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MOG-IgG Positivity Does Not Equal MOGAD: Diagnostic Pitfall and Misapplication of the International MOGAD Panel Proposed Criteria in Real-World Practice

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Background and Purpose Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) has been increasingly recognized, yet concerns remain regarding the overuse and misinterpretation of MOG-IgG testing. The recently published MOGAD diagnostic criteria emphasize selective testing and rigorous interpretation in the context of compatible clinical syndromes and supportive features. We investigated, in real-world practice, the extent to which these criteria are appropriately applied and the frequency and characteristics of their misapplication at a referral center.

Methods We retrospectively reviewed patients referred to the National Cancer Center with externally reported MOG-IgG positivity between January 2021 and December 2024. External assay results were based on laboratory-specific cutoffs, which had not been verified against clinically validated thresholds. Final diagnoses were determined by expert consensus after comprehensive evaluation, applying the 2023 international MOGAD diagnostic criteria.

Results Fifty-seven patients with external MOG-IgG positivity were referred, of whom 48 (84.2%) had been labeled as MOGAD. Upon re-evaluation, only 39 patients (68.4%) met the diagnostic criteria. Of the 18 non-confirmed patients, 5 (27.8%) manifested nonspecific symptoms incompatible with core demyelinating events, 9 patients (50.0%) received an alternative diagnosis, and 4 (22.2%) presented core events but lacked supportive features.

Conclusions Over one-third of patients with externally reported positive results did not meet diagnostic criteria, illustrating the risk of non-targeted MOG-IgG testing and overinterpretation of antibody results. Selective test utilization and strict adherence to diagnostic criteria in the context of appropriate clinical syndromes and supportive findings are essential to prevent overdiagnosis and inappropriate treatment.

Keywords myelin oligodendrocyte glycoprotein antibody-associated disease; diagnostic errors; autoantibodies; clinical practice pattern.

INTRODUCTION

Since its recognition as a distinct clinical entity, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) has attracted growing attention among neurologists, prompting the widespread adoption of MOG-IgG testing in clinical practice. Prior studies have demonstrated that live cell-based assays for MOG-IgG are highly specific, but their positive predictive value depends strongly on antibody titer: clear-positives are consistently reproducible across laboratories and reliably indicate true MOGAD, whereas low-positive results are less specific and can also be detected in patients with other neurological diseases or even in healthy individuals.[1,2] Accordingly, the 2023 international consensus diagnostic criteria for MOGAD emphasize that testing should be reserved for patients with compati-

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ble clinical syndromes, that low-positive results require additional clinical and radiologic supportive features, and that more appropriate alternative diagnoses such as multiple sclerosis (MS) should be excluded.[3]

However, the assay is frequently used indiscriminately as a screening tool, even in patients with low pre-test probability, thereby increasing the risk of false-positive results. This concern is further complicated in Korea, where most commercial laboratories report MOG-IgG results as median fluorescence intensity (MFI) ratios with laboratory-specific cutoffs that have not been validated against clinical outcomes.[3] Accordingly, results classified as positive by these cutoffs represent "unknown titer status," yet are often interpreted as clear positives, contributing to diagnostic misclassification and inappropriate treatment. We therefore aimed to investigate current diagnostic practice by examining the frequency and the nature of misapplication of diagnostic criteria at a referral center in Korea.

METHODS

Study population

We retrospectively reviewed medical records of patients referred to the National Cancer Center in Korea between January 2021 and December 2024 with reported MOG-IgG positivity from external commercial laboratories. The diagnostic status and the reason for the referral were classified as either an established diagnosis of MOGAD or a provisional/deferred diagnosis requiring further evaluation. Additional data collected included demographic characteristics, clinical presentation of the index event prompting MOG-IgG testing, clinical course, immunosuppressive therapies (IST; corticosteroids for >3 months, oral immunosuppressants, rituximab, intravenous immunoglobulin G, or tocilizumab), MRI findings, cerebrospinal fluid profiles, and details of antibody testing.

Assay methods

A follow-up MOG-IgG test was performed using an in-house live cell-based assay with validated titers, 4 primarily by indirect immunofluorescence (IF) with visual scoring (graded 0–4 according to the extent and brightness of ring-like staining at a 1:20 serum dilution), with additional flow cytometry (fluorescence-activated cell sorting at a 1:40 dilution) in selected cases. Samples with an IF visual score ≥1+ or an MFI ratio ≥3.4 were defined as positive, and those below these thresholds were defined as negative.[3,4] Clear positive results were defined as those with an IF score ≥2+ or an MFI ratio ≥6.8.[3] Aquaporin-4 (AQP4) antibodies were analyzed using live cell-based flow cytometry.[5] External assays were performed at two commercial centers in Korea using live cell-based flow cytometry assays, which may exhibit minor inter-laboratory variability. Assay results were interpreted according to laboratory-specific cutoffs that had not been clinically validated against patient-level diagnostic data.

Diagnostic adjudication

Final diagnoses were determined by three neuroimmunologists at our center through a two-step consensus process. In the initial step, each reviewer independently assessed whether each case met the 2023 international MOGAD diagnostic criteria based on the clinical, radiological, and basic laboratory information,[3] while being blinded to the external MFI ratio and in-house assay results. In the second step, the reviewers jointly discussed each case by integrating all available data, including the external MFI ratio and in-house assay findings, to reach a final consensus diagnosis, with any disagreements resolved by majority vote.

Ethical approval and statistical analysis

The study was approved by the Institutional Review Board at the National Cancer Center (NCC2014-0146), and written informed consent was obtained from all participants. Categorical variables were summarized as counts and percentages, and continuous variables as medians with interquartile ranges (IQRs).

RESULTS

A total of 57 patients with externally reported MOG-IgG positivity were referred to the National Cancer Center. The median age at onset was 35.5 years (IQR, 27.0–46.1 years), and 22 (38.6%) were male. At the time of referral, 40 patients (70.2%) had a disease duration of less than 1 year. Forty-eight patients (84.2%) had been designated as established MOGAD at the referring institution, while 9 patients (15.8%) were referred with a provisional/deferred diagnosis for further evaluation and second opinion regarding MOG-IgG positivity.

Upon re-evaluation, 39 (68.4%) of 57 patients fulfilled the 2023 international MOGAD diagnostic criteria, all of whom demonstrated both core clinical syndromes and supportive features, irrespective of their initial MFI ratio. The remaining 18 (31.6%) did not meet the criteria; among them, 10 patients (55.6%) had been mislabeled as MOGAD at the referring institution. Demographic and clinical characteristics of patients with confirmed MOGAD and non-confirmed MOGAD are described in Table 1. Within the non-MOGAD group, 5 (27.8%) exhibited non-specific symptoms incompatible with core demyelinating events, 9 patients (50.0%) received alternative diagnoses based on clinical red flags or

more plausible etiologies,[3] including MS (*n*=3), vascular disease (*n*=2; spinal cord infarction and spinal dural arteriovenous fistula), neoplasia (*n*=2; brainstem glioma and spinal intramedullary tumor), autoimmune encephalitis (*n*=1), and AQP4-IgG-positive neuromyelitis optica spectrum disorder (*n*=1). The remaining 4 patients (22.2%) presented with optic neuritis (*n*=3) or myelitis (*n*=1) but lacked supportive clinical and radiological features required for confirmation. In these 18 patients, the absence of supportive features reflected negative or non-suggestive findings on appropriate diagnostic evaluations, rather than incomplete diagnostic work-up. Detailed information on these 18 patients is provided in Supplementary Table 1 (in the online-only Data Supplement).

Except for the three patients ultimately diagnosed with MS, none of the non-confirmed patients presented with a relapsing course at referral. One MS patient had been misclassified as MOGAD and treated with IST instead of MS-specific disease-modifying therapy. Two additional patients in the non-confirmed group were also started on immunotherapy without sufficient indication—one after a single episode of optic neuritis and the other without a core demyelinating syndrome.

External MFI ratio data were available for 42 patients (27 confirmed MOGAD, 15 non-confirmed). The median MFI ratio was higher in the confirmed group (24.1; IQR, 7.4–34.1) than in the non-confirmed group (4.6; IQR, 3.1–5.1). Notably, all 19 patients with an MFI ratio ≥10 were ultimately diagnosed with MOGAD, whereas only 8 (34.8%) of 23 patients with ratios <10 fulfilled the diagnostic criteria. The value of the MFI ratio ≥10 represents an empirically observed level associated with diagnostic confirmation in this cohort, rather than a validated or proposed diagnostic threshold.

In-house MOG-IgG assay was performed in 54 patients, yielding 21 clear positives, 11 low positives, 2 borderline results, and 20 negatives. Among these, 39 patients had paired external MFI ratios and in-house results with a median interval of one month (IQR, 1.0–6.8 months) between the two tests. Of 18 patients with an external MFI ratio ≥10, 14 (77.8%) consistently showed clear positive results on in-house test-

Table 1. Demographic and clinical characteristics of confirmed MOGAD patients and non-confirmed patients

Characteristic	MOGAD (*n*=39)	Non-MOGAD (*n*=18)
Male	13 (33.3)	9 (50.0)
Age at onset (yr)	31.8 [20.7–44.2]	40.8 [35.7–55.4]
Patients with disease onset <1 yr at referral	30 (77.0)	10 (55.6)
Diagnosis status at referral		
Established MOGAD diagnosis	38 (97.4)	10 (55.6)
Provisional/deferred diagnosis	1 (2.6)	8 (44.4)
Clinical phenotype of the index event*		
Non-specific symptoms	0 (0.0)	5 (27.8)
Acute optic neuropathy	18 (62.1)	4 (22.3)
Acute myelopathy	13 (33.3)	7 (38.9)
Acute focal cerebral syndrome	4 (10.3)	0 (0.0)
Acute brainstem syndrome	4 (10.3)	1 (5.6)
Acute encephalopathy	2 (5.1)	1 (5.6)
Cortical encephalitis	1 (2.6)	0 (0.0)
Relapsing course at the first visit	10 (25.6)	3 (16.7)
Receiving IST† at the first visit	12 (66.7)	3 (16.7)
Presence of supportive clinical and MRI findings	39 (100)	1 (5.6)
External MOG-IgG MFI ratio	24.1 [7.4–34.1]	4.6 [3.1–5.1]
In-house MOG-IgG results‡		
Clear positive	21 (53.8)	0 (0.0)
Low positive	5 (12.8)	6 (33.3)
Borderline or negative	12 (30.8)	10 (55.6)
Not performed	1 (2.6)	2 (11.1)

Values are presented as median [IQR] or number (%).
*Index event refers to the clinical presentation that prompted MOG-IgG testing. Some patients had overlapping phenotypes (e.g., optic neuritis with myelopathy) and were counted in each relevant category; †IST included corticosteroids for >3 months, oral immunosuppressants, rituximab, intravenous immunoglobulin G, or tocilizumab; ‡In-house MOG-IgG test was performed at a median of 1 month after the initial external testing.
IQR, interquartile range; IST, immunosuppressive therapy; MFI, median fluorescence intensity; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease.

ing. In contrast, among 21 patients with an external MFI ratio <10, 14 (66.7%) reverted to borderline or negative results on follow-up.

DISCUSSION

In our real-world referral cohort, more than one-third of patients referred with MOG-IgG positivity from the external assays did not meet the 2023 international diagnostic criteria. However, the majority had been labeled as MOGAD, and several non-confirmed patients had even been exposed to inappropriate immunotherapy. These observations highlight that current practice remains prone to misapplication of diagnostic criteria, with consequent risk of diagnostic misclassification.

Regarding the nature of misclassification, about one-quarter of false-positive cases occurred in patients without core demyelinating syndromes, representing situations where MOG-IgG testing was clinically unnecessary. In addition, a considerable proportion was attributed to alternative neurological disorders, frequently accompanied by red flags against MOGAD.[3] Previous studies have shown that occasional MOG-IgG positivity has been reported in healthy controls,[6] and that MOG-IgG testing in low pre-test probability markedly reduced the positive predictive value of the assay.[1,7] Nevertheless, our findings indicate that MOG-IgG testing is frequently applied outside of appropriate clinical contexts, and that assay results are often overinterpreted relative to clinical judgment. These results emphasize the importance of maintaining a broad differential diagnosis and rigorously excluding more plausible etiologies, which remain essential components of the diagnostic triad of MOGAD.

A subset of patients presented with optic neuritis or myelitis but lacked supportive features. Although some may ultimately be reclassified as MOGAD if subsequent attacks with typical presentations occur, the diagnosis of MOGAD should be deferred at present. Given the absence of clinically validated cutoffs, MFI-based results should be regarded as an unknown titer status necessitating supportive features. Nevertheless, all had previously been labeled as MOGAD, likely reflecting the misinterpretation of external MFI-based positivity as clear positives while disregarding the need for supportive features. Importantly, validation studies of the 2023 diagnostic criteria have shown that nearly all patients with clear-positive results exhibited them even though not mandated by the criteria.[8,9] These findings indicate that supportive features capture key characteristics of MOGAD and complement antibody testing in establishing diagnostic confidence. In patients without clear-positive antibody results, the absence of supportive features should prompt consideration of alternative inflammatory etiologies, with follow-up and periodic reassessment rather than premature assignment of a MOGAD diagnosis.

While exploratory, higher MFI ratios on external commercial assays appeared to provide meaningful stratification. In our cohort, an empirically applied cutoff of ≥10 was associated with a 100% positive predictive value, as all such patients fulfilled the 2023 diagnostic criteria. These high-titer patients were also more likely to remain seropositive on follow-up testing at a median interval of one month, even after acute treatment, suggesting greater reproducibility across different testing conditions. By contrast, only 34.8% of patients with MFI ratios <10 met the diagnostic criteria, underscoring the need for cautious interpretation of low-level positivity within the appropriate clinical and radiologic context. These observations are in line with previous studies showing that the positive predictive value of MOG-IgG tests increases in a titer-dependent manner,[2,7,10] reinforcing the importance of cautious interpretation of low-titer results.

This study has limitations, including its retrospective, single-center design in a referral population, which may limit the generalizability of the findings and the estimated frequency of misapplication of diagnostic criteria. In some cases, absence of longitudinal follow-up after the initial consultation at our institute hindered confirmation of an alternative diagnosis. Conversely, a strength of this study is that it represents the first real-world assessment in Korea of both the frequency and nature of inappropriate application of the MOGAD diagnostic criteria, offering insights to guide clinician education and future diagnostic strategies.

Our study highlights major diagnostic pitfalls of MOGAD in current practice, largely attributable to indiscriminate MOG-IgG testing and misinterpretation of assay results. Although the clinical spectrum of MOGAD may broaden in the future, accurate diagnosis at present requires recognition of core clinical features, selective application of MOG-IgG testing, and appropriate interpretation of the antibody results. Such an approach is critical to prevent misdiagnosis and overtreatment and to more clearly distinguish patients with true MOGAD from those with alternative conditions.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2025.0529.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Kang YR, Kim KH, and Hyun JW report no potential conflicts of interest related to this study. Kim HJ received a grant from the National Research Foundation of Korea and research support from Aprilbio and Eisai; received consultancy/speaker fees from Alexion, Aprilbio, Altos Biologics, Biogen, Celltrion, Daewoong, Eisai, GC Pharma, Handok, Horizon Therapeutics, Kaigene, Kolon Life Science, MDimune, Mitsubishi Tanabe Pharma, Merck Serono, Novartis, Roche, Sanofi Genzyme, Teva-Handok, and UCB; is a co-editor for the Multiple Sclerosis Journal and an associated editor for the *Journal of Clinical Neurology*.
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