-132)	IPD	0.277
Lui, et al., 2021 [69]	14	39 (15-150)	9	100 (18-300)	IPD	**0.034**
Hennes, et al., 2017 [8]	40	24[#]	25	24[#]	AD	—
Tea, et al., 2019 [71]	8	31.5 (17-77)	8	34 (18-99)	IPD	0.792
Senanayake, et al., 2019 [72]	4	12 (12-24)	13	84 (36-204)	AD	**0.010**
Wegener-Panzer, et al., 2020 [73]	2	18 (12-24)	4	45 (24-48)	IPD	0.153
Baumann, et al., 2015 [76]	10	27.5 (14-81)	4	41.5 (30-67)	IPD	0.357
Armangue, et al., 2020 [79]	53	24 (12-24)	11	24[#]	IPD	0.535
Nakajima, et al., 2015 [80]	4	27.5 (15-53)	3	30 (22-52)	IPD	1
Mao, et al., 2019 [81]	10	13.5 (12-20)	10	30.5 (12-63)	IPD	**0.013**
Zhang, et al., 2021 [83]	25	33 (14-57)	6	42.5 (16-63)	AD	0.339
Huda, et al., 2021 [6]	34	35 (12-82)	41	107 (12-400)	IPD	**<0.0001**
Nosadini, et al., 2023 [89]	33	29 (12-122)	18	51.5 (18-130)	AD	**0.032**
Yao, et al., 2022 [91]	3	17 (12-23)	1	20[&]	IPD	1
Nguyen, et al., 2024 [94]	3	52 (21-86)	2	132.5 (114-151)	IPD	0.200

ZhangBao, et al., 2023 [95]	6	61 (60-66)	38	120 (66-326)	IPD	**<0.001**
Wang, et al., 2022 [98]	1	16[&]	2	42 (12-72)	IPD	1
Wendel, et al., 2022 [99]	65	36 (24-60)[$]	44	60 (36-84)[$]	AD	**0.008**
Guzman, et al., 2023 [100]	1	12[&]	2	33 (30-36)	IPD	0.667
Gastaldi, et al., 2022 [10]	44	28.5 (14-142)	36	40 (14-320)	IPD	**0.003**
Wu, et al., 2023 [101]	3	24 (13-36)	1	26[&]	IPD	1
Roy, et al., 2023 [107]	3	34 (30-37)	7	32 (16-98)	IPD	1
Xu, et al., 2023 [109]	9	32 (13-48)	13	35 (13-58)	IPD	0.547
Horellou, et al., 2023 [111]	7	54 ± 32.4*	8	103.2 ± 57.6*	AD	0.152
Salunkhe, et al., 2023 [113]	1	36[&]	2	24 (12-36)	IPD	1
Liyanage, et al., 2024 [39]	65	33.5 (19.8-50.5)[$]	137	64 (28.4-115.2)[$]	AD	**0.003**
Nguyen, et al., 2023 [118]	5	48 (18-90)	5	66 (16-192)	IPD	1
Zhang, et al., 2022 [120]	8	12[#]	4	12[#]	AD	—
Tzanetakos, et al., 2022 [122]	4	22.5 (19-33)	3	18 (18-49)	IPD	0.629
Nguyen, et al., 2024 [124]	34	35.8 (26.4-49.5)[$]	27	71.9 (33.1-110.9)[$]	AD	**0.017**
Fadda, et al., 2022 [125]	4	76.5 (38-90)	7	84 (12-132)	IPD	0.649
Vosoughi, et al., 2023 [126]	2	60 (12-108 months)	2	54 (36-72)	IPD	1
Zeng, et al., 2023 [128]	9	36 (24-48)	6	31.5 (26-64)	IPD	0.814
Wang, et al., 2023 [131]	17	12[#]	8	12[#]	AD	—
Song, et al., 2022 [132]	14	17 (13-37)	3	35 (16-39)	IPD	0.229

*Mean ± SD
^Original study defined as “disease duration at last follow-up”
[&]Single participant follow-up duration
[$]Median (IQR)
[#]All included participants had the same follow-up duration
IPD=individual participant data, AD=aggregate data

Supplementary Table 6: Investigating the association of serial serum MOG-IgG measurement at various sample collection intervals and relapsing disease course								
Based on ≥2 serum MOG-IgG results ≥3 months apart								
Predictor of Relapsing Disease Course	Studies (n)	Total Participants (n)	Monophasic Participants (n)	Relapsing Participants (n)	OR (95% CI) of Relapsing Disease Course	Univariable Random-Effects Meta-Analysis P-value	I^2	Egger's Test P-value
Serial Serum MOG-IgG Status								
Transient seropositivity	48	777	178	72	2.70 (1.82–3.99)	<0.0001	0%	0.2829
Persistent seropositivity			245	282				
Based on ≥2 serum MOG-IgG results ≥6 months apart								
Predictor of Relapsing Disease Course	Studies (n)	Total Participants (n)	Monophasic Participants (n)	Relapsing Participants (n)	OR (95% CI) of Relapsing Disease Course	Univariable Random-Effects Meta-Analysis P-value	I^2	Egger's Test P-value
Serial Serum MOG-IgG Status								
Transient seropositivity	44	671	150	59	2.28 (1.51–3.43)	<0.0001	0%	0.2642
Persistent seropositivity			211	251				
Based on ≥2 serum MOG-IgG results ≥12 months apart								
Predictor of Relapsing Disease Course	Studies (n)	Total Participants (n)	Monophasic Participants (n)	Relapsing Participants (n)	OR (95% CI) of Relapsing Disease Course	Univariable Random-Effects Meta-Analysis P-value	I^2	Egger's Test P-value
Serial Serum MOG-IgG Status								
Transient seropositivity	41	567	147	43	2.82 (1.79–4.45)	<0.0001	0%	0.8388
Persistent seropositivity			169	208				

Supplementary Table 7: Investigating the multivariable association of serial serum MOG-IgG measurement at various sample collection intervals and relapsing disease course alongside participant-level demographics.

When persistent seropositivity is defined as ≥2 positive measurements ≥3 months apart

Predictor of Relapsing Disease Course*		Total Participants (n)	Monophasic Participants (n)	Relapsing Participants (n)	OR (95% CI) of Relapsing Disease Course	P value^
Serial MOG-IgG status						
	Transient seropositivity	32	23	9	1.00 (reference)	
	Persistent seropositivity	96	18	78	14.56 (2.17-97.89)	**0.0059**
Sex						
	Male	59	25	34	1.00 (reference)	
	Female	69	16	53	1.07 (0.27-4.23)	0.9255
Age						
	Paediatric (<18)	77	27	50	1.00 (reference)	
	Adult (≥18)	51	14	37	1.51 (0.17-13.54)	0.7123
Phenotype						
	Brain/Brainstem	23	7	16	1.00 (reference)	—
	ADEM	26	18	8	0.05 (0.003-0.84)	**0.0373**
	ON	20	8	12	0.99 (0.07-13.66)	0.9957
	TM	5	3	2	0.20 (0.01-6.43)	0.3595
	ADEM+ON	16	1	15	5.58 (0.15-205.13)	0.3497
	ON+TM	10	2	8	6.67 (0.12-360.21)	0.3512
	Mixed	28	2	26	10.87 (0.61-193.27)	0.1042

^Analysis was with a one-stage IPD meta-analysis with multivariable logistic mixed-effects regression. There was substantial heterogeneity (I^2=76.93%).
*Minimum subgroup sample size criterion (n ≥5); phenotype 'Other' was excluded due to insufficient participant numbers (n=3)

When persistent seropositivity is defined as ≥2 positive measurements ≥6 months apart

Predictor of Relapsing Disease Course*		Total Participants (n)	Monophasic Participants (n)	Relapsing Participants (n)	OR (95% CI) of Relapsing Disease Course	P value^
Serial MOG-IgG status						
	Transient seropositivity	24	16	8	1.00 (reference)	0.1428
	Persistent seropositivity	86	17	69	5.09 (0.58–44.86)	
Sex						
	Male	50	20	30	1.00 (reference)	0.5194
	Female	60	13	47	1.65 (0.36–7.60)	
Age						
	Paediatric (<18)	64	20	44	1.00 (reference)	0.7347
	Adult (≥18)	46	13	33	1.61 (0.10–24.81)	
Phenotype						
	Brain/Brainstem	22	7	15	1.00 (reference)	—
	ADEM	19	12	7	0.06 (0.002–2.10)	0.1220
	ON	16	6	10	1.89 (0.08–46.60)	0.6960
	TM	5	3	2	0.24 (0.01–12.12)	0.4746
	ADEM+ON	16	1	15	10.45 (0.15–726.97)	0.2783
	ON+TM	10	2	8	8.36 (0.13–543.20)	0.3189
	Mixed	22	2	20	8.64 (0.38–197.78)	0.1770

^Analysis was with a one-stage IPD meta-analysis with multivariable logistic mixed-effects regression. There was substantial heterogeneity (I^2=94.1%).
*Minimum subgroup sample size criterion (n ≥5); phenotype 'Other' was excluded due to insufficient participant numbers (n=2)

When persistent seropositivity is defined as ≥2 positive measurements ≥12 months apart

Predictor of Relapsing Disease Course*		Total Participants (n)	Monophasic Participants (n)	Relapsing Participants (n)	OR (95% CI) of Relapsing Disease Course	P value^
Serial MOG-IgG status						
	Transient seropositivity	21	13	8	1.00 (reference)	
	Persistent seropositivity	75	15	60	5.79 (0.70–47.78)	0.1030
Sex						
	Male	46	18	28	1.00 (reference)	
	Female	50	10	40	1.26 (0.26–6.13)	0.7766
Age						
	Paediatric (<18)	53	16	37	1.00 (reference)	
	Adult (≥18)	43	12	31	1.09 (0.09–13.45)	0.9459
Phenotype						
	Brain/Brainstem	16	4	12	1.00 (reference)	—
	ADEM	16	11	5	0.04 (0.002–1.00)	0.0503
	ON	14	2	18	1.70 (0.08–37.57)	0.7357
	TM	5	5	9	0.20 (0.01–7.72)	0.3875
	ADEM+ON	15	1	14	3.39 (0.08–146.58)	0.5250
	ON+TM	10	2	8	5.28 (0.10–279.55)	0.4111
	Mixed	20	3	2	4.32 (0.22–85.67)	0.3373

^Analysis was with a one-stage IPD meta-analysis with multivariable logistic mixed-effects regression. There was substantial heterogeneity (I^2=82.9%).
*Minimum subgroup sample size criterion (n ≥5); phenotype ‘Other’ was excluded due to insufficient participant numbers (n=2)

Supplementary Table 8: Random-effects meta-analysis of means to investigate serum GFAP and NfL biomarker levels during different disease activity

Predictor	Study	Age Category	Remission				Attack			
			Samples (n)	Mean	SD (±)	Overall mean (95% CI)	Samples (n)	Mean	SD (±)	Overall mean (95% CI)
GFAP	Kim, et al., 2020 [19]	Adult	9	75.33 pg/mL	20.17 pg/mL	97.78 (75.60–119.97) pg/mL	7^	89.71 pg/mL	21.65 pg/mL	176.75 (64.99–288.51) pg/mL
	Chang, et al., 2021 [20]	Combined	19	158.42 pg/mL	232.22 pg/mL		23^	309.65 pg/mL	367.19 pg/mL	
	Hyun, et al., 2021 [21]	Adult	54	107.07 pg/mL	47.14 pg/mL		17	185.88 pg/mL	81.25 pg/mL	
	Aktas, et al., 2023 [34]	Adult	8	107.14 pg/mL	42.71 pg/mL		—	—	—	
NfL	Kim, et al., 2020 [19]	Adult	9	11.11 pg/mL	4.99 pg/mL	17.25 (10.12–24.37) pg/mL	7^	18.72 pg/mL	23.11 pg/mL	71.45 (40.44–103.46) pg/mL
	Chang, et al., 2021 [20]	Combined	19	44.16 pg/mL	78.08 pg/mL		23^	68.26 pg/mL	84.83 pg/mL	
	Hyun, et al., 2021 [21]	Adult	55	22.31 pg/mL	35.49 pg/mL		17	164.76 pg/mL	154.12 pg/mL	
	Luo, et al., 2021[22]	Combined	47	13.00 pg/mL	11.71 pg/mL		22	59.55 pg/mL	60.58 pg/mL	
	Aktas, et al., 2023 [34]	Adult	8	30.29 pg/mL	27.91 pg/mL		—	—	—	
	Horellou, et al., 2023 [111]	Paediatric	—	—	—		15^	89.72 pg/mL	22.38 pg/mL	
	Wendel, et al., 2022 [119]	Paediatric	—	—	—		19^	73.68 pg/mL	87.77 pg/mL	

Supplementary Table 9: Qualitative assessment of studies reporting novel biomarkers.					
Biomarker	**Sample Size (n)**	**Study**	**Specimen**	**Key Findings**	**Classification of Evidence***
Properties of serum MOG-IgG					
MOG epitope binding pattern	55	[41]	Serum	• 0% (0/10) of individuals with non-P42 MOG-IgG had a monophasic course compared to 18.3% (2/11) with P42 MOG-IgG (p=0.476) • P42 MOG-IgG was associated with fewer total attacks during follow-up (median 2.0, IQR 1.8-3.5) compared to non-P42 MOG-IgG (median 2.5, IQR 2.0-5.0) (p=0.722)	Class III
	202	[39]	Serum	• Non-P42 MOG-IgG conferred significantly increased risk for relapsing course compared to P42 MOG-IgG (HR 1.7, 95% CI 1.15–2.60) (p=0.009) • Among individuals with uON at onset, non-P42 MOG-IgG conferred significantly increased risk of relapsing course compared to P42 MOG-IgG (HR 2.7, 95% CI 1.06–6.98) (p=0.038) • Epitope binding pattern was highly stable over time	Class II
Immune cells					
Complement-dependent cytotoxicity (CDC) and antibody-dependent cellular phagocytosis (ADCP)	56 total; 25 MOGAD	[117]	Serum	• High-throughput assays assessed effector functions (complement activation (CA), CDC, ADCP, and antibody-dependent cellular cytotoxicity (ADCC)) of MOG-IgG from sera of individuals with MOGAD • Engagement of effector functions was bimodal; 67% (12.18) of serum samples induced CDC while 33% (6/18) did not • Magnitude of CDC and ADCP was significantly elevated closer to relapse (p=0.058 and p=0.011, respectively) • CDC and ADCP assays have potential to predict disease activity as well as individual response to complement inhibitor therapies	Class III
PBMCs	29 total; 12 MOGAD	[48]	Serum	• PBMCs collected at onset were stimulated with rh-MOG • Th17-cells increased significantly in individuals with a monophasic course but not	Class III

				a relapsing course (p = 0.03 and p=0.25, respectively) • CD4+Foxp3+ Tregs increased significantly in individuals with a monophasic course but not a relapsing course (p = 0.046 and p=0.375, respectively) • CD45RA-Foxp3+ Tregs decreased significantly in individuals with a relapsing course but not with a monophasic course (p = 0.021; p-value for monophasic group not stated)	
	96 total; 26 MOGAD	[59]	Serum	• Th17-cells were significantly increased in MOGAD, AQP4-IgG seropositive NMOSD, and MS compared to HCs at attack (p=0.001, p<0.001, and p=0.005, respectively) and remission (p=0.033, p=0.005, and p=0.004, respectively) • Th17/Treg ratios were significantly increased in MOGAD, AQP4-IgG seropositive NMOSD, and MS compared to HCs at attack (p=0.004, p<0.001, and p=0.006, respectively) and remission (p=0.019, p<0.001, and p=0.005, respectively) • Th17-cells were significantly increased in MOGAD, AQP4-IgG seropositive NMOSD, and MS at attack compared to remission (paired sample comparison) (p=0.015, p=0.012, and p=0.018, respectively)	Class II
	41 total; 17 MOGAD	[63]	Serum	• Plasmablasts were significantly lower at attack in MOGAD compared to AQP4-IgG seropositive NMOSD (p < 0.05) • Transitional B-cells were significantly elevated at remission in MOGAD compared to HCs and AQP4-IgG seropositive NMOSD (all p<0.01) • MOGAD attack and remission B- and T-cell subsets were not explicitly compared	Class II
Peripheral blood count index ratios, including:	156 total; 17 MOGAD	[78]	Serum	• NLR was significantly elevated at attack compared to remission in MOGAD (p<0.001)	Class II

• Neutrophil percentage (N%) • Neutrophil-to-lymphocyte ratio (NLR) • Platelet-to-lymphocyte ratio (PLR) • Monocyte-to-lymphocyte ratio (MLR) • Eosinophil-to-lymphocyte ratio (ELR) • Systemic immune-inflammation index (SII) • Systemic inflammation response index (SIRI)				• NLR was significantly elevated at attack in MOGAD compared to MS ($p<0.001$)	
	304 total; 26 MOGAD	[97]	Serum	• Total white blood cell count, neutrophil count, monocyte count, NLR, and MLR were all significantly elevated at attack compared to controls ($p=0.0001$, $p<0.0001$, $p=0.0191$, $p=0.0002$, and $p=0.0320$, respectively)	Class II
	81 total; 31 MOGAD	[110]	Serum	• NLR, PLR, and MLR collected at onset were significantly elevated in MOGAD compared to HCs (all $p<0.001$) • NLR and PLR collected at onset were significantly elevated in MOGAD compared to MS ($p<0.001$ and $p=0.001$, respectively) • PLR was significantly positively associated with relapsing course in MOGAD (OR=1.016, 95% CI 1.001–1.031) ($p=0.038$)	Class II
	39	[129]	Serum	• NLR, PLR and N% were significantly elevated at attack compared to remission (all $p<0.001$) • ELR was significantly lower at attack compared to remission ($p<0.001$)	Class II
	125 total; 25 MOGAD	[131]	Serum	• Onset MLR was significantly lower in individuals with relapsing MOGAD (median 0.18, IQR 0.14-0.26) compared to monophasic MOGAD (median 0.29, IQR 0.24-0.44) ($p=0.013$) • ROC analysis found that onset MLR predicted relapsing course with sensitivity and specificity of 75.0% and 88.2%, respectively • Onset MLR < 0.200 was significantly associated with relapsing course ($p=0.005$) • There were no statistically significant associations with NLR, PLR, SII, or SIRI and disease course	Class II
Immune molecules					
Complement	210 total; 109 MOGAD	[75]	Serum	• Complement proteins C5a, SC5b9, Ba, and Bb were significantly elevated in MOGAD compared to paediatric controls (PCs), relapsing MS (RMS), anti-aquaporin-4 antibody (AQP4-IgG) seropositive	Class II

				neuromyelitis optica spectrum disorder (NMOSD), and healthy donors (HDs) (all p≤0.0001) • Complement protein C3a was significantly elevated in MOGAD compared to PCs, RMS, and HDs (p≥0.0001, p≤0.001, and p≤0.0001, respectively) but not significantly different to AQP4-IgG NMOSD • Complement protein factor H was significantly elevated in MOGAD compared to RMS (p≤0.001) but not significantly different to PCs, AQP4-IgG seropositive NMOSD, or HDs • Within the MOGAD group, no difference in any complement protein levels at attack compared to remission nor individuals with monophasic compared to relapsing course	
Cytokines and chemokines	93 total; 21 MOGAD	[43]	Serum	• IL-1β, IL-5, IL-6, IL-10, IL-12p70, IL-17A, tumour necrosis factor (TNF)-α, and interferon (IFN)-γ levels were measured in attack and remission samples • IL-1β (macrophage and dendritic cell-related cytokine) was significantly elevated in MOGAD compared to AQP4-IgG seropositive NMOSD (p<0.001) • IL-10 (regulatory T-cell-related cytokine) was significantly elevated in MOGAD compared to MS and other inflammatory demyelinating diseases (IDDs) (p=0.004 and p=0.002, respectively) • IL-12p70 (macrophage and dendritic cell-related cytokine) was significantly elevated in MOGAD compared to AQP4-IgG seropositive NMOSD and IDDs (both p=0.003) • No significant difference between groups in levels of TNF-α, IFN-γ, IL-5, IL-6, and IL-17A • Th1 dominance was more prominent in MOGAD compared to MS, but similar to AQP4-IgG seropositive NMOSD	Class I

				• IL-1β levels were significantly increased at attack compared to remission most markedly in MOGAD as well as AQP4-IgG seropositive NMOSD, and MS (all $p<0.001$)	
	134 total; 40 MOGAD	[92]	Serum	• 65 cytokines, chemokines, and related molecules like growth factors and soluble receptors were measured in attack and remission samples • Both antibody-associated demyelinating diseases, MOGAD and AQP4-IgG seropositive NMOSD, had similar patterns of increased cytokines and chemokines compared to MS • IL-6 was significantly elevated in MOGAD compared to MS ($p<0.001$) but not significantly different to AQP4-IgG seropositive NMOSD, carrying implications for potential therapeutic IL-6 blockade • Within the MOGAD group, no significant differences in levels measured at attack compared to remission nor between individuals with monophasic compared to relapsing course	Class III
	69 total; 11 MOGAD	[116]	Serum and CSF	• IL-2, IL- 4, IL-6, IL-10, and IL-33 levels were measured at attack, pre- and post-treatment with IV methylprednisolone; there were no remission samples for comparison • Pre-treatment, serum IL-2, IL-6, and IL-10 were significantly increased in MOGAD compared to healthy controls (HCs) ($p<0.01$, $p<0.05$, and $p<0.01$, respectively), while IL-4 and IL-33 were significantly decreased in MOGAD compared to HCs (both $p<0.05$) • Post-treatment, serum IL-6, IL-10, and IL-33 were significantly increased in MOGAD compared to HCs ($p<0.01$, $p<0.05$, and $p<0.05$, respectively), while IL-2 and IL-4 were significantly decreased in MOGAD compared to HCs (both $p<0.05$) • Pre-treatment, CSF cytokines were all significantly increased (IL-33 > IL-10 > IL-4	Class III

				> IL-2) in MOGAD ($p<0.01$, $p<0.01$, $p<0.05$, and $p<0.05$, respectively) and AQP4-IgG seropositive NMOSD ($p<0.05$, $p<0.01$, $p<0.05$, and $p<0.05$, respectively) compared to HCs, but more so in MOGAD • Metrics of BBB dysfunction (CSF QAlb, IgG index, and 24-h IgG synthesis rate) were all significantly elevated in MOGAD (all $p<0.01$) and AQP4-IgG seropositive NMOSD ($p<0.05$, $p<0.01$, and $p<0.05$, respectively) compared to HCs, but more so in MOGAD	
	55 total; 18 MOGAD	[133]	Serum and CSF	• Cytokines relevant to vascular remodelling were measured in samples obtained pre-treatment and at attack or near attack (median 14 (range 1-81) days from attack to sampling); there were no remission samples for comparison • Serum hepatocyte growth factor (HGF) was significantly elevated in both MOGAD and AQP4-IgG seropositive NMOSD compared to HCs ($p=0.0022$ and $p<0.001$, respectively) • Serum fibroblast growth factor-2 (FGF-2) was significantly elevated in MOGAD compared to HCs ($p=0.0070$) • No significant difference in serum or CSF IL-6 between MOGAD and AQP4-IgG seropositive NMOSD; no HC measurement for comparison	Class III
Lipocalin-2 (LCN2)	39 total; 6 MOGAD	[123]	Serum	• LCN2 levels were significantly higher in MOG-IgG seropositive ON (mean 50.96 ng/mL, SD not stated) at onset attack compared to MOG-IgG seronegative ON (mean 37.60 ng/mL) and HCs (30.86 ng/mL) ($p=0.037$) • LCN2 levels significantly positively correlated with MOG-IgG titres ($r=0.553$, $p=0.0141$) • ROC analysis found that LCN2 level of 36.2 ng/mL predicted ON relapse with sensitivity and specificity of 62.5% and 81.8%,	Class III

				respectively; this was not statistically significant (p=0.133)	
sTREM2	38 total; 19 MOGAD	[103]	Serum and CSF	• sTREM2 levels were significantly elevated in serum and CSF of children with MOGAD compared to non-neuroinflammatory disorder controls (p=0.0012 and p<0.001, respectively); all samples were collected at attack	Class III
TNFAIP3	68 total; 24 MOGAD	[62]	Serum	• TNFAIP3 levels were significantly reduced at attack compared to remission and HCs (p=0.04 and p=0.0001, respectively)	Class II
Neurological injury molecules					
GFAP	49 total; 16 MOGAD	[19]	Serum	• No significant difference between GFAP levels in MOGAD at attack and remission	Class I
	152 total; 42 MOGAD	[20]	Serum	• GFAP levels were significantly elevated in AQP4-IgG seropositive NMOSD (median 274.1, IQR 109.2-1680.6 pg/mL) and MOGAD (median 136.7, IQR 97.8-220.1 pg/mL) compared to HCs (median 61.4, IQR 49.7-81.0 pg/mL) (all p < 0.001)	Class I
	41 total; 15 MOGAD	[21]	Serum	• GFAP levels were not significantly elevated at attack in MOGAD	Class II
	225 total; 7 MOGAD	[34]	Serum	• GFAP levels were elevated (> 2 SDs from HD means) in 14% (1/7) of individuals with MOGAD at baseline • There was no significant attack-related pattern of GFAP in MOGAD	Class I
NfL	49 total; 16 MOGAD	[19]	Serum	• No significant difference between NfL levels at attack and remission	Class I
	152 total; 42 MOGAD	[20]	Serum	• NfL levels were significantly higher in AQP4-IgG seropositive NMOSD (median 17.6, IQR 9.6–48.1 pg/mL), MOGAD (median 27.2, IQR 10.8–54.8 pg/mL), and RRMS (median 24.5, IQR 14.5–58.3 pg/mL) compared to HCs (median 7.4, IQR 5.6–9.4 pg/mL) (all p<0.001)	Class I

				• NfL levels were significantly higher at attack (median 34.1, IQR 17.6–64.3 pg/mL) compared to remission (median 2.5, IQR 9.1–48.4 pg/mL) in MOGAD (p=0.049)	
	41 total; 15 MOGAD	[21]	Serum	• NfL levels were elevated in all (17/17) attack samples compared to 24% (14/59) of remission samples (p<0.0001)	Class II
	120 total; 49 MOGAD	[22]	Serum	• NfL levels in adults were significantly higher at attack (median 31.0, IQR 15.8-81.2 pg/mL) compared to remission (median 8.1, IQR 5.7-14.4 pg/mL) and HCs (median 10.3, IQR 8.1-13.3 pg/mL) (p=0.001 and p=0.004, respectively) • NfL levels in children were significantly higher at attack (median 46.8, IQR 5.8-130.2 pg/mL) compared to remission (median 13.1, IQR 4.7-35.7 pg/mL) and HCs (median 8.2, IQR 6.4-11.3 pg/mL) (p=0.001 and p=0.007, respectively)	Class I
	36 total; 18 MOGAD	[65]	Serum	• NfL levels were increased at onset then stable or decreased with no significant elevation at subsequent attacks	Class III
	76 total; 38 MOGAD	[67]	Serum	• NfL levels at onset were significantly higher in individuals with severe attacks (median 15.3 pg/mL, range 4-101.5 pg/mL) compared to individuals with mild-to-moderate attacks (median 7.3 pg/mL, range 2.1–23.0 pg/mL) (p=0.002), independent of age and sex • NfL levels at onset did not significantly correlate with subsequent relapse rate	Class II
	225 total; 7 MOGAD	[34]	Serum	• NfL levels were elevated (>2 SDs from HD means) in 43% (3/7) of individuals with MOGAD at baseline • There was no significant attack-related pattern of NFL in MOGAD	Class I
	27 total; 15 MOGAD	[111]	Serum	• NfL levels were significantly elevated within 3 months of onset in MOGAD (mean 89.72 ± 22.38 pg/mL) compared to HCs (mean 12.47 ± 2.47 pg/mL) (p=0.0012)	Class II
	164 total; 19 MOGAD	[119]	Serum	• NfL levels collected within 3 months of onset were significantly higher in children with MOGAD (median 56.7, range 4.1–	Class I

				372.8 pg/mL), other ADS (median 26.5, range 1.5–2444.3 pg/mL), and MS (median 39.1, range 4.2–474.7 pg/mL) compared to controls with other neurological diseases (median 7.5, range 3.0–31.8 pg/mL) (all p<0.001)	
Tau	49 total; 16 MOGAD	[19]	Serum	• Tau levels were significantly higher at attack (median 0.5, IQR 0.4–0.5 pg/mL) compared to remission (median 0.2, IQR 0.1–0.3 pg/mL) (p=0.027)	Class I
	225 total; 7 MOGAD	[34]	Serum	• Tau levels were not elevated (> 2 SDs of HD means) at baseline in any individuals with MOGAD nor was any significant attack-related pattern observed	Class I
Ubiquitin Carboxy-terminal Hydrolase L1 (UCHL1)	225 total; 7 MOGAD	[34]	Serum	• UCHL1 levels were not elevated (> 2 SDs of HD means) at baseline in any individuals with MOGAD nor was any significant attack-related pattern observed	Class I
Genetics					
HLA genotype	576 total; 95 MOGAD	[66]	Serum	• Frequency of DQB1*05:02 allele was significantly higher at 18.95% in MOGAD compared to 10.71% in controls (OR=1.95, 95% CI 1.25–3.0) (p=0.002) • Age subgroup analysis revealed a significant association for paediatric-onset MOGAD with DQB1*05:02 (OR=2.43, 95% CI 1.39–4.11) (p=0.001) and DRB1*16:02 (OR=3.28, 95% CI 1.55–6.25) (p=0.001) but no significant associations for adult-onset MOGAD • 80% (8/10) of paediatric-onset MOGAD carriers of the DQB1*05:02–DRB1*16:02 haplotype had a relapsing course compared to 37% (15/41) of non-carriers (p=0.030)	Class II
Metabolic and endocrine molecules					
Homocysteine	20	[114]	Serum	• Homocysteine was elevated at onset in 40% (8/20) of individuals with late-onset (≥ 50 years) MOGAD; of those, 87.5% (7/8) had a monophasic course and 12.5% (1/8) had a relapsing course • Homocysteine was normal at onset in 60% (12/20) of individuals with late-onset	Class III

				MOGAD; of those, 50% (6/6) had a monophasic course and 50% (6/6) had a relapsing course • No findings reached statistical significance (p=0.158)	
Prolactin	138 total; 15 MOGAD	[102]	Serum	• No significant difference between prolactin levels in MOGAD at attack and remission	Class II
Thiol	85 total; 8 MOGAD	[58]	Serum	• Total thiol and native thiol levels were significantly lower in samples collected at attack compared to remission in a combined cohort of MOGAD, AQP4-IgG seropositive NMOSD, and MS	Class III
Thyroid function profile	261 total; 26 MOGAD	[93]	Serum	• FT4 levels were significantly higher in relapsing MOGAD (mean 16.46 ± 3.14 pM) compared to monophasic MOGAD (mean 13.68 ± 1.46 pM) (p=0.03) • ROC analysis found that FT4 level 15.125 pM predicted relapsing disease course with sensitivity and specificity of 72.7% and 87.5%, respectively	Class III
Extracellular matrix molecules					
MFAP4	152 total; 22 MOGAD	[115]	CSF	MFAP4 levels were significantly reduced at attack compared to remission (p=0.001)	Class II
*Classification of evidence was assessed using the American Academy of Neurology (AAN) Criteria for Rating Diagnostic Accuracy Studies.					

Supplementary References

1. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. The Lancet Neurology. 2023;22(3):268-82.
2. Baumann M, Hennes E-M, Schanda K, et al. Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): Extending the spectrum of MOG antibody positive diseases. Multiple sclerosis (Houndmills, Basingstoke, England). 2016;22(14):1821-9.
3. Kwon YN, Kim B, Ahn S, et al. Serum level of IL-1β in patients with inflammatory demyelinating disease: Marked upregulation in the early acute phase of MOG antibody associated disease (MOGAD). Journal of Neuroimmunology. 2020;348.
4. Kim H, Lee E-J, Kim S, et al. Serum biomarkers in myelin oligodendrocyte glycoprotein antibody-associated disease. Neurology(R) neuroimmunology & neuroinflammation. 2020;7(3).
5. Wendel E-M, Baumann M, Barisic N, et al. High association of MOG-IgG antibodies in children with bilateral optic neuritis. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society. 2020;27:86-93.
6. Pröbstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology. 2011 Aug 9;77(6):580-8.
7. Hyun J-W, Woodhall MR, Kim S-H, et al. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. Journal of neurology, neurosurgery, and psychiatry. 2017;88(10):811-7.
8. Hoftberger R, Sepulveda M, Armangue T, et al. Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease. Multiple sclerosis (Houndmills, Basingstoke, England). 2015;21(7):866-74.
9. Horellou P, de Chalus A, Giorgi L, et al. Regulatory T Cells Increase After rh-MOG Stimulation in Non-Relapsing but Decrease in Relapsing MOG Antibody-Associated Disease at Onset in Children. Frontiers in immunology. 2021;12:679770.
10. Chang X, Huang W, Wang L, et al. Serum Neurofilament Light and GFAP Are Associated With Disease Severity in Inflammatory Disorders With Aquaporin-4 or Myelin Oligodendrocyte Glycoprotein Antibodies. Frontiers in immunology. 2021;12:647618.
11. Jarius S, Lechner C, Wendel EM, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 2: Results from 108 lumbar punctures in 80 pediatric patients. Journal of neuroinflammation. 2020;17(1):262.
12. Cobo-Calvo A, Ruiz A, D'Indy H, et al. MOG antibody-related disorders: common features and uncommon presentations. Journal of neurology. 2017;264(9):1945-55.
13. Hyun J-W, Kim SY, Kim Y, et al. Absence of attack-independent neuroaxonal injury in MOG antibody-associated disease: Longitudinal assessment of serum neurofilament light chain. Multiple sclerosis (Houndmills, Basingstoke, England). 2021:13524585211063756.
14. Ikeda A, Watanabe Y, Kaba H, Kaneko K, Takahashi T, Takeshita S. MRI findings in pediatric neuromyelitis optica spectrum disorder with MOG antibody: Four cases and review of the literature. Brain & development. 2019;41(4):367-72.
15. Lopez-Chiriboga AS, Majed M, Fryer J, et al. Association of MOG-IgG Serostatus With Relapse After Acute Disseminated Encephalomyelitis and Proposed Diagnostic Criteria for MOG-IgG-Associated Disorders. JAMA neurology. 2018;75(11):1355-63.

16. Waters P, Fadda G, Woodhall M, et al. Serial Anti-Myelin Oligodendrocyte Glycoprotein Antibody Analyses and Outcomes in Children with Demyelinating Syndromes. JAMA Neurology. 2020;77(1):82-93.
17. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain (London, England : 1878). 2017;140(12):3128-38.
18. Hino-Fukuyo N, Haginoya K, Takahashi T, et al. Long-term outcome of a group of Japanese children with myelin-oligodendrocyte glycoprotein encephalomyelitis without preventive immunosuppressive therapy. Brain & development. 2019;41(9):790-5.
19. Serin HM, Yilmaz S, Simsek E, et al. Clinical spectrum, treatment and outcome of myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease in children: a tertiary care experience. Acta neurologica Belgica. 2021;121(1):231-9.
20. Jarius S, Pellkofer H, Siebert N, et al. Cerebrospinal fluid findings in patients with myelin oligodendrocyte glycoprotein (MOG) antibodies. Part 1: Results from 163 lumbar punctures in 100 adult patients. Journal of neuroinflammation. 2020;17(1):261.
21. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation. 2016 Sep 26;13(1):279.
22. Oliveira LM, Apostolos-Pereira SL, Pitombeira MS, Bruel Torretta PH, Callegaro D, Sato DK. Persistent MOG-IgG positivity is a predictor of recurrence in MOG-IgG-associated optic neuritis, encephalitis and myelitis. Multiple sclerosis (Houndmills, Basingstoke, England). 2019;25(14):1907-14.
23. Arslan B, Arslan GA, Tuncer A, Karabudak R, Dincel AS. Evaluation of Thiol Homeostasis in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorders. Frontiers in neurology. 2021;12:716195.
24. Liu J, Mori M, Sugimoto K, et al. Peripheral blood helper T cell profiles and their clinical relevance in MOG-IgG-associated and AQP4-IgG-associated disorders and MS. Journal of neurology, neurosurgery, and psychiatry. 2020;91(2):132-9.
25. de Mol CL, Wong Y, van Pelt ED, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. Mult Scler. 2020 Jun;26(7):806-14.
26. Rostasy K, Mader S, Schanda K, et al. Anti-myelin oligodendrocyte glycoprotein antibodies in pediatric patients with optic neuritis. Archives of neurology. 2012;69(6):752-6.
27. Rostasy K, Mader S, Hennes EM, et al. Persisting myelin oligodendrocyte glycoprotein antibodies in aquaporin-4 antibody negative pediatric neuromyelitis optica. Multiple sclerosis (Houndmills, Basingstoke, England). 2013;19(8):1052-9.
28. Saxena S, Lokhande H, Gombolay G, Raheja R, Rooney T, Chitnis T. Identification of TNFAIP3 as relapse biomarker and potential therapeutic target for MOG antibody associated diseases. Sci Rep-uk. 2020;10(1):12405.
29. Luo W, Chen Y, Mao S, et al. Serum neurofilament light chain in adult and pediatric patients with myelin oligodendrocyte glycoprotein antibody-associated disease: Correlation with relapses and seizures. Journal of neurochemistry. 2021.
30. Tanaka S, Hashimoto B, Izaki S, Oji S, Fukaura H, Nomura K. Clinical and immunological differences between MOG associated disease and anti AQP4 antibody-positive neuromyelitis optica spectrum disorders: Blood-brain barrier breakdown and peripheral plasmablasts. Multiple sclerosis and related disorders. 2020;41:102005.
31. Han JY, Kim SY, Kim H, et al. Clinico-radiological characteristics of anti-myelin oligodendrocyte glycoprotein antibody-associated autoimmune encephalitis in children. Developmental medicine and child neurology. 2022.

32. Mariotto S, Gastaldi M, Grazian L, et al. NfL levels predominantly increase at disease onset in MOG-Abs-associated disorders. Multiple sclerosis and related disorders. 2021;50:102833.
33. Sun X, Qiu W, Wang J, et al. Myelin oligodendrocyte glycoprotein-associated disorders are associated with HLA subtypes in a Chinese paediatric-onset cohort. Journal of neurology, neurosurgery, and psychiatry. 2020;91(7):733-9.
34. Mariotto S, Ferrari S, Gastaldi M, et al. Neurofilament light chain serum levels reflect disease severity in MOG-Ab associated disorders. Journal of Neurology, Neurosurgery and Psychiatry. 2019;90(11):1293-6.
35. Alshamrani F, Alnajashi H, Shosha E, Casserly C, Morrow SA. Case Series: Myelin Oligodendrocyte Glycoprotein-Immunoglobulin G-Related Disease Spectrum. Frontiers in neurology. 2020;11:89.
36. Dale RC, Tantsis EM, Merheb V, et al. Antibodies to MOG have a demyelination phenotype and affect oligodendrocyte cytoskeleton. Neurology(R) neuroimmunology & neuroinflammation. 2014;1(1):e12.
37. Lui A, Chong J, Flanagan E, et al. High titers of myelin oligodendrocyte glycoprotein antibody are only observed close to clinical events in pediatrics. Multiple sclerosis and related disorders. 2021;56:103253.
38. Dubey D, Pittock SJ, Krecke KN, et al. Clinical, Radiologic, and Prognostic Features of Myelitis Associated With Myelin Oligodendrocyte Glycoprotein Autoantibody. JAMA neurology. 2019;76(3):301-9.
39. Hennes E-M, Baumann M, Schanda K, et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. Neurology. 2017;89(9):900-8.
40. Tea F, Lopez JA, Ramanathan S, et al. Characterization of the human myelin oligodendrocyte glycoprotein antibody response in demyelination. Acta neuropathologica communications. 2019;7(1):145.
41. Senanayake B, Jitprapaikulsan J, Aravinthan M, et al. Seroprevalence and clinical phenotype of MOG-IgG-associated disorders in Sri Lanka. Journal of neurology, neurosurgery, and psychiatry. 2019;90(12):1381-3.
42. Wegener-Panzer A, Cleaveland R, Wendel E-M, et al. Clinical and imaging features of children with autoimmune encephalitis and MOG antibodies. Neurology(R) neuroimmunology & neuroinflammation. 2020;7(4).
43. Zhou J, Lu X, Ji T, et al. Follow-up study on Chinese children with relapsing MOG-IgG-associated central nervous system demyelination. Multiple Sclerosis and Related Disorders. 2019;28:4-10.
44. Keller CW, Lopez JA, Wendel E-M, et al. Complement Activation Is a Prominent Feature of MOGAD. Annals of neurology. 2021;90(6):976-82.
45. Baumann M, Sahin K, Lechner C, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. Journal of neurology, neurosurgery, and psychiatry. 2015;86(3):265-72.
46. Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. Journal of Neurology, Neurosurgery & Psychiatry. 2018;89(2):127.
47. Benetou C, Berti F, Hemingway C, Hacochen Y, Lim M. Neutrophil-to-lymphocyte ratio correlates with disease activity in myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) in children. Multiple Sclerosis and Related Disorders. 2020;45:102345.

48. Armangue T, Olive-Cirera G, Martinez-Hernandez E, et al. Associations of paediatric demyelinating and encephalitic syndromes with myelin oligodendrocyte glycoprotein antibodies: a multicentre observational study. The Lancet Neurology. 2020;19(3):234-46.
49. Nakajima H, Motomura M, Tanaka K, et al. Antibodies to myelin oligodendrocyte glycoprotein in idiopathic optic neuritis. Bmj Open. 2015;5(4):e007766.
50. Mao L, Yang L, Kessi M, et al. Myelin Oligodendrocyte Glycoprotein (MOG) Antibody Diseases in Children in Central South China: Clinical Features, Treatments, Influencing Factors, and Outcomes. Frontiers in neurology. 2019;10:868.
51. Siritho S, Sato DK, Kaneko K, Fujihara K, Prayoonwiwat N. The clinical spectrum associated with myelin oligodendrocyte glycoprotein antibodies (anti-MOG-Ab) in Thai patients. Multiple sclerosis (Houndmills, Basingstoke, England). 2016;22(7):964-8.
52. Zhang M, Du X, Zhou S, et al. Clinical characteristics, disease course, and outcomes of paediatric patients with myelin oligodendrocyte glycoprotein-Ab associated disease: A retrospective clinical study. Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2021;94:1-7.
53. Jitprapaikulsan J, Chen JJ, Flanagan EP, et al. Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein Autoantibody Status Predict Outcome of Recurrent Optic Neuritis. Ophthalmology. 2018 2018/10/01/;125(10):1628-37.
54. Huda S, Whittam D, Jackson R, et al. Predictors of relapse in MOG antibody associated disease: a cohort study. BMJ Open. 2021;11(11):e055392.
55. Dauby S, Dive D, Lutteri L, et al. Comparative study of AQP4-NMOSD, MOGAD and seronegative NMOSD: a single-center Belgian cohort. Acta neurologica Belgica. 2021.
56. Solmaz I, Oncel IH, Konuskan B, et al. Role of serostatus in pediatric neuromyelitis optica spectrum disorders: A nationwide multicentric study. Multiple sclerosis and related disorders. 2023;77:104847.
57. Seok JM, Jeon MY, Chung YH, et al. Clinical characteristics of myelin oligodendrocyte glycoprotein antibody-associated disease according to their epitopes. Frontiers in neurology. 2023;14:1200961.
58. Martin K, Srikanth P, Kanwar A, Falardeau J, Pettersson D, Yadav V. Clinical and radiographic features of a cohort of adult and pediatric subjects in the Pacific Northwest with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Multiple Sclerosis and Related Disorders. 2024;81:105130.
59. Liao D, Zhong L, Yang L, et al. Clinical and radiological features, treatment responses and prognosis in pediatric patients with co-existing anti-N-methyl-D-aspartate receptor and myelin oligodendrocyte glycoprotein antibody-associated encephalitis: A single center study. Multiple Sclerosis and Related Disorders. 2024;81:105133.
60. Nosadini M, Eyre M, Giacomini T, et al. Early Immunotherapy and Longer Corticosteroid Treatment Are Associated With Lower Risk of Relapsing Disease Course in Pediatric MOGAD. Neurology: Neuroimmunology and NeuroInflammation. 2023;10(1):e200065.
61. Kang Q, Liao H, Yang L, et al. Clinical analysis of 173 pediatric patients with antibody-mediated autoimmune diseases of the central nervous system: a single-center cohort study. Frontiers in Immunology. 2023;14:1140872.
62. Yao T, Zeng Q, Xie Y, et al. Clinical analysis of adult MOG antibody-associated cortical encephalitis. Multiple sclerosis and related disorders. 2022;60:103727.
63. Bauer A, Rudzki D, Berek K, et al. Increased peripheral inflammatory responses in myelin oligodendrocyte glycoprotein associated disease and aquaporin-4 antibody positive neuromyelitis optica spectrum disorder. Frontiers in Immunology. 2022;13:1037812.

64. Rechtman A, Zveik O, Haham N, Freidman-Korn T, Vaknin-Dembinsky A. Thyroid hormone dysfunction in MOGAD and other demyelinating diseases. Journal of the Neurological Sciences. 2024;457:122866.
65. Nguyen L, Miles DK, Harder L, et al. Increased Intracranial Pressure in Pediatric Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. Neurology(R) neuroimmunology & neuroinflammation. 2024;11(1).
66. Zhangbao J, Huang W, Zhou L, et al. Clinical feature and disease outcome in patients with myelin oligodendrocyte glycoprotein antibody-associated disorder: A Chinese study. Journal of Neurology, Neurosurgery and Psychiatry. 2023;94(10):825-34.
67. Montalvo M, Khattak J, Redenbaugh V, et al. Acute Symptomatic Seizures Secondary to Myelin Oligodendrocyte Glycoprotein Antibody-associated Disorder. Neurology. 2022;98(18 SUPPL).
68. Aktas O, Hartung H-P, Smith MA, et al. Serum neurofilament light chain levels at attack predict post-attack disability worsening and are mitigated by inebilizumab: analysis of four potential biomarkers in neuromyelitis optica spectrum disorder. Journal of neurology, neurosurgery, and psychiatry. 2023;94(9):757-68.
69. Akaishi T, Misu T, Fujihara K, et al. White blood cell count profiles in anti-aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorder and anti-myelin oligodendrocyte glycoprotein antibody-associated disease. Sci Rep-uk. 2023;13(1):6481.
70. Wang W, Yin J, Fan Z, et al. Case Report: Four Cases of Cortical/Brainstem Encephalitis Positive for Myelin Oligodendrocyte Glycoprotein Immunoglobulin G. Frontiers in Neurology. 2022;12:775181.
71. Wendel EM, Thonke HS, Bertolini A, et al. Temporal Dynamics of MOG Antibodies in Children With Acquired Demyelinating Syndrome. Neurology: Neuroimmunology and NeuroInflammation. 2022;9(6):e200035.
72. Guzman J, Vera F, Soler B, et al. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD) in Chile: lessons learned from challenging cases. Multiple Sclerosis and Related Disorders. 2023;69:104442.
73. Gastaldi M, Foiadelli T, Greco G, et al. Prognostic relevance of quantitative and longitudinal MOG antibody testing in patients with MOGAD: a multicentre retrospective study. Journal of neurology, neurosurgery, and psychiatry. 2022.
74. Wu Y, Zhou H, Ci X, Lin L, Zhang D, Lu J. Clinical characteristic of myelin oligodendrocyte glycoprotein antibody associated cortical encephalitis in adults and outcomes following glucocorticoid therapy. Frontiers in Aging Neuroscience. 2023;14:1076361.
75. Liu H, Zhang X, Chen W, Xu Y, Lin X, Lin A. The relationship between plasma prolactin levels and clinical manifestations with neuromyelitis optica spectrum disorders. Neurological Sciences. 2024;45(2):699-707.
76. Zhou A, Zhang W, Ren C, Zhou J, Chang H, Ren X. High levels of cerebrospinal fluid soluble triggering receptor expressed on myeloid cells 2 might be a biomarker of activity in pediatric patients with MOG-AD. Frontiers in Pediatrics. 2022;10:908527.
77. Zhou J, Li J, Ren C, et al. Mycophenolate mofetil: An alternative disease-modifying agent for MOG-IgG-associated disorders in childhood: A single-center bidirectional cohort study. Multiple Sclerosis and Related Disorders. 2022;68:104128.
78. Yang Y, Zhang C, Cao C, Su W, Zhao N, Yue W. Clinical Features of Patients with Myelin Oligodendrocyte Glycoprotein Antibody–Associated Disease and Isolated Seizure Symptoms. Neuropsychiatric Disease and Treatment. 2024;20:61-7.
79. Wang X, Zhao R, Yang H, Liu C, Zhao Q. Two rare cases of myelin oligodendrocyte glycoprotein antibody-associated disorder in children with leukodystrophy-like imaging findings. BMC Neurology. 2023;23(1):247.

80. Roy S, Vasileiou E, Barreras P, et al. Longitudinal evaluation of serum MOG-IgG titers in MOGAD after initiation of maintenance immunoglobulin: A case series. Multiple Sclerosis Journal. 2023.
81. Lee W-J, Kwon YN, Kim B, et al. MOG antibody-associated encephalitis in adult: clinical phenotypes and outcomes. Journal of neurology, neurosurgery, and psychiatry. 2023;94(2):102-12.
82. Xu Q, Yang X, Qiu Z, et al. Clinical features of MOGAD with brainstem involvement in the initial attack versus NMOSD and MS. Multiple Sclerosis and Related Disorders. 2023;77:104797.
83. Lin L, Ji M, Wu Y, Hang H, Lu J. Neutrophil to lymphocyte ratio may be a useful marker in distinguishing MOGAD and MS and platelet to lymphocyte ratio associated with MOGAD activity. Multiple Sclerosis and Related Disorders. 2023;71:104570.
84. Horellou P, Flet-Berliac L, Leroy C, et al. Early blood neurofilament light chain and myelin oligodendrocyte glycoprotein antibody levels associate with different disease courses of myelin oligodendrocyte glycoprotein-associated disease in children. Brain communications. 2023;5(2):fcad063.
85. Hacohen Y, Absoud M, Woodhall M, et al. Autoantibody biomarkers in childhood-acquired demyelinating syndromes: Results from a national surveillance cohort. Journal of Neurology, Neurosurgery and Psychiatry. 2014;85(4):456-61.
86. Salunkhe M, Gupta P, Singh RK, et al. Clinical and radiological spectrum of anti-myelin oligodendrocyte glycoprotein (MOG) antibody encephalitis: single-center observational study. Neurological Sciences. 2023;44(7):2475-89.
87. Huang Y, Luo W, Cheng X, et al. Clinical and imaging features of patients with late-onset myelin oligodendrocyte glycoprotein antibody-associated disease. Multiple Sclerosis and Related Disorders. 2024;82:105405.
88. Samadzadeh S, Olesen MN, Wirenfeldt M, et al. Microfibrillar-associated protein 4 as a potential marker of acute relapse in inflammatory demyelinating diseases of the central nervous system: Pathological and clinical aspects. Multiple Sclerosis Journal. 2023;29(14):1721-35.
89. Liyanage G, Trewin BP, Lopez JA, et al. The MOG antibody non-P42 epitope is predictive of a relapsing course in MOG antibody-associated disease. Journal of neurology, neurosurgery, and psychiatry. 2024.
90. Wang M, Xia D, Sun L, Bi J, Xie K, Wang P. Interleukin-33 as a Biomarker Affecting Intrathecal Synthesis of Immunoglobulin in Neuromyelitis Optica Spectrum Disorder and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. European Neurology. 2023;86(4):256-62.
91. Yandamuri SS, Filipek B, Obaid AH, et al. MOGAD patient autoantibodies induce complement, phagocytosis, and cellular cytotoxicity. JCI Insight. 2023;8(11):e165373.
92. Nguyen L, Wang CX, Conger DL, Sguigna PV, Singh S, Greenberg BM. Subclinical optic neuritis in pediatric myelin oligodendrocyte glycoprotein antibody-associated disease. Multiple Sclerosis and Related Disorders. 2023;76:104802.
93. Wendel E-M, Bertolini A, Kousoulos L, et al. Serum neurofilament light-chain levels in children with monophasic myelin oligodendrocyte glycoprotein-associated disease, multiple sclerosis, and other acquired demyelinating syndrome. Multiple sclerosis (Houndmills, Basingstoke, England). 2022;28(10):1553-61.
94. Zhang S, Qiao S, Li H, et al. Risk Factors and Nomogram for Predicting Relapse Risk in Pediatric Neuromyelitis Optica Spectrum Disorders. Frontiers in Immunology. 2022;13:765839.

95. Aubart M, Roux C-J, Durrleman C, et al. Neuroinflammatory Disease following Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Children. The Journal of pediatrics. 2022;247:22-8.e2.
96. Tzanetakos D, Tzartos JS, Vakrakou AG, et al. Cortical involvement and leptomeningeal inflammation in myelin oligodendrocyte glycoprotein antibody disease: A three-dimensional fluid-attenuated inversion recovery MRI study. Multiple sclerosis (Houndmills, Basingstoke, England). 2022;28(5):718-29.
97. Kim J-H, Lee H, Oh J, Suk K, Chun BY. Increased Plasma Lipocalin-2 Levels in Patients with Myelin Oligodendrocyte Glycoprotein-IgG-Positive Optic Neuritis. Journal of clinical medicine. 2022;11(9).
98. Nguyen L, Wang CX, Hernandez RS, Greenberg BM. Clinical analysis of myelin oligodendrocyte glycoprotein antibody-associated disease in a diverse cohort of children: A single-center observational study. Multiple sclerosis and related disorders. 2024;84:105497.
99. Fadda G, Waters P, Woodhall M, et al. Serum MOG-IgG in children meeting multiple sclerosis diagnostic criteria. Multiple sclerosis (Houndmills, Basingstoke, England). 2022:13524585221093789.
100. Vosoughi AR, Muccilli A, Schneider R, Rotstein D, Micieli JA. Recovery of Vision in Myelin Oligodendrocyte Glycoprotein-IgG Optic Neuritis Without Treatment: A Case Series. Journal of Neuro-Ophthalmology. 2023;43(4):E126-E8.
101. Jiang Y, Tan C, Li X, et al. Clinical features of the first attack with leukodystrophy-like phenotype in children with myelin oligodendrocyte glycoprotein antibody-associated disorders. International Journal of Developmental Neuroscience. 2023;83(3):267-73.
102. Zeng W, Yu L, Wu J, et al. Clinical characteristics and long-term follow-up outcomes of myelin oligodendrocyte glycoprotein antibody-associated disease in Han Chinese participants. Medicine (United States). 2023;102(40):E35391.
103. Baek S-I, Ro S, Chung YH, et al. Novel index, neutrophil percentage (%) is a useful marker for disease activity in MOG antibody-associated disease. Multiple sclerosis and related disorders. 2023;76:104796.
104. Singh B, Cruz-Flores S, Chaudhry MR, Piriyawat P, Ponce CP. Psychiatric manifestations of anti-MOG antibody disease. Neuroimmunology Reports. 2022;2:100073.
105. Wang L, Xia R, Li X, Shan J, Wang S. Systemic inflammation response index is a useful indicator in distinguishing MOGAD from AQP4-IgG-positive NMOSD. Frontiers in Immunology. 2023;14:1293100.
106. Song X, Ma J. Clinical characteristics of myelin-oligodendrocyte glycoprotein antibody-positive pediatric autoimmune encephalitis without demyelination: A case series. Frontiers in Immunology. 2022;13:1050688.
107. Masuda H, Mori M, Uzawa A, et al. Elevated serum levels of bone morphogenetic protein-9 are associated with better outcome in AQP4-IgG seropositive NMOSD. Sci Rep-uk. 2023;13(1):3538.

Chapter 3 | Discussion and Concluding Remarks

This concluding chapter synthesises our key findings and their implications for clinical practice. The strengths and limitations of this project are considered. Finally, we highlight future directions and propose a series of relevant recommendations for this undertaking.

Summary of Key Findings

MOGAD is an inflammatory autoantibody-mediated demyelinating pathology of the CNS. Two key differential diagnoses of MOGAD include NMOSD – a primary autoantibody-mediated astrocytopathy with subsequent demyelination – and MS – an inflammatory demyelinating condition with lesions composed of activated macrophages and microglia and CD8 + T-cells, with fewer CD4 + T-cells and B-cells [1-3]. MOGAD follows either a monophasic or relapsing disease course, with relapse reported to affect 72% of individuals when follow-up is extended beyond 5-years [4]. The morbidity burden associated with MOGAD is significant; it has been reported that the median EDSS at recovery following later episodes was higher than the median EDSS at recovery following earlier episodes, which suggests that neurological disability accumulates with relapse [5]. Relapse prediction in MOGAD is an integral yet elusive goal that has the potential to guide early immunosuppressive therapies and limit the accrual of disability in relapsing individuals while simultaneously ensuring monophasic individuals are not unnecessarily exposed to long-term immunosuppression. To date, numerous clinical factors have been assessed for disease course prediction. Male sex, TM onset attack phenotype, and corticosteroid wean ≥1-month duration have all been associated with a reduced risk of relapse [6]. There is mixed evidence regarding age at onset and relapse risk, with one group reporting that age at onset >16 years was associated with reduced risk of relapse [6], while another group found that young adult age at onset (>18-40 years) was associated with increased risk of relapse compared with older adult age at onset (>40-years)[7]. Rapid corticosteroid taper and corticosteroid withdrawal have been shown to confer increased risk of relapse [5, 8, 9]. Laboratory biomarkers capable of predicting relapse offer another attractive solution to this conundrum of disease course prediction. Primary studies in the field of MOGAD have been consistently challenged by limited sample sizes due to the incidence rarity of this disease – estimated at 1.6-3.4 per 1,000,000 person-years [10, 11]. We conducted a systematic review and meta-analysis to investigate the capability of laboratory biomarkers to predict disease course, as well as differentiate remission compared to attack disease activity, while addressing the common constraint in this research field of underpowered statistical analyses.

We were able to quantitatively analyse at least 1710 individuals from a total of 106 included studies; however, 6 studies specified sample numbers not participant numbers for part or all of their dataset. Firstly, we examined biomarkers for capability to predict relapsing course. Most pertinently, we demonstrated that persistent seropositivity (≥2 positive serum MOG-IgG measurements collected ≥3 months apart) was significantly associated with relapsing course.

This relationship remained statistically significant when individual-level covariables (age, sex, and phenotype) were examined in multivariable analysis and when sample collection interval was lengthened to ≥6 and ≥12 months apart. Multivariable analysis also highlighted the significant association of ADEM phenotype with monophasic course.

These findings prompted us to further examine longitudinal serum MOG-IgG trends. We found that individuals with a relapsing course seroreverted to MOG-IgG negative status significantly later than monophasic individuals. Furthermore, relapsing course and female sex were associated with an overall significantly reduced likelihood of seroreverting to MOG-IgG negative status. In contrast, ADEM phenotype was significantly associated with an increased likelihood of reverting to MOG-IgG negative status, which is in line with the earlier association between ADEM phenotype and monophasic course.

Next, we examined biomarkers for capability to differentiate between remission and attack in individuals with known diagnosis of MOGAD. Our primary findings were twofold. Firstly, serum MOG-IgG titre – semi-quantitatively categorised as negative, low positive, or clear positive as per the latest international MOGAD diagnostic criteria [12] – effectively discriminated between remission and attack. Both low positive and clear positive titres were significantly associated with attack, with clear positive titre demonstrating a more pronounced association than low positive titre. Negative titre was significantly associated with remission disease state. Secondly, CSF leukocytosis (≥5 cells/μL), compared to a normal WCC, was significantly associated with attack. It remains to be seen whether serum GFAP and NfL have a role in disease activity monitoring in MOGAD as our meta-analysis was limited by considerable heterogeneity with regards to these more novel candidate biomarkers.

Biomarkers collected at disease onset or in the first collected biospecimen that correlate with disease course offer valuable guidance for overall relapse risk stratification and therapeutic decisions regarding chronic immunosuppression; however, an important caveat is that these biomarkers do not necessarily inform timing of relapses. In comparison, biomarkers collected throughout disease that associate with nearby disease activity offer complementary value for prediction of relapse timing and the necessity of prompt acute immunosuppression.

Currently, serum MOG-IgG itself is the strongest biomarker of MOGAD disease course and activity. Nonetheless, it is a blunt tool with the following key limitations: (i) determining persistent seropositivity requires serial serum MOG-IgG measurement, which confers an inherit delay for this to assist with relapse risk stratification, (ii) the range of titres within the

clear positive category is extremely broad, (iii) further reference data to characterise additional thresholds appropriately sensitive and specific for prediction of attack or remission are currently lacking, (iv) longitudinal sampling has revealed that titres may fluctuate independently of attacks [13], and (v) international standardization of all CBAs is required.

Implications for Clinical Practice

The findings of this study have clear and significant clinical implications. In Chapter 2, we were able to propose the following recommendations for clinicians: (i) serial measurement of serum MOG-IgG at 3-6 month intervals in the 12 months following disease onset may be considered to stratify risk of relapsing disease course; however, increased burden of sample collection and cost are important caveats, (ii) measurement of serum MOG-IgG titre may be diagnostically useful in settings of clinical uncertainty whereby an individual, who has an existing diagnosis of MOGAD, has symptoms that are not clearly attributable to a relapse of MOGAD, and (iii) balancing the risk of lumbar puncture procedure, the presence of CSF leukocytosis may be a useful auxiliary finding to diagnose MOGAD attack after CNS infection has been effectively ruled out. Our systematic review with meta-analysis was the first of its kind to examine biomarkers of disease course and activity in MOGAD and, thus, these recommendations reflect the highest quality evidence available and may be readily adopted into clinical practice.

Nonetheless, there are important limitations to our work that must be discussed. First and foremost, treatment status at time of sample collection could not be accounted for due to limited reporting in the primary literature. Unfortunately, this methodological decision does not reflect the real-world context. We hypothesise that immunosuppressants acting via mechanisms of B- and T-cell depletion would likely reduce serum MOG-IgG titre and promote seroreversion to negative status. Omission of treatment status at time of sample collection may have underestimated serum MOG-IgG titres as well as the longitudinal trends of serial MOG-IgG measurements. Secondly, there was substantial between-study methodological diversity including sample size, geographic location, sample collection timing, and treatment status, which contributed to considerable heterogeneity in several of our analyses. We hypothesise that the extent of between-study methodological diversity observed was, in part, a contextual product of the fact that MOGAD is a relatively newly defined clinical entity and this field of research is rapidly expanding. The first consensus international diagnostic criteria for MOGAD

only recently became available in 2023 [12]. These guidelines were instrumental in unifying the current scientific and clinical understanding of MOGAD.

Future Directions and Recommendations

Our work highlights compelling areas for future research. As aforementioned, given the low frequency of MOGAD, we anticipate international multicentre collaboration as well as meta-analysis to be core pillars underpinning this field of research. We have recommended key definitions for disease course, disease activity, and sample collection timing in the Supplementary Material of Chapter 2, with the goal of improving consistency of reporting and reducing the impact of between-study heterogeneity in future meta-analyses. Moreover, we encourage the reporting of individual participant data where possible to increase the number of studies eligible for inclusion in future meta-analyses. A significant number of potentially eligible studies were excluded from our meta-analysis because data was reported solely in aggregate format and unable to be extracted.

Further characterisation of serum MOG-IgG titre thresholds, for example, 'negative', 'low positive', 'moderate clear positive', 'high clear positive', and 'very high clear positive', to increase granularity of this biomarker has the potential to improve its clinical usefulness for disease state discrimination. Importantly, such reference thresholds would need to be established for each CBA available globally.

Finally, our findings may be extended to generate a tool capable of algorithmically incorporating individual-level clinical and laboratory parameters to estimate risk of relapse and guide personalised treatment recommendations. This would complement a recently proposed predictive risk score [14].

Concluding Remarks

This work contributes significantly to the landscape of relapse prediction in MOGAD. We demonstrated that relapsing disease course was significantly associated with persistent seropositivity, lower likelihood of seroreversion to MOG-IgG negative status, and delayed seroreversion compared to monophasic individuals. Moreover, serum MOG-IgG titre and CSF WCC effectively discriminated between remission and attack. The common constraint of

limited sample sizes due to rarity of MOGAD incidence was addressed with meta-analysis, which ultimately enabled the proposal of several clinical recommendations with the highest quality evidence available. Additionally, these findings established a framework of key definitions for future studies to adopt, with the goal of improving reporting consistency.

References

1. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004 Dec 11-17;364(9451):2106-12.
2. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med. 2005 Aug 15;202(4):473-7.
3. Lopez JA, Denkova M, Ramanathan S, Dale RC, Brilot F. Pathogenesis of autoimmune demyelination: from multiple sclerosis to neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody-associated disease. Clin Transl Immunology. 2021;10(7):e1316.
4. Trewin BP, Brilot F, Reddel SW, Dale RC, Ramanathan S. MOGAD: A comprehensive review of clinicoradiological features, therapy and outcomes in 4699 patients globally. Autoimmunity Reviews. 2025 2025/01/03/;24(1):103693.
5. Ramanathan S, Mohammad S, Tantsis E, et al. The clinical course, therapeutic responses, and outcomes in relapsing MOG antibody-associated demyelination. Multiple Sclerosis. 2017;23(13):NP1.
6. Huda S, Whittam D, Jackson R, et al. Predictors of relapse in MOG antibody associated disease: a cohort study. BMJ Open. 2021;11(11):e055392.
7. Satukijchai C, Mariano R, Messina S, et al. Factors Associated With Relapse and Treatment of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease in the United Kingdom. JAMA Netw Open. 2022 Jan 4;5(1):e2142780.
8. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain (London, England : 1878). 2017;140(12):3128-38.
9. Trewin BP, Dale RC, Qiu J, et al. Oral corticosteroid dosage and taper duration at onset in myelin oligodendrocyte glycoprotein antibody-associated disease influences time to first relapse. J Neurol Neurosurg Psychiatry. 2024 Oct 16;95(11):1054-63.
10. O'Connell K, Hamilton-Shield A, Woodhall M, et al. Prevalence and incidence of neuromyelitis optica spectrum disorder, aquaporin-4 antibody-positive NMOSD and MOG antibody-positive disease in Oxfordshire, UK. J Neurol Neurosurg Psychiatry. 2020 Oct;91(10):1126-8.
11. de Mol CL, Wong Y, van Pelt ED, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. Mult Scler. 2020 Jun;26(7):806-14.
12. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. The Lancet Neurology. 2023;22(3):268-82.
13. Gastaldi M, Foiadelli T, Greco G, et al. Prognostic relevance of quantitative and longitudinal MOG antibody testing in patients with MOGAD: a multicentre retrospective study. Journal of neurology, neurosurgery, and psychiatry. 2022.
14. Xu Y, Meng H, Fan M, et al. A Simple Score (MOG-AR) to Identify Individuals at High Risk of Relapse After MOGAD Attack. Neurol Neuroimmunol Neuroinflamm. 2024 Nov;11(6):e200309.