REVIEW OPEN ACCESS

Use of Fluid Biomarkers in NMOSD and MOGAD

Clinical and Research Applications

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) are inflammatory disorders of the CNS with distinct immunopathologic mechanisms and treatment responses and partially overlapping clinical phenotypes. The identification of aquaporin-4 (AQP4)-IgG and MOG-IgG has transformed disease classification and diagnosis, enabled a classification of antibody-defined subgroups, and facilitated the development of targeted therapies. However, optimal use of these biomarkers in clinical practice requires careful interpretation within the appropriate clinical and radiologic context. This review synthesizes current evidence on established and emerging fluid biomarkers in NMOSD and MOGAD, with emphasis on analytical performance, biological relevance, and clinical utility. We review antibody detection using cell-based assays, highlighting differences between live and fixed platforms and the impact of antigen conformation on sensitivity and specificity, particularly for MOG-IgG. Common causes of false-positive and false-negative results are discussed, including low-titer reactivity, testing in low pretest probability populations, treatment-related antibody titer reduction, and assay-specific limitations. The diagnostic challenges posed by indiscriminate testing in adult cohorts with multiple sclerosis, in whom disease prevalence markedly exceeds that of MOGAD, are emphasized. We also discuss the role of repeat testing during acute attacks and paired serum-CSF analysis in improving diagnostic confidence when results are equivocal or discordant. Beyond disease-defining antibodies, we examine biomarkers of tissue injury and immune activation. Serum and CSF neurofilament light chain and glial fibrillary acidic protein provide complementary measures of neuroaxonal and astrocytic damage and show associations with attack severity, disease activity, relapse risk, and long-term disability. Cytokines, chemokines, and complement components reflect inflammatory pathways, including IL-6–driven immune activation in NMOSD and MOGAD and complement-mediated astrocytopathy in NMOSD, and may support mechanistic stratification and treatment monitoring in both conditions. We further review the contribution of CSF analysis, neuropathology, genetics, and antigen discovery platforms to refine disease classification, particularly in seronegative or atypical presentations. Finally, we outline priorities for future research, including assay harmonization, standardized sampling protocols, longitudinal biomarker profiling, and integrative multiomic approaches. Collectively,

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Supplementary Material

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Glossary

ADEM = acute disseminated encephalomyelitis; **AQP4** = aquaporin-4; **CBA** = cell-based assay; **GFAP** = glial fibrillary acidic protein; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated disease; **NfL** = neurofilament light chain; **NMOSD** = neuromyelitis optica spectrum disorder; **PML** = progressive multifocal leukoencephalopathy.

advances in biomarker science have the potential to improve diagnostic precision, guide individualized therapeutic strategies, and support de-escalation decisions in NMOSD and MOGAD.

Introduction

Biomarkers are central to understanding the biology of neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody (MOG-IgG)-associated disease (MOGAD) and have reshaped how these diseases are diagnosed and monitored. Beyond the clear diagnostic utility of aquaporin4-IgG (AQP4-IgG) and MOG-IgG, several other biomarkers offer valuable insight into disease activity/mechanisms and potential association with disease activity/course. Serum glial fibrillary acidic protein (GFAP) is emerging as a sensitive marker of astrocytic injury in AQP4-IgG NMOSD, with elevations correlating with relapse severity. Neurofilament light chain (NfL) reflects neuroaxonal damage and rises during acute attacks across multiple inflammatory disorders, including MOGAD. Additional cytokines and chemokines play mechanistic roles in NMOSD and MOGAD pathogenesis and may support prediction of relapse risk or treatment response. Together, these biomarkers form an integrated framework that supports diagnosis and can be used to inform/facilitate therapeutic decisions.[1,2]

The aim of this review was to summarize current knowledge on biomarkers across NMOSD and MOGAD, including diagnostic antibodies and immune and neuroaxonal injury markers. We discuss how these biomarkers relate to the clinical state, the factors that influence test performance/results report, and the causes of both false-positive and false-negative results. This review provides a practical framework for using biomarkers to support accurate diagnosis, monitor disease activity, and guide treatment decisions.

Optimizing Current Assays and Interpretation in Clinical Practice

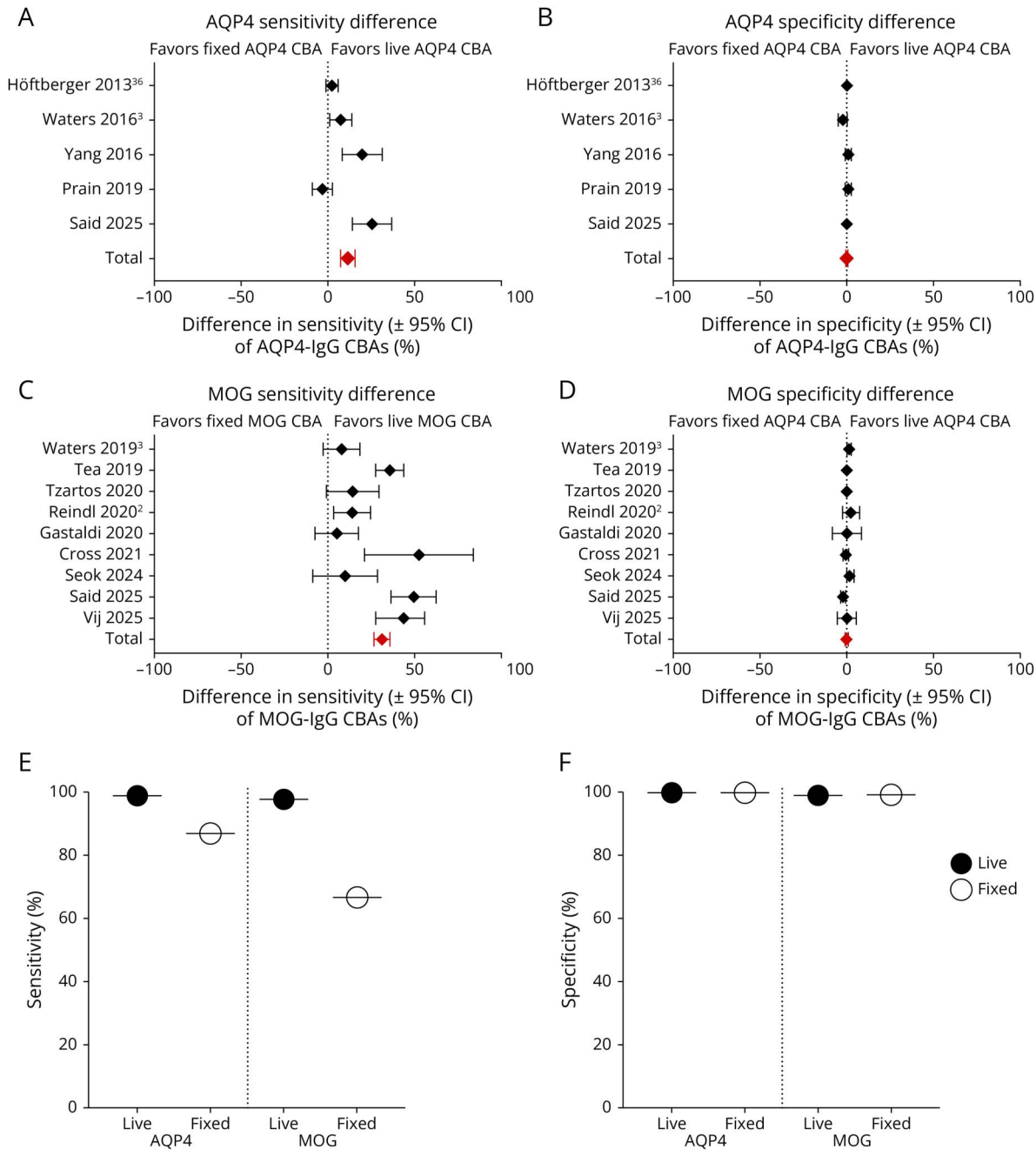
Cell-based assays (CBAs) are the preferred method for detection of both AQP4-IgG and MOG-IgG. ELISA is not recommended for MOG-IgG testing because antibody binding is highly dependent on native antigen conformation.[2] Although ELISA has better performance for AQP4-IgG detection, lower sensitivity and specificity and a higher risk of nonspecific binding in comparison with CBAs have been reported.[3]CBAs differ primarily in whether the antibody in the serum or CSF comes into contact with the antigen before any fixation in live CBAs or after fixation with agents such as formaldehyde, alcohol, or acetone in fixed CBAs.[4] These methodological differences affect antigen conformation and, consequently, test performance.

Agreement between live and fixed cell-based assays is high for both antibodies, but discordance remains clinically relevant. For AQP4-IgG, discordance occurs in ~1 in 25 samples, indicating high specificity with few false positives but reduced sensitivity of fixed assays resulting in false negatives. For MOG-IgG, discordance is higher (~1 in 12), reflecting greater variability in performance; fixed assays show both more false negatives and some false positives. Across both antibodies, false-positive and false-negative results are more frequent in samples with low/borderline antibody titers. Live assays demonstrate higher sensitivity, particularly for MOG-IgG, and are therefore preferred when clinical suspicion is high or results are discordant with the clinical phenotype (Figure 1).[e1-e14]

Direct comparisons of live and fixed assays show meaningful discordance. In 5 blinded studies evaluating 1,302 serum samples for AQP4-IgG, 1,253 (96%) were concordant, comprising 262 AQP4-IgG-positive and 991 negative results. However, 49 samples (approximately 1 in 25) were discordant ($p = 0.0001$, McNemar; Figure 1, A and B). For MOG-IgG, 10 studies assessed 2,223 samples, with 2035 (92%) concordant (297 positive, 1738 negative) and 189 (8.5%; 1 in 12.5) discordant (Figure 1, C and D). Although specificity is high between platforms, the live assay has superior sensitivity, particularly for MOG-IgG (Figure 1 E and F, eTable 1).[e1-e14]

Clinical phenotypes are often used as a pragmatic benchmark when evaluating assay accuracy. This approach considers positive results in patients with compatible presentations as true positives and those with incompatible presentations as false positives, recognizing that technical false positives and low-level antibodies can occur in individuals with and without compatible presentation. Across 5 studies including 306 AQP4-IgG–positive sera from patients with NMOSD-compatible presentations, live assays detected 302 of 306 (99%), including 43 unique positives. Fixed assays detected 266 of 306 (87%), with 6 unique positives. The mean sensitivity difference was 11.8% in favor of live assays (median

Figure 1 Difference in Sensitivity and Specificity of Live and Fixed AQP4-IgG and MOG-IgG Cell-Based Assays



The difference in sensitivity (A) and specificity (B) of live and fixed AQP4-IgG cell-based assays in head-to-head studies is shown. Five studies compared different live AQP4-IgG tests with a commercial fixed AQP4-IgG test. The live tests are 11.8% more sensitive than the fixed tests (supplemental references 1–5). The difference in sensitivity (C) and specificity (D) of live and fixed MOG-IgG cell-based assays in head-to-head studies is shown. Nine studies compared different live MOG-IgG tests with a commercial fixed MOG-IgG test. The live tests are on average 31.1% more sensitive than the fixed tests (supplemental references 1, 6–14). Overview of the sensitivity (E) and specificity (F) of live and fixed AQP4 and MOG assays that have been compared head to head on the same sera across 5 and 9 studies, respectively. Both tests are highly specific.[e1-e14] AQP4 = aquaporin-4; CBA = cell-based assay.

9.7%, range −3.0% to 25.7%). Specificity in 996 controls was comparable: 99.7% (993/996) for live assays and 99.8% (994/996) for fixed assays.[e1-e14]

As with many antibody tests, higher antibody titers measured by CBA improve confidence in results and can support clinical interpretation. However, CBAs have their limitations. They measure antibody binding and not function, serum is more frequently tested rather than CSF, infrequent sampling intervals, comparability across laboratories, and the quantitative limits of resolution of titration, which cannot detect changes <50% of target-specific IgG. Accurate interpretation requires understanding the assay used and its performance characteristics within the local laboratory. Despite their value,

antibody and fluid biomarker results must be interpreted carefully because both false-negative and false-positive findings occur. False negatives arise when antibody levels fall below assay limit for detection, which can happen during remission, after corticosteroids, IV immunoglobulins and, more significantly, after plasma exchange, or when using assays with lower sensitivity. Some data suggest that antibody titers also vary naturally over time, meaning a single negative result cannot reliably exclude NMOSD or MOGAD if the clinical and radiologic features remain suggestive.[5]

False positives present a different challenge. Low-titer or borderline MOG-IgG results may reflect nonspecific binding, the presence of MOG-IgG that can bind to cells overexpressing MOG in the healthy population, background inflammation, or technical issues inherent to certain assays.[6]

Human errors, such as mislabeling, sample handling, contamination, and dilution mistakes, as well as variation in test substrate or microscopes issues, such as bulb intensity or differences in light filter bandwidths used may also contribute to incorrect results. Because these biomarkers carry significant diagnostic and therapeutic implications, unexpected or discordant findings require confirmation and accurate interpretation in light of concomitant clinical and imaging features. Of note, discordance between the biomarker and the clinical and imaging phenotype should prompt re-evaluation rather than unquestioned acceptance of the serologic result.

When fixed CBAs are used, negative results should be followed by repeat testing with a live CBA if clinical or radiologic features are suggestive of MOGAD, as the live tests are more sensitive. False-positive results are more common for MOG-IgG, and testing should therefore be restricted to patients with compatible clinical or MRI features. Because multiple sclerosis is more prevalent than MOGAD in adults, with some variation across genetic backgrounds, indiscriminate testing of typical adult MS cohorts increases the likelihood of false-positive MOG-IgG results and reduces the positive predictive value, particularly in high-prevalence MS settings.[7] False-positive AQP4-IgG results are uncommon with CBAs but may occur at low titers; repeat or longitudinal testing may help clarify clinical relevance.[1]

Antibody Retesting and Monitoring

Diagnostic Implications

Seronegative NMOSD remains a diagnostic challenge. This group likely reflects a heterogenous set of syndromic presentations rather than a single biologically defined entity. Seronegative MOGAD is not recognized as a distinct disease, but some patients with compatible clinical-radiological features may test negative. When alternative diagnoses have been reasonably excluded and clinical suspicion for NMOSD or MOGAD remains high, repeat antibody testing can be useful. Antibodies are more often detected at onset or during acute attacks, and retesting is most informative when performed at the time of new neurologic symptoms. In a recent study of 100 patients with MOGAD tested with live CBA, of which 61 were tested during an acute attack, 4 (6.6%) were initially tested negative.[8] Treatment, especially those directly targeting antibodies, can affect antibody levels: High-dose corticosteroids/IV immunoglobulins and particularly plasma exchange and chronic immunosuppression may reduce antibody levels below detection thresholds. Seroconversion from negative to positive is uncommon and of 933 patients initially testing positive for AQP4-IgG, 830 stayed positive and among 9,308 patients with an initial negative test, only 53 later converted to positive.[9] For this reason, testing is ideally performed at onset before treatment or, if negative at onset and NMOSD/MOGAD are highly suspected, can be repeated at relapse using live CBAs, particularly if onset sample was analyzed after treatment or with less sensitive techniques.

Prognostic Implications

The role of serum antibody monitoring in confirmed AQP4-IgG NMOSD and MOGAD is complex and is partially influenced by the ability of measuring titer rather than function. In NMOSD, AQP4-IgG titers typically rise during relapses and fall during remission, but substantial interindividual and interassay variability exist. Some patients show no clear titer change with clinical activity, others show reduction in serum titers at relapse.[5] At onset, AQP4-IgG titers do not correlate with initial attack severity or final EDSS, although an East Asian study reported higher titers in patients with optic neuritis compared with myelitis after age adjustment.[10] The use of EDSS, which emphasizes ambulation and does not adequately capture visual disability, may partly explain inconsistent correlations. Sequential titers also do not reliably predict the severity of future attacks, although immunosuppression may prevent titer rises during relapses. Early titers at onset show significant but weak associations with annualized relapse rate. More pronounced changes in titers correlate strongly with the number of relapses within the subsequent 6 months, but around half of these changes are not followed by a change in relapse frequency.[10] Most AQP4-IgG–positive patients remain seropositive in the long term. Approximately 103 (11%) serorevert to negative status, a pattern seen mainly in younger individuals with lower baseline titers; however, approximately half of these seroreversions are transient, and relapses may still occur.[9] The proportion of seroreversion to negativity is higher (44, 25.7%) in cohorts in which all patients receive immunosuppressive therapy.[11]

In MOGAD, the significance of MOG-IgG titers varies between children and adults. In children, high-onset titers are more common in acute disseminated encephalomyelitis (ADEM) presentations and in those younger than 5 years. In adults, onset titers tend to be higher in patients with severe visual or motor impairment, but they do not predict long-term relapse risk or disability outcomes.[12] During follow-up, persistently high titers in remission correlate with increased

relapse risk in both children and adults.[5,13] In children, relapse rates are higher in those who remain seropositive compared with those who serorevert,[14] whereas according to some data in adults, relapse risk does not differ according to serostatus.[15] Serial MOG-IgG testing is not currently used in routine practice, and it remains controversial whether this should guide treatment decisions. Persistently high titers after onset may support initiating chronic immunosuppression. Conversely, sustained low titers or seroconversion may support treatment discontinuation in patients who have remained clinically stable for 5 years. However, titers may decline over time regardless of treatment, limiting their reliability as a stand-alone marker of treatment response.[6]

Some recent data reported an association between MOG-IgG epitopes and disease course in MOGAD. In particular, the relapse-free period is shorter in adult patients with non-P42 MOG-IgG, which is a strong predictor of relapsing course in patients with unilateral optic neuritis and is associated with high relapse risk.[16]

Antibody Discovery

The discovery of AQP4-IgG and, more recently, MOG-IgG has been pivotal in distinguishing NMOSD-AQP4+ and MOGAD from other conditions. These antibodies not only delineate distinct disease entities but also illuminate underlying mechanisms and therapeutic targets. Nevertheless, a subset of patients with NMOSD-like or MOGAD-like syndromes, including ADEM, remain seronegative.[e15] Their close clinical and radiologic resemblance to antibody-positive disease suggests that antibody-mediated processes may still be involved and that additional, as yet unidentified, pathogenic antibodies likely exist, such as the recently described MOG-IgA antibodies underlie distinct subgroups of double seronegative patients.[17,e16] Tissue-based assays have been among the most effective tools for discovering novel autoantibodies. Immunohistochemistry on rodent brain tissue enables detection of serum or CSF antibodies that bind conformational extracellular epitopes on neurons or glial cells. When characteristic staining patterns emerge, immunoprecipitation followed by mass spectrometry can identify candidate antigens, which are then validated using cell-based assays.[e17] This approach has underpinned the discovery of some neuronal surface antibodies in autoimmune encephalitis. In some instances, antigen identification can be guided solely by the anatomical distribution of immunoreactivity, as demonstrated for AQP4.[18] However, tissue-based methods are limited when antibodies recognize species-specific epitopes that are poorly conserved in rodents; MOG-IgG illustrates this because it binds stronger to human than rodent MOG,[19] although a substantial proportion of human MOG-IgG also bind to rodent MOG.[20]

Other antigen discovery platforms, phage display, protein microarrays, and yeast display have also identified novel targets.[21-23] Phage display screens antibodies against peptides expressed on bacteriophages, but the alteration of native folding and post-translational modifications restricts detection of conformational epitopes.[22] Protein microarrays present large numbers of immobilized proteins, often denatured or intracellular, limiting identification to linear or nonsurface epitopes.[22] Yeast display offers improved structural preservation by expressing antigens on the yeast cell surface, although its application in neuroimmunology remains limited.[23] Because these methods generally cannot present antigens in native conformation, they tend to detect antibodies against linear or intracellular targets,[21] which are less likely to be pathogenic. While technological advances are essential for identifying new antigens, meticulous clinical and radiologic phenotyping remains indispensable. Detailed characterization of seronegative patients with highly suggestive clinical/biomarkers/pathologic features is crucial for steering antigen discovery efforts and prioritizing cases for comprehensive immunologic investigation.

CSF Analysis

In NMOSD, CSF cell counts can vary widely and may include lymphocytes, neutrophils, or eosinophils, with elevated pleocytosis reaching up to 1,000 cells/mm^3 in some cases. Oligoclonal bands (OCBs) are found in approximately 30–40% of patients and may be transient. In MOGAD, CSF white cell counts are also variably elevated, typically with a lymphocytic predominance and might be also influenced by infectious triggers. A white blood cell count greater than 50 is not uncommon in MOGAD, sometimes with values exceeding 100–200 that can mimic CNS infections. OCBs are rare, occurring in up to 15% of cases, and can be transient.[24] Kappa free light chain (k-FLC) may aid in differentiating between MS, NMOSD, and MOGAD. Marked elevations favor MS over MOGAD, although smaller increases may be seen across all conditions. Optimal k-FLC index cutoffs of 18.5 (MS vs MOGAD) and 12.1 (MS vs NMOSD) have recently been proposed, offering diagnostic performance comparable with oligoclonal bands.[25] Polyspecific antiviral antibody responses against measles, rubella, or varicella are uncommon in NMOSD (1/12, 8%) and MOGAD (7/33, 21%), in contrast with their higher frequency in MS (48/96, 50%).[26]

CSF-only detection of anti-AQP4 antibodies is rare, with only isolated cases reported, in some cases with a noncompatible phenotype.[27] Larger cell-based assay cohorts confirm that isolated CSF AQP4-IgG positivity and intrathecal AQP4-IgG synthesis are uncommon (1/23, 4.3%) and that CSF testing in seronegative individuals provides limited additional diagnostic yield.

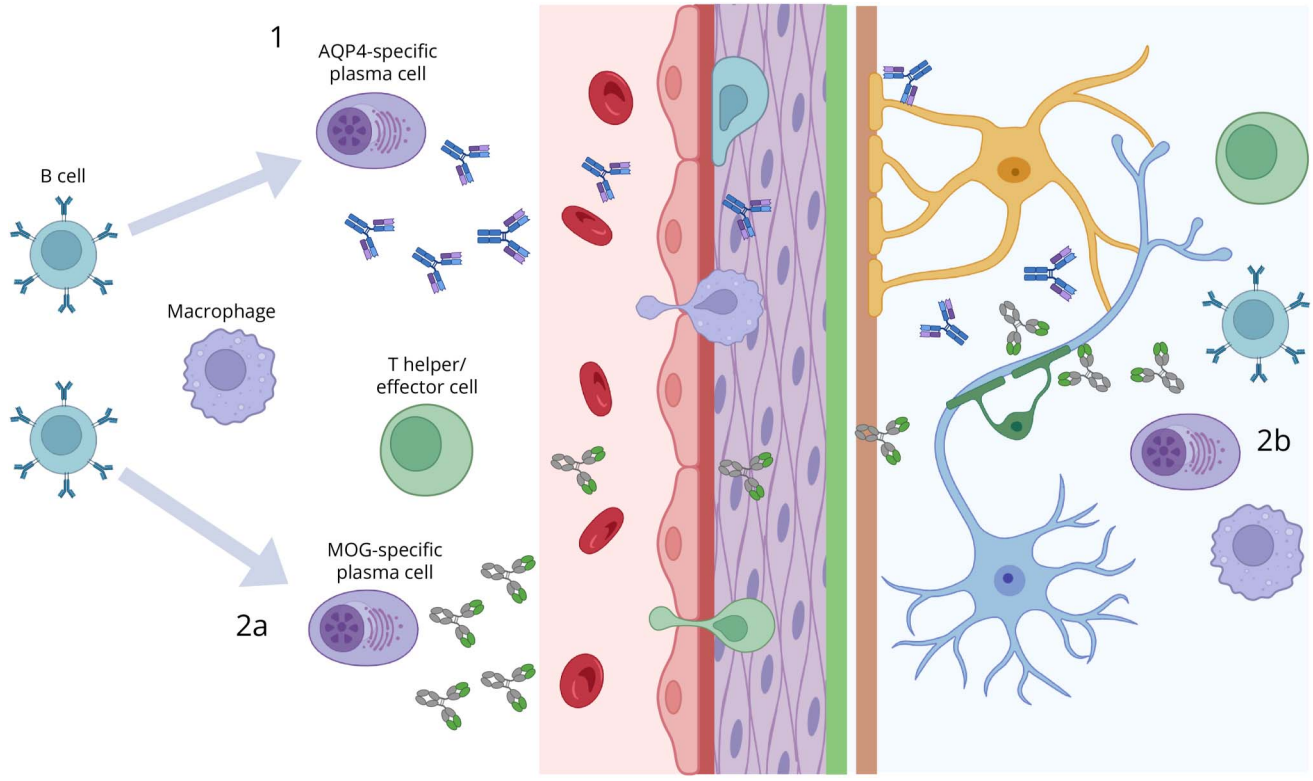
Although contradictory data have been reported in the literature, paired serum/CSF MOG-IgG positivity can occur in 5 of 28 (18%) to up to 66 of 74 (89%) cases with MOGAD. Isolated CSF positivity is reported in 0 to up to 9 of 83–31 of

255 (11–12%) cases, giving an overall sensitivity of 90%, specificity of 98–99%, and PPV of 98% for diagnosis in an appropriate clinical context. CSF-only MOG-IgG is more often observed in adults and in patients with brain/spinal cord involvement and is linked with poorer outcomes, while paired positivity correlates with greater disability at nadir. In cases of low-positive serum results, CSF positivity supports a true-positive finding, and paired testing can help distinguish false-positive serum results by increasing diagnostic confidence.[27-30] A single neuropathologic case with isolated CSF MOG-IgG has been reported, describing a compatible pathologic phenotype.[31] However, one study reported a very low rate of CSF-only MOG-IgG positivity (7/1,016, 0.7%), often associated with alternative diagnoses (4/7 cases), with low sensitivity (2.63%) and PPV (1.97%).[32] CSF-only positivity is also rare in children and may indicate alternative diagnoses, including MS.[33] Technical issues and methodological difference can explain these discordant findings, with international standardization needed. Current criteria suggest that CSF-restricted MOG-IgG supports a diagnosis of MOGAD only when accompanied by a core demyelinating event, AQP4-IgG seronegativity, ≥1 supporting clinical/MRI feature, and exclusion of alternative diagnoses, similar to patients with low or unconfirmed serum titers.[34] Figure 2 reports a model for AQP4-IgG and MOG-IgG immunopathology showing AQP4-IgG and MOG-IgG production by peripheral plasma cells with immune cell cooperation. Inflammation and blood-brain barrier damage facilitate their access to CNS. Intrathecal MOG-IgG production can also occur. After entering the CNS, AQP4-IgG targets astrocyte AQP4 channels, while MOG-IgG targets myelin/oligodendrocytes.

Pathology

Because the diagnosis of MOGAD and NMOSD is based on clinical criteria, MRI features, and detection of MOG-IgG or AQP4-IgG, brain/spinal cord biopsy is rarely indicated and is generally reserved for atypical or tumefactive presentations to exclude mimics.[35] Because biopsy samples are typically small and may capture only part of a lesion, interpretation can be challenging. Diagnostic yield is optimized by sampling active lesion areas, ideally including the lesion edge, and by avoiding or pausing corticosteroid treatment beforehand.

Figure 2 Proposed Model for AQP4-IgG and MOG-IgG Immunopathology



Proposed model for AQP4-IgG (1) and MOG-IgG (A, B) immunopathology showing B-cell differentiation into plasma cells, cooperation of T helper cells, macrophages, and T effector cells. AQP4 antibodies are mainly produced in the periphery and enter the CNS through areas of physiologically increased permeability or by extracellular pathways, supported by local inflammation and blood-brain barrier damage. AQP4-IgG then bind to the AQP4 water channel, primarily located on the endfeet of astrocytes (1). A similar process occurs in MOGAD, with MOG-specific plasma cells producing MOG-IgG in the periphery and then entering the CNS (A). However, intrathecal production of MOG-IgG can also occur (B), as demonstrated by cases with CSF only MOG-IgG positivity. The main target of MOG-IgG is MOG, located in the outermost surface of the myelin sheath and the plasma membrane of oligodendrocytes (Created in BioRender. Mariotto, S (2026) BioRender.com/a910w9q). AQP4 = aquaporin-4; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; NMOSD = neuromyelitis optica spectrum disorder.

Early AQP4-IgG–positive NMOSD lesions are characterized by astrocyte loss (Figure 3, A and B) with reduced AQP4 immunoreactivity, prominent edema, astrocytic dystrophy with clasmatodendrosis, which is a degenerative change in astrocytes characterized by swelling of the cytoplasm and retraction, clumping, and beading of their processes (Figure 3B), and perivascular and/or subpial deposition of the terminal complement complex C9neo in a rosette or rim pattern. Inflammatory infiltrates include granulocytes and eosinophils alongside macrophages (Figure 3C), abundant T cells, and perivascular B cells and plasma cells.[36] In later lesion stages, C9neo deposition may be absent, whereas C4d deposition at the glia limitans may persist (Figure 3D).[37]

MOGAD shows a spectrum of demyelinating pathology ranging from purely perivenous (ADEM-like) lesions to mixed perivenous and confluent white matter demyelination (Figure 3, E and F), often with intracortical or subpial involvement.[35,38,39] A notable feature is relative preservation of oligodendrocyte lineage cells, consistent with frequent and sometimes complete remyelination, also supported by MRI evidence of lesions resolution (Figure 3G). Macrophages are present in perivascular spaces and demyelinating areas and only rarely form a lesion rim, except in tumefactive cases. Inflammatory infiltrates are dominated by $CD4^+$ T cells, which outnumber $CD8^+$ T cells (Figure 3, H and I), and granulocytes may also be present. Astrocytes show reactive gliosis with preserved AQP4 expression. In a subset of cases, deposition of C9neo together with strong C4d staining is observed in actively demyelinating areas, supporting a humoral-mediated disease mechanism.[37]

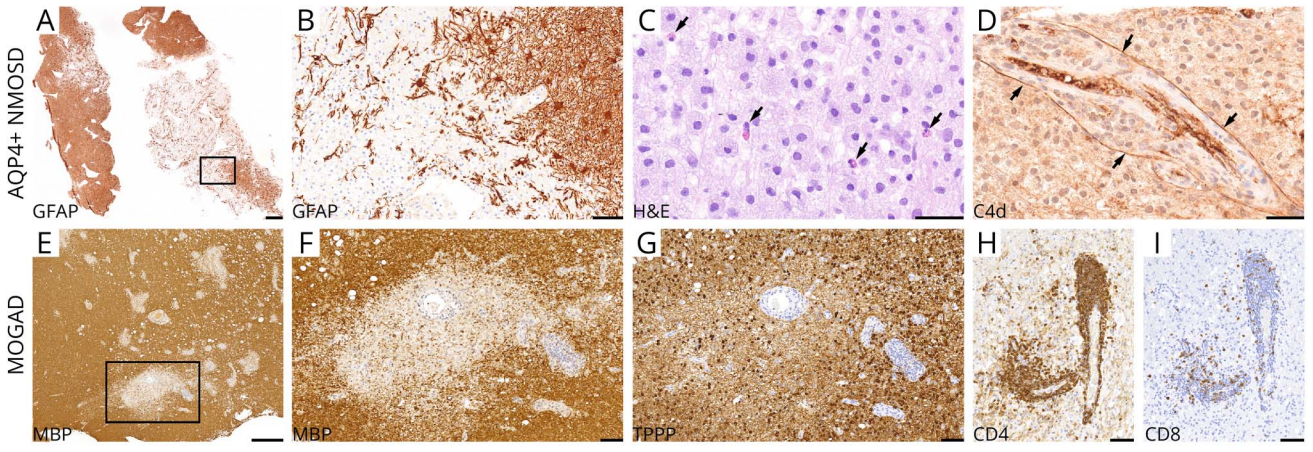
In routine practice, the neuropathologic workup of inflammatory white matter biopsies begins with exclusion of a neoplasm. Histochemistry and immunohistochemistry for myelin, axons, and macrophages establish the demyelinating nature of a lesion. In challenging cases, particularly small biopsies with prominent gliosis, molecular analyses such as DNA methylation profiling or targeted gene panels may be required to exclude glioma. Demyelination may also be encountered in addition to MS, in infectious disease such as progressive multifocal leukoencephalopathy (PML), genetic disorders such as Alexander disease or other leukodystrophies, and in sentinel lesions of lymphoma. PML is suggested by bizarre astrocytes and confirmed by JC virus immunohistochemistry, while abundant Rosenthal fibers favor diagnoses such as pilocytic astrocytoma or Alexander disease.

In cases with ADEM-like pathology and dense perivascular inflammation, differentiation from a lymphoproliferative disease, vasculitis, or viral encephalitis may be difficult. Ancillary studies, including B-cell markers, Ki-67, EBV in situ hybridization, clonality testing, and CSF-based liquid biopsy approaches, can enable rapid diagnosis of CNS lymphoma.[e18] When first-line pathogen testing is negative, metagenomic next-generation sequencing increases diagnostic yield in CNS biopsies.[e19] Necrosis may be seen in NMOSD but is rare in MOGAD, and alternative diagnoses such as necrotizing encephalitis or infarction should then be considered.

Neuronal, Axonal, Glial, and Immune Fluid Biomarkers

Body fluid biomarkers have substantial potential for improving diagnosis, prognosis, stratification, and treatment monitoring in NMOSD and MOGAD. Progress, however, is

Figure 3 NMOSD and MOGAD Neuropathology



A stereotactic biopsy of a patient with AQP4+ NMOSD shows an inflammatory white matter lesion with loss of astrocytes and some dystrophic astrocytes at the lesion border (A, B, GFAP; rectangle in A enlarged in B). The inflammatory infiltrates are characterized by many foamy macrophages, lymphocytes, and significant numbers of eosinophils (C, H&E; arrows). Complement C4d deposition shows a rim pattern at the perivascular glia limitans (D, C4d; arrows). A biopsy specimen of a patient with MOGAD shows prominent perivascular demyelination (E, F, MBP; rectangle in E enlarged in F) with considerable preservation of oligodendrocytes (G, TPPP). The inflammatory infiltrates are characterized by abundant $CD4^+$ T cells (H) that outnumber $CD8^+$ T cells (I). Scale bars: A, E: 400 mm; B, F, G–I: 80 mm; C, D: 40 mm. AQP4 = aquaporin-4; GFAP = glial fibrillary acidic protein; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; NMOSD = neuromyelitis optica spectrum disorder.

constrained by limited standardization of biobanking and assay validation, which undermines reproducibility and cross-center comparability. Standardized CSF and serum acquisition, processing, and storage, guided by existing lumbar puncture recommendations and CSF/serum handling frameworks, are essential to minimize preanalytical variability, particularly in multicenter studies.[e20] The BioMS-eu consortium provides widely adopted protocols for harmonized sample collection and exchange across neurologic diseases. Although some biomarkers (e.g., antibodies and selected cytokines) are relatively stable, uniform processing remains preferable. Figure 4 presents the utility of different blood and CSF biomarkers in NMOSD and MOGAD.

Neural Biomarkers

Among emerging candidates, NfL[40] and GFAP[41] are the most extensively studied. Preanalytical assessments indicate that serum NfL and GFAP are largely unaffected by common handling variations.[42] The Global Biomarker Standardization Consortium recently issued an evidence-based protocol for blood biomarker handling whose principles, time-to-processing limits, controlled freeze-thaw cycles, and batch consistency apply broadly to neuroimmunologic research. As biomarkers transition toward clinical use and clinical trials, adherence to harmonized procedures will be critical for ensuring reliability, enabling cross-center comparison, and validating emerging markers. Moreover, as new analytical platforms enter the market, it is crucial that NfL and GFAP measurements are standardized. Recent work using serum samples proposes standardized windows: in NMOSD, 4 weeks after attack for NfL and 1–8 weeks for GFAP to characterize relapse activity and >6 months for remission assessments.[43] In MOGAD, peak NfL and GFAP levels occur at 6 and 5 weeks after the attack, with steady state reached at 4.7 and 4.2 months, respectively.[44] External validation is required before these timings can inform clinical management or trial design. Of note, using the Z-score, which considers adjustment for age/BMI[e21] based on data from a large reference cohort, rather than absolute values helps to achieve most accurate measurements.[e22]

Diagnostic Implications

Markers of astrocytic and oligodendrocytic injury may also support differential diagnosis. In seropositive NMOSD, higher CSF-GFAP distinguishes the disease from other neurologic conditions, including seronegative NMOSD.[45,46] In MOGAD, elevated CSF-MBP without astrocytic damage points to primary oligodendrocyte involvement. Using advanced technologies, serum GFAP increase is quite specific for NMOSD, although it can increase in MS in correlation with disease progression.[45,e24] Of note, CSF GFAP levels increase has been demonstrated also in GFAP autoimmunity, with similar levels as those detected in seropositive NMOSD.[e25] Tau elevations during MOGAD relapses without parallel NfL changes suggest oligodendrocytopathy, although these observations require replication.[45] However, specific diagnostic threshold has not been identified as well as clear diagnostic advantage to antibody testing.

Prognostic Implications

Some data also show that these biomarkers have possible predictive value across MOGAD and AQP4-NMOSD. In NMOSD, attack-phase sNfL predicts long-term disability,[47] while remission sGFAP levels higher than 170 μg/mL have been linked to increased relapse risk,[48] although this association was not reproduced in a retrospective cohort that used different remission definitions.[43] In MOGAD, sNfL independently predicted future relapses in an 89-patient multicenter study, and in both MOGAD and NMOSD, higher sNfL correlates with subsequent disability outcomes.[48,49] GFAP also relates to current disability in MOGAD[49] and current/future disease activity in NMOSD.[50] CSF 14-3-3 levels have been associated with higher EDSS scores.[51]

Immune Biomarkers

Cytokine profiling shows consistent upregulation of Th1 (IFN-γ, TNF-α, and IP-10) and Th17 (IL-6, IL-8, and GM-CSF) pathways, along with IL-1ra, MCP-1, MIP1-α, and MIP1-β in both conditions and support differential diagnosis with MS. MOGAD additionally features increases in IL-10 and B-cell cytokines (BAFF, APRIL, BCL/CXCL13, and CCL19). IL-6 is the most consistently associated cytokine, correlating with disease activity and severity.[52] Raised CSF IL-6 can be seen across a range of primary and secondary neuroinflammatory disorders,[53] and while the diagnostic specificity is low, it may support treatment decisions. On this basis, anti-IL6R treatment has been approved for the treatment of NMOSD, and an ongoing trial is evaluating its effect in MOGAD, supported by its reported effect in reducing relapse probability in MOGAD.[e26] Serum and CSF IL6 are elevated in MOGAD, similarly to NMOSD and differently from MS, further supporting its role in both these conditions.[54,e27] Furthermore, recent evidence has shed light on distinct immune signatures and dysregulated B-cell responses in MOGAD.[55]

Complement-dependent cytotoxicity is a primary pathobiological mechanism in AQP4-Ab NMOSD,[e15] with anti-complement medication shown to prevent relapses and disability and support attack recovery.[56] Although complement is one of the activated pathways also in MOGAD,[19] the MAC formation is lower, particularly in patients with milder attacks.[57] In MOGAD, CSF-C5b-9 correlates with attack severity measured with EDSS and predicts long-term confirmed EDSS 3.0, whereas CSF C4a/4 predicts relapses.[58] Complement-mediated cell injury could be a prognostic biomarker in NMOSD also because attack severity correlates with sera complement-activating activity.

Genetics

The genetic architecture of NMOSD is less well characterized than in MS, but reports of familial clustering support a possible heritable component.[59] Differences in reported HLA associations likely reflect population allele frequency variation

Figure 4 Blood and CSF Biomarkers in NMOSD and MOGAD (s = serum)

Biomarkers	Disease	Diagnosis utility	Clinical/prognostic utility
GFAP, NFL, MBP, TAU, UCH-L1	NMOSD	↑ sGFAP vs other inflammatory CNS conditions ↑ sTau vs seronegative NMOSD ↑ sUCH-L1 vs seronegative NMOSD	• sNfL and sGFAP increase during attacks and reduce after treatments • sNfL during attacks correlates with disability and may predict disability worsening • sGFAP at attacks correlates with disability • sGFAP at remission may predict relapses (conflicting data)
	MOGAD	↑ CSF-MBP (not specific) ↑ s-Tau (need further confirmation)	• sNfL during attacks correlates with disability and may predict future relapses/outcome • sGFAP during attacks correlates with disability
Cytokines	NMOSD and MOGAD	↑ IL-6, IL-8, GM-CSF, IL-10, IFN-γ, TNF-α, IP-10, IL-1ra, MIP1-α, MIP1-β, MCP-1 vs MS (in CSF)	• s and CSF-IL-6 and IL-17 are increased during NMOSD relapses • s and CSF-IL-6 are associated with disability in NMOSD and may predict relapses • sIL-6, BAFF, CXCL10, IL-10 are associated with disease severity in non-ON MOGAD • sBAFF may predict disease course in MOGAD
Complement factors	NMOSD	↑ C1q, C1s, C5, FH, sC5b-9, C10-inhibitor in serum	• sC3, C4, C5b-9 are elevated during attacks • sC3a correlates with disability
	MOGAD	↑ C3a (need further confirmation) CSF ↑ C5a (need further confirmation) CSF	• CSF C5b-9 is associated with more severe attacks and long-term disability • CSF C4a and C4a/C4 ratio are associated with relapse and may predict relapses
Other biomarkers	NMOSD	↑ Serum interleukin-2 receptor (sIL-2R) (needed further confirmation) ↑ sTREM2	
	MOGAD	↑ Serum interleukin-2 receptor (sIL-2R) (needed further confirmation)	• Serum interleukin-2 receptor (sIL-2R) at onset may predict relapses (needed further confirmation) • Serum homocystein may predict relapses and poor recovery • sTREM2 may be related to worse disabilty (needed for validation)

MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; NMOSD = neuromyelitis optica spectrum disorder

and disease heterogeneity, with many earlier studies underpowered to examine AQP4-IgG–positive cases separately. More recent analyses have strengthened the evidence base: A Korean study comparing AQP4-IgG–positive NMOSD patients with healthy controls[e28] confirmed HLA-DRB103:01 as the principal risk allele, consistent with the findings from a Dutch cohort.[e29] The Korean study also showed that the HLA-DRB112:02–DQB1*03:01 haplotype was associated with spinal involvement, greater nadir severity, and shorter time to second attack.

By contrast, no consistent HLA associations have been identified for MOGAD. Studies from the United Kingdom[e30] and the Netherlands[e29] involving predominantly European

patients reported no significant HLA class II associations. The Dutch cohort noted a lower (nonsignificant) frequency of HLA-A68, while the UK study found a reduced prevalence of HLA-C03:04. A study of Han Chinese patients, however, identified the HLA-DQB105:02–DRB116:02 haplotype as a pediatric-specific MOGAD risk factor associated with more severe attacks and a multiphasic disease course.[e31]

In double-seronegative patients, especially in children, monogenic neuroinflammatory disorders should also be considered.[60] Conditions such as type I interferonopathies, cytotoxic T-lymphocyte antigen 4 haploinsufficiency, missense variants in RAN binding protein 2–associated acute necrotizing encephalopathy, deficiency of adenosine deaminase 2, retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations, Coats-plus, fas-associated death domain–associated disease, familial hemophagocytic lymphohistiocytosis, and biotinidase deficiency may mimic NMOSD or MOGAD with recurrent optic neuritis, longitudinally extensive myelitis, encephalopathy, or stroke-like episodes. Early recognition is essential to avoid misclassification and enable timely genetic evaluation.

Future Directions

The growing recognition of NMOSD and MOGAD has coincided with expanding access to antibody assays, advanced imaging, and emerging fluid biomarkers. Future work must focus on harmonizing assay platforms through international standardization initiatives, establishing consensus thresholds for positivity, defining context-specific reporting standards, and developing a universally accessible accurate assay. For MOG-Ab in particular, coordinated efforts are needed to align live and fixed CBAs, calibrate quantitative readouts, and incorporate confirmatory strategies such as paired CSF-serum analysis when clinical suspicion is high. Finally, reducing barriers to antibody testing in underserved areas of the Global South, where NMOSD and MOGAD are likely underdiagnosed and potentially more prevalent than in Western populations, is essential. Dry blood or plasma spot approaches may help improve accessibility of diagnostic testing.[54,e32]

Longitudinal serologic and biomarker studies may help stratify relapse risk, guide de-escalation decisions, and identify subgroups with distinct immunopathologic pathways. Machine learning approaches integrating antibody titers, cytokine signatures, and structural/functional MRI metrics may, in time, support individualized prognostication, select prominent pathogenic mechanisms also useful for drug selections, and support personalized treatment algorithms and may help clarify the relevance of subclinical disease activity in these diseases for overall prognosis.

Biomarker discovery is a major future direction. Serum GFAP and NfL are promising indicators of astrocytic and neuroaxonal injury and may help confirming NMOSD relapses, assess acute attack severity, and evaluate treatment response. Multiomic technologies, transcriptomics, single-cell immune profiling, and proteomics offer the potential to identify molecular endotypes that bridge the gap between seropositive and seronegative diseases. Such work may ultimately reveal novel antigens, immunologic circuits, or genetic susceptibilities that permit diagnostic reclassification and targeted therapy selection. Moreover, extended biomarker research will provide novel insights into pathomechanisms and environmental determinants of these diseases. A nonexhaustive list of examples comprises the recent description of MOG-IgA or IgG3 antibodies in few patients with demyelinating CNS diseases[17]; research into the importance of the microbiome in driving CNS autoimmunity; and the role of the aryl hydrocarbon receptor as a critical link between the exposome, the gut, and the CNS.[e33]

Therapeutic strategies will also evolve. For AQP4-IgG NMOSD, complement inhibition, IL-6 receptor blockade, and B-cell depletion have transformed relapse prevention. Defining which seronegative phenotypes benefit from these mechanisms is a priority. For MOGAD, the absence of proven preventive therapies underscores the need for controlled trials informed by biological markers of relapse risk. Ongoing trials are exploring the effect of anti-IL6R, anti-neonatal FC receptor, azathioprine, anti-CD20, and anti-CD19 CAR-T treatment and will hopefully lead to approved treatments. Extracellular vesicles showed a possible role in the pathogenesis of several CNS disorders, including immune-mediated ones, and might be used as surrogate promising differential diagnosis markers and as carriers for biochemical molecules acting as potential targeted therapy. The potential for treatment tapering or discontinuation, particularly in monophasic disease or in patients who serorevert to antibody negative, requires rigorous study within prospective cohorts.

Finally, future research should address diagnostic and therapeutic uncertainty in atypical or mixed neuroinflammatory presentations. Integration of advanced neuroimaging modalities, genetic testing pathways, and biomarker panels may reduce reliance on empiric immunotherapy, prevent misclassification, and support precision treatment decisions. Multicenter consortia (like the MEDEN network), pediatric-adult harmonization efforts, and large-scale biobanks will be central to these goals.

Author Contributions

S. Mariotto: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data; A. Cobo-Calvo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data; M. Khalil: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; T. Armangue: drafting/revision of the manuscript for content, including medical writing for content;

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References

1. Sechi E. NMOSD and MOGAD. *Continuum (Minneap Minn)*. 2024;30(4):1052-1087. doi:10.1212/CON.0000000000001454

2. Reindl M, Schanda K, Woodhall M, et al. International multicenter examination of MOG antibody assays. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(2):e674. doi: 10.1212/NXI.0000000000000674
3. Waters P, Reindl M, Saiz A, et al. Multicentre comparison of a diagnostic assay: aquaporin-4 antibodies in neuromyelitis optica. *J Neurol Neurosurg Psychiatr*. 2016; 87(9):1005-1015. doi:10.1136/jnnp-2015-312601
4. Waters PJ, McKeon A, Leite MI, et al. Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. *Neurology*. 2012;78(9):665-669; discussion 669. doi:10.1212/WNL.0b013e318248dec1
5. Nasello M, Woodhall M, Xue H, et al. Quantitative analysis of aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) antibodies titres: correlation with relapses. *Brain Commun*. 2025;7(5):fcaf312. doi:10.1093/braincomms/fcaf312
6. Sechi E, Buciuc M, Pittock SJ, et al. Positive predictive value of myelin oligodendrocyte glycoprotein autoantibody testing. *JAMA Neurol*. 2021;78(6):741-746. doi: 10.1001/jamaneurol.2021.0912
7. Wendel EM, Thonke HS, Bertolini A, et al. Temporal dynamics of MOG antibodies in children with acquired demyelinating syndrome. *Neurol Neuroimmunol Neuroinflamm* 2022;9(6):e200035. doi:10.1212/NXI.0000000000200035
8. Kim KH, Kim S-H, Park NY, Hyun J-W, Kim HJ. Validation of the international MOGAD panel proposed criteria. *Mult Scler* 2023;29(13):1680-1683. doi:10.1177/ 13524585231198754
9. Majed M, Valencia Sanchez C, Bennett JL, et al. Alterations in aquaporin-4-IgG serostatus in 986 patients: a laboratory-based longitudinal analysis. *Ann Neurol*. 2023; 94(4):727-735. doi:10.1002/ana.26722
10. Akaishi T, Takahashi T, Nakashima I, et al. Repeated follow-up of AQP4-IgG titer by cell-based assay in neuromyelitis optica spectrum disorders (NMOSD). *J Neurol Sci*. 2020;410:116671. doi:10.1016/j.jns.2020.116671
11. Wang Z, Tan H, Huang W, et al. Fluctuations in serum aquaporin-4 antibody titers: the clinical significance in neuromyelitis optica spectrum disorder. *J Neurol*. 2025; 272(6):403. doi:10.1007/s00415-025-13137-6
12. Cobo-Calvo A, Sepúlveda M, Rollot F, et al. Evaluation of treatment response in adults with relapsing MOG-Ab-associated disease. *J Neuroinflammation*. 2019;16(1): 134. doi:10.1186/s12974-019-1525-1
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. *J Neurol Neurosurg Psychiatr*. 2023;94(3):201-210. doi:10.1136/jnnp-2022-330237
14. Waters P, Fadda G, Woodhall M, et al. Serial anti-myelin oligodendrocyte glycoprotein antibody analyses and outcomes in children with demyelinating syndromes. *JAMA Neurol*. 2020;77(1):82-93. doi:10.1001/jamaneurol.2019.2940
15. Cobo-Calvo A, Ruiz A, Rollot F, et al. Clinical features and risk of relapse in children and adults with myelin oligodendrocyte glycoprotein antibody-associated disease. *Ann Neurol*. 2021;89(1):30-41. doi:10.1002/ana.25909
16. 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. *J Neurol Neurosurg Psychiatr*. 2024;95(6):544-553. doi:10.1136/jnnp-2023-332851
17. Ayroza Galvão Ribeiro Gomes AB, Kulsvehagen L, Lipps P, et al. Immunoglobulin A antibodies against myelin oligodendrocyte glycoprotein in a subgroup of patients with central nervous system demyelination. *JAMA Neurol*. 2023;80(9):989-995. doi: 10.1001/jamaneurol.2023.2523
18. 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; 202(4):473-477. doi:10.1084/jem.20050304
19. Wetzel NS, Kulsvehagen L, Lecourt A-C, et al. Patient-derived monoclonal myelin oligodendrocyte glycoprotein autoantibodies mediate cytotoxicity. *Neurol Neuroimmunol Neuroinflamm*. 2026;13(1):e200520. doi:10.1212/NXI.0000000000200520
20. Sepúlveda M, Armangue T, Martinez-Hernandez E, et al. Clinical spectrum associated with MOG autoimmunity in adults: significance of sharing rodent MOG epitopes. *J Neurol*. 2016;263(7):1349-1360. doi:10.1007/s00415-016-8147-7
21. Mandel-Brehm C, Benson LA, Tran B, et al. ZSCAN1 autoantibodies are associated with pediatric paraneoplastic ROHHAD. *Ann Neurol*. 2022;92(2):279-291. doi: 10.1002/ana.26380
22. McKeon A, Lesnick C, Vorasoot N, et al. Utility of protein microarrays for detection of classified and novel antibodies in autoimmune neurologic disease. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(5):e200145. doi:10.1212/NXI.0000000000200145
23. Chao G, Lau WL, Hackel BJ, Sazinsky SL, Lippow SM, Wittrup KD. Isolating and engineering human antibodies using yeast surface display. *Nat Protoc*. 2006;1(2): 755-768. doi:10.1038/nprot.2006.94
24. Flanagan EP. Neuromyelitis optica spectrum disorder and other non-multiple sclerosis central nervous system inflammatory diseases. *Continuum (Minneap Minn)*. 2019;25(3):815-844. doi:10.1212/CON.0000000000000742
25. Tan H, Deng X, ZhangBao J, et al. KFLC-index distinguishes multiple sclerosis from anti-myelin oligodendrocyte glycoprotein and aquaporin 4 diseases in a Chinese cohort. *J Neurol Neurosurg Psychiatr*. 2025;96(12):1175-1184. doi:10.1136/jnnp-2025-335953
26. D'Cunha MA, Pandit L, Sudhir A. MRZ-reaction maybe influenced by immunization status and is not exclusive to multiple sclerosis. *J Neurol Sci*. 2025;468:123365. doi: 10.1016/j.jns.2024.123365
27. Redenbaugh V, Fryer JP, Cacciaguerra L, et al. Diagnostic utility of MOG antibody testing in cerebrospinal fluid. *Ann Neurol*. 2024;96(1):34-45. doi:10.1002/ana.26931
28. Mariotto S, Gajofatto A, Batzu L, et al. Relevance of antibodies to myelin oligodendrocyte glycoprotein in CSF of seronegative cases. *Neurology*. 2019;93(20): e1867-e1872. doi:10.1212/WNL.0000000000008479
29. Carta S, Cobo Calvo Á, Armangué T, et al. Significance of myelin oligodendrocyte glycoprotein antibodies in CSF: a retrospective multicenter study. *Neurology*. 2023; 100(11):e1095–e1108. doi:10.1212/WNL.0000000000201662
30. Matsumoto Y, Kaneko K, Takahashi T, et al. Diagnostic implications of MOG-IgG detection in sera and cerebrospinal fluids. *Brain*. 2023;146(9):3938-3948. doi: 10.1093/brain/awad122
31. Carta S, Höftberger R, Bolzan A, et al. Antibodies to MOG in CSF only: pathological findings support the diagnostic value. *Acta Neuropathol*. 2021;141(5):801-804. doi: 10.1007/s00401-021-02286-3
32. Reynolds M, Tan I, Nguyen K, et al. The clinical relevance of MOG antibody testing in cerebrospinal fluid. *Ann Clin Transl Neurol*. 2024;11(9):2514-2519. doi:10.1002/ acn3.52163
33. Olivé-Cirera G, Bruijstens AL, Fonseca EG, et al. MOG antibodies restricted to CSF in children with inflammatory CNS disorders. *Neurology*. 2024;102(7):e209199. doi: 10.1212/WNL.0000000000209199
34. Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. *Lancet Neurol*. 2023;22(3):268-282. doi:10.1016/S1474-4422(22)00431-8
35. Höftberger R, Guo Y, Flanagan EP, et al. The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody. *Acta Neuropathol*. 2020;139(5):875-892. doi:10.1007/s00401-020-02132-y
36. Misu T, Höftberger R, Fujihara K, et al. Presence of six different lesion types suggests diverse mechanisms of tissue injury in neuromyelitis optica. *Acta Neuropathol*. 2013; 125(6):815-827. doi:10.1007/s00401-013-1116-7
37. Landt C, Held F, Kolotourou K, et al. Complement c4d informs the differential diagnosis of inflammatory demyelinating CNS diseases. *Neurol Neuroimmunol Neuroinflamm*. 2026;13(2):e200528. doi:10.1212/NXI.0000000000200528
38. Takai Y, Misu T, Kaneko K, et al. Myelin oligodendrocyte glycoprotein antibody-associated disease: an immunopathological study. *Brain*. 2020;143(5):1431-1446. doi:10.1093/brain/awaa102
39. Valencia-Sanchez C, Guo Y, Krecke KN, et al. Cerebral cortical encephalitis in myelin oligodendrocyte glycoprotein antibody-associated disease. *Ann Neurol*. 2023;93(2): 297-302. doi:10.1002/ana.26549
40. Khalil M, Teunissen CE, Lehmann S, et al. Neurofilaments as biomarkers in neurological disorders—towards clinical application. *Nat Rev Neurol*. 2024;20(5):269-287. doi:10.1038/s41582-024-00955-x
41. Abdelhak A, Foschi M, Abu-Rumeileh S, et al. Blood GFAP as an emerging biomarker in brain and spinal cord disorders. *Nat Rev Neurol*. 2022;18(3):158-172. doi:10.1038/ s41582-021-00616-3
42. van Lierop ZYGJ, Verberk IMW, van Uffelen KWJ, et al. Pre-analytical stability of serum biomarkers for neurological disease: neurofilament-light, glial fibrillary acidic protein and contactin-1. *Clin Chem Lab Med*. 2022;60(6):842-850. doi:10.1515/cclm-2022-0007
43. Kim S-H, Gomes ABAGR, Schindler P, et al. Blood-based biomarkers for identifying disease activity in AQP4-IgG-positive neuromyelitis optica spectrum disorder. *JAMA Neurol*. 2025;82(2):168-175. doi:10.1001/jamaneurol.2024.4400
44. Gomes ABAGR, Kim S-H, Pretzsch R, et al. Neurofilament light chain as a discriminator of disease activity status in MOG antibody-associated disease. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(1):e200347. doi:10.1212/NXI.0000000000200347
45. Dinoto A, Sechi E, Flanagan EP, et al. Serum and cerebrospinal fluid biomarkers in neuromyelitis optica spectrum disorder and myelin oligodendrocyte glycoprotein associated disease. *Front Neurol*. 2022;13:866824. doi:10.3389/fneur.2022.866824
46. Hyun J-W, Kim Y, Kim KH, et al. CSF GFAP levels in double seronegative neuromyelitis optica spectrum disorder: no evidence of astrocyte damage. *J Neuroinflammation*. 2022;19(1):86. doi:10.1186/s12974-022-02450-w
47. 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. *J Neurol Neurosurg Psychiatr*. 2023;94(9):757-768. doi:10.1136/jnnp-2022-330412
48. Aktas O, Smith MA, Rees WA, et al. Serum glial fibrillary acidic protein: a neuromyelitis optica spectrum disorder biomarker. *Ann Neurol*. 2021;89(5):895-910. doi: 10.1002/ana.26067
49. 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. *J Neurol Neurosurg Psychiatr*. 2025;96(9):884-892. doi:10.1136/jnnp-2024-335137
50. Schindler P, Grittner U, Oechtering J, et al. Serum GFAP and NfL as disease severity and prognostic biomarkers in patients with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. *J Neuroinflammation*. 2021;18(1):105. doi: 10.1186/s12974-021-02138-7
51. Villacieros-Álvarez J, Sepulveda M, Valls-Carbó A, et al. Cerebrospinal 14-3-3 protein levels as a neuroaxonal biomarker in aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(5):e200432. doi:10.1212/NXI.0000000000200432
52. Villacieros-Álvarez J, Espejo C, Arrambide G, et al. Profile and usefulness of serum cytokines to predict prognosis in myelin oligodendrocyte glycoprotein antibody-associated disease. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(3):e200401. doi: 10.1212/NXI.0000000000200401
53. Pozzilli V, Thambiliyagodage MP, Mankad K, et al. CSF IL-6 in children with neuroinflammatory conditions. *Eur J Paediatr Neurol*. 2025;58:42-49. doi:10.1016/ j.ejpn.2025.07.013

54. Fu Y, Bi J, Yan Y, et al. Rapid immunodot AQP4 assay for neuromyelitis optica spectrum disorder. *JAMA Neurol*. 2023;80(10):1105-1112. doi:10.1001/jamaneurol.2023.2974
55. Schmid J, Alberti C, Power L, et al. Immune signatures link myelin oligodendrocyte glycoprotein antibody-associated disease to other autoantibody-mediated conditions. *Sci Transl Med*. 2025;17(819):eadw0358. doi:10.1126/scitranslmed.adw0358
56. Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *Ann Neurol*. 2023;93(6):1053-1068. doi:10.1002/ana.26626
57. Kaneko K, Kuroda H, Matsumoto Y, et al. Different complement activation patterns following C5 cleavage in MOGAD and AQP4-IgG+NMOSD. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(5):e200293. doi:10.1212/NXI.0000000000200293
58. Villacieros-Álvarez J, Lunemann JD, Sepulveda M, et al. Complement activation profiles predict clinical outcomes in myelin oligodendrocyte glycoprotein antibody-associated disease. *Neurol Neuroimmunol Neuroinflamm*. 2025;12(1):e200340. doi:10.1212/NXI.0000000000200340
59. Wannaphut C, Ongphichetmetha T, Satiraphan P, et al. Familial neuromyelitis optica spectrum disorders: case series and systematic review. *Mult Scler Relat Disord*. 2023;73:104627. doi:10.1016/j.msard.2023.104627
60. Saucier L, Rossor T, Gorman MP, Santoro JD, Hacohen Y. Diagnosis and management of children with atypical neuroinflammation. *Neurology*. 2025;104(9):e213537. doi:10.1212/WNL.0000000000213537

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