Timing of MOG-IgG Testing Is Key to 2023 MOGAD Diagnostic Criteria

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Abstract

Background and Objectives
Myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD) is a recently identified autoimmune demyelinating disorder of the CNS affecting both adults and children. Diagnostic criteria for MOGAD have recently been published. We aimed to validate the 2023 MOGAD diagnostic criteria in a real-world cohort of patients with atypical CNS inflammation.

Methods
All patients referred to the National neuromyelitis optica spectrum disorder (NMOSD) specialized service at The Walton Center NHS Foundation Trust between 2012 and 2023 with an atypical demyelinating syndrome were evaluated. We systematically applied the 2023 MOGAD diagnostic criteria and previous 2018 International Diagnostic Recommendations for MOG encephalomyelitis to our retrospective cohort.

Results
474 patients were screened and 66 were excluded for lack of clinical information. Preexisting diagnoses within our cohort included the following: MOGAD, n = 127; AQP4-IgG NMOSD, n = 125; seronegative NMOSD, n = 33; multiple sclerosis (MS), n = 10; and other diagnoses, n = 113. Of patients with preexisting MOGAD, 97% (123/127) fulfilled the 2023 MOGAD diagnostic criteria. Three patients with a low-positive MOG-IgG did not meet supportive features though 2/3 had insufficient investigations. Alternative diagnoses could not be excluded in 1 patient with MS-MOGAD overlap. No patients with a non-MOGAD diagnosis were found to fulfill the 2023 diagnostic criteria. The sensitivity and specificity of the 2023 MOGAD diagnostic criteria were 97% and 100% with no false positives, improving on 2018 International Diagnostic Recommendations for MOG encephalomyelitis. Low-positive MOG-IgG results were more often associated with a longer time from disease onset to sampling (p < 0.001). In addition, in patients with a MOG-IgG1 test within 6 months of clinical onset, approximately 25% can become low positive by 6 months. Of patients with preexisting MOGAD, 9% (12/127) had insufficient investigations and examinations to fully evaluate additional supportive features. However, in those who were completely evaluated, supportive features were fulfilled in 97% (111/115).

Discussion
The 2023 MOGAD diagnostic criteria were highly sensitive and specific and closely align with historically established cases of MOGAD. However, because additional supportive features are stipulated for patients with a low-positive MOG-IgG result, missed diagnoses may occur due to delayed testing or insufficient investigations.

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compared using Mann-Whitney U tests. Kaplan-Meier survival analysis was used to describe longitudinal serologic data in patients with preexisting MOGAD with an available MOG-IgG1 test within 6 months of onset. All statistical analyses were performed using SPSS version 25.0 and R version 4.2.1.

**Standard Protocol Approvals, Registrations, and Patient Consents**
The study was approved by the Research Ethics Service, NRES Committee London- Hampstead, Ref. no. 15/LO/1433. All patients provided written informed consent.

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

**Results**
Four hundred seventy-four consecutive referrals for atypical demyelinating syndromes between 2012 and 2023 were received. Sixty-six were excluded because of insufficient clinical information (Figure 1).

Of the remaining 408 patients, 125 (31%) were positive for AQP4-IgG and had a diagnosis of AQP4-IgG NMOSD (MOG-Ig test available in 122/125, 100% negative). The remaining 283 patients were negative to AQP4-IgG, and the MOG-Ig test results were as follows: clear positive, n = 103 (100/103 on MOG-IgG1 assay, 1/103 on MOG IgG (Fc) assay, and 2/103 on MOG (H + L) assay), low positive, n = 25 (25/25 on MOG-IgG1 assay), isolated CSF MOG-IgG positive, n = 1, and negative, n = 154 (152/154 on MOG-IgG1, 2/154 on MOG [H + L]).

CSF MOG-IgG were tested in 10% of our overall cohort (40/408), and 11/40 had a diagnosis of MOGAD. We found MOG-IgG in the CSF in 2/40 cases; both had a diagnosis of MOGAD with one being negative on serum testing for MOG-IgG.

Of 127 patients with a preexisting diagnosis of MOGAD, 79% (100/127) had a clear positive MOG-IgG1 result, 18% (23/127) had a low-positive MOG-IgG1 test, and 1/127 had isolated positive CSF MOG-IgG. Three patients were negative to MOG-IgG1 (2%; 3/127). However, they all had positive MOG-Ig results on other assays, 2/3 were positive on MOG (H + L), and 1/3 was positive on EUROWIHN MOG-IgG (Fc). In this very patient, due to the discordant result between EUROWIHN MOG-IgG (Fc) and MOG-IgG1 test, IgG subclasses were tested. This patient was positive to MOG-IgG3 only.

Of patients with a preexisting diagnosis other than MOGAD (non-MOGAD) and negative for AQP4-IgG, 154/156 had a negative MOG-IgG test (seronegative NMOSD n = 33; MS n = 10; and other diagnoses n = 111). Two patients had a low-positive MOG-IgG1 result (chronic small vessel ischemia, n = 1, and optic neuropathy, n = 1). Details of these diagnoses are summarized in eTable 1 (links.lww.com/NXI/A940).

Figure 1 Flowchart—Serology and Clinical Diagnoses

- AQP4-IgG = aquaporin-4 IgG; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; NMOSD = neuromyelitis optica spectrum disorder. *100/103 MOG-IgG1, 1/103 MOG-IgG (Fc), 2/103 MOG (H + L); **152/154 MOG-IgG1, 2/154 MOG (H + L).
2023 MOGAD Diagnostic Criteria Are Highly Sensitive and Specific

To assess the performance of the 2023 MOGAD diagnostic criteria in patients with an existing MOGAD diagnosis, we applied the diagnostic steps as indicated in the criteria (Figure 2). Demographics of this group were as follows: 55% were female (70/127), the median age at presentation was 30 years (range 3–71), and 91% were Caucasian.

All patients satisfied step 1 with the presence of a core clinical demyelinating event. The second step was the assessment of MOG-IgG serology. A clear positive MOG-IgG result was observed in 81% (103/127) of patients. The application of additional supportive clinical and radiologic features was required in 19% (24/127) of preexisting MOGAD diagnoses, 23 patients with low-positive MOG-IgG1, and 1 patient with isolated CSF MOG-IgG. These patients were all negative for AQP4-IgG.

Supportive features were fulfilled in 88% (21/24) of these patients. Three patients did not fulfill additional supportive features though 2 patients had insufficient investigations to fully evaluate for their presence. These 3 patients were judged to not fulfill 2023 MOGAD diagnostic criteria and were categorized as false negatives. The final step was the exclusion of a better alternative diagnosis, and 1 further patient with an MS-MOGAD overlap syndrome was categorized as false negative.

Figure 2 Application of 2023 MOGAD Diagnostic Criteria to Preexisting MOGAD Cohort

AQP4-IgG = aquaporin-4 IgG; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.
Overall, sensitivity was high with 97% (123/127) of cases with preexisting MOGAD fulfilling 2023 MOGAD diagnostic criteria. Specificity was also excellent with none of the 281 non-MOGAD cases fulfilling the criteria when applied. For comparison, the 2018 International Recommendations were also evaluated in our patients.10 Figure 3 presents the comparative test performance characteristics within our cohort.

Reasons for False-Negative Classification
We identified 2 reasons why 4 patients with preexisting MOGAD did not fulfill 2023 diagnostic criteria:

1. Supportive criteria not met—Three patients with a core clinical demyelinating event and a low-positive MOG-IgG1 did not meet additional supportive features. Two patients with optic neuritis did not have an MRI of the orbits with contrast and/or did not have documented optic disc swelling. One patient with transverse myelitis did not have LETM, H-sign, or conus involvement on MRI.

2. Inability to exclude a better diagnosis—One patient presented with relapsing longitudinally extensive transverse myelitis and persistent sphincter dysfunction. Although the clinical phenotype was suggestive of MOGAD, it was felt that a competing diagnosis of MS could not be excluded because of the presence of persistent periventricular lesions perpendicularly orientated to the corpus callosum and unmatched CSF oligoclonal bands.

Performance of MOGAD Diagnostic Supportive Features
The supportive clinical features, in patients with complete investigations, identified 21/22 (95%) cases with a low-positive MOG-IgG1 score as MOGAD. To further investigate the specificity of the supportive criteria, we evaluated their presence in the entire cohort (Figure 4).

Overall, 329/356 (92%) of the patients with sufficient investigations conducted fulfilled the 2023 supportive criteria in our clinical cohort of consecutive patients. A high proportion of seropositive NMOSD patients (97% [98/101]) and seronegative NMOSD patients (97% [31/33]) also fulfilled supportive features for MOGAD, unsurprisingly highlighting the high proportion with overlapping clinical characteristics and the importance of accurate serologic testing. Proportions of patients presenting supportive features in each diagnostic group are shown in Figure 4A. Of the range of clinical presentations observed, patients with optic neuritis were the most likely to have insufficient investigations or examinations performed (Figure 4B).

Timing of Testing Is Critical to MOG-IgG Interpretation
Because this is a retrospective cohort, not all patients were tested for MOG-IgG at disease onset. Previous publications show that MOG-IgG antibody titers lower over time, and 3 patients (3%) with a clear positive test result did not meet supportive criteria; hence, timing of the assay may have a diagnostic impact. Including only patients tested within 6 months of clinical onset, the Kaplan-Meier analysis shows that approximately 25% of patients become low positive by 6 months and approximately 50% of patients become seronegative by 12 months (Figure 5).

To further examine the impact of lowering titers over time, we compared the time to sampling from onset in patients with a first MOG-IgG clear positive result (n = 86) and with a first low-positive result (n = 33). The median time to the MOG-IgG assay was significantly longer in the low-positive MOG-IgG group (205 days [interquartile range (IQR) 50–3,314] vs 38.5 [IQR 26–179], p < 0.01, Figure 6).

Patients who were tested within 30 days of their clinical syndrome made up a small proportion of the MOGAD cohort (33/127). Of them, 18/33 patients had a clear positive MOG-IgG1 result within 30 days of clinical onset and a second MOG-IgG1 result within 6–12 months. Half (9/18) became MOG-IgG1 negative, 28% (5/18) became MOG-IgG1 low positive, and 22% (4/18) remained MOG-IgG1 clear positive in the first year. Of note, 1 patient who became low positive at 80 days and subsequently seronegative at 249 days did not meet the supportive criteria. His clinical presentation was a short cervical transverse myelitis with excellent recovery after steroids, his disease course remained monophasic, and the lesion resolved on subsequent scans.
Prior Treatment Did Not Significantly Affect MOG-IgG Results
In 60% (76/127) of patients with MOGAD, immunomodulatory treatment was given 3 months before the first MOG-IgG assay (100% high-dose corticosteroids, 18% PLEX and 4% IVIg). There was no difference in the frequency of low-positive MOG-IgG1 results between patients who did and did not receive treatment before testing ($p = 0.4$).
Discussion

This study demonstrates the application of the 2023 MOGAD diagnostic criteria in a real-world cohort. We run a specialized service for patients with atypical demyelinating disorders and those with clinical presentations that overlap with NMOSD, a challenging group for the 2023 MOGAD diagnostic criteria. In our unselected consecutive cohort of 474 patients referred between 2012 and 2023, the 2023 MOGAD diagnostic criteria performed exceptionally well. They identified 123/127 (97%) of cases we consider to be MOGAD with no false-positive patients identified, improving on the 2018 International Recommendations. Additional supportive clinical and MRI features are required with a low-positive MOG-IgG result or isolated positive CSF MOG-IgG result. When appropriately assessed, the supportive clinical criteria identified 95% of patients who had a low-positive MOG-IgG result, including 1 who was uniquely CSF positive. However, 92% of the entire cohort also fulfilled the supportive criteria. This is not surprising in a clinically biased cohort from a specialist referral center, but it does add weight to the antibody test result and highlight the importance of test accuracy and contemporaneous testing. With this considered, in the stepwise structure of the criteria, the supportive features are helping maintain the criteria’s sensitivity while the

Figure 5 Kaplan-Meier Survival Analysis in Patients With MOGAD With a MOG-IgG1 Test Within 6 Months of Clinical Onset

(A) time from onset to low-positive MOG-IgG1. (B) time from onset to negative MOG-IgG1.

Figure 6 Median Time (IQR and Range) From Clinical Onset to First Available MOG-IgG1 in Patients With MOGAD With a First Clear Positive vs First Low-Positive Result

IQR = interquartile range.
serology optimizes specificity. The one patient with MOGAD who did not fulfill the supportive criteria had transverse myelitis without an LETM, the H-sign, or conus involvement on imaging. Of note, his antibodies were tested at 205 days from onset.

Timing of testing is important to support the diagnosis of MOGAD. In this cohort, 3% of patients with a clear positive antibody test result did not fulfill the supportive features. In our MOG-IgG antibody–positive cohort tested within 6 months from onset, antibody titers declined over time showing that approximately 25% of patients can return a low-positive result by 6 months and approximately 50% can return a negative result by 12 months, in keeping with previous studies.11 Because this is a retrospective cohort, the testing was not always at disease onset. Patients who had a low-positive first result were tested significantly further into their disease course than the clear positives (median time 205 vs 38.5 days, p < 0.01). Further to this, of 33 patients who had a MOG-IgG test within 30 days of disease onset and a second test 6–12 months later, only 4/18 remained clear positive at 12 months. One patient, who did not fulfill supportive criteria became low positive at 80 days (and negative at 249 days) and hence would not have fulfilled the clinical criteria for MOGAD if the antibody test had been delayed. Given these results, a MOGAD diagnosis may be missed in patients who were not tested at presentation. This will be inevitable in patients presenting before the development and refinement of the MOG-IgG assay but will likely continue in smaller numbers going forward if patients do not receive timely serologic evaluation. MOGAD is defined by the presence of MOG-IgG, but we continue to see cases with a clinical and radiologic phenotype suggestive of MOGAD in the absence of MOG-IgG. Testing during relapses is likely to be an important factor in addressing the proportion of patients with “seronegative” MOGAD. The optimal timing of MOG-IgG retesting and whether a lower MOG-IgG cutoff could be used in relapsing patients warrants further study. Future iterations of the diagnostic criteria may need to consider the timing of serology in relation to clinical onset or relapses.

Within patients with MOGAD, 12/127 (9%) had a lack of specific investigations or examination to assess the supportive clinical and MRI features and all had optic neuritis. In the overall cohort, we observed most of the patients who lacked investigations and examination presented with optic neuritis 42/46 (91%) and did not have dedicated orbital imaging, the administration of contrast, or documented fundoscopy. This finding highlights a potential pitfall but one that could be readily addressed with early specialist advice or guidance on standard investigations and examination for optic neuritis.12

In MOGAD, IgG1 is the predominant IgG subclass,13 and most of our cases were identified with a MOG-IgG1 test, which is highly specific.2 However, recent reports suggest a minority of patients with non-IgG1 MOG antibodies may also fulfill MOGAD diagnostic criteria.13 We identified 1 patient with MOGAD with MOG-IgG3 antibodies who was negative on the MOG-IgG1 assay. The patient was a female with a short transverse myelitis as a core demyelinating event and a subsequent monophasic course. Further work is needed to better understand clinical relevance of MOG-IgG subclasses other than IgG1, the test specificity when looking for non-IgG1 subclasses, and the frequency of these patients.14

When a patient fulfills criteria for more than 1 disease, the diagnosis becomes complicated. We identified 1 patient who fulfilled the diagnostic criteria for MOGAD and MS. This is likely to be a rare occurrence, but further validation of the 2023 MOGAD diagnostic criteria with an MS control population would be of merit.

This study has several limitations. This was a retrospective study of modest sample size from a single specialist center with a referral bias toward atypical demyelinating cases. Although the study population differed from an unselected case mix, the use of an atypical demyelination cohort provided a robust test of the specificity of the MOGAD diagnostic criteria, which was excellent. Including cases with preexisting MOGAD where the pretest probability for MOGAD was high, we were also able to robustly assess sensitivity. In providing care to a primarily adult population, we have not been able to assess the diagnostic criteria in children or compare performance between adults and children. This would be important to assess in future studies. Serum testing was not always performed at disease onset or at regular intervals, and in rare cases, there was variation in the methodology of MOG-IgG testing. However, we believe these data provide a robust examination of the new clinical criteria in a real-world adult MOGAD cohort. The lack of standardized timing of testing limited our ability to define the precise time point at which MOG-IgG becomes low positive or negative. However, we were able to estimate the latest time points of these occurrences emphasizing the importance of early testing.

MOG-IgG is not widely or routinely tested on the CSF in the UK; thus, cases of CSF-only positive MOGAD were rare in our cohort. There is evolving evidence that CSF testing can be helpful in adult cases, hence its inclusion within the new MOGAD diagnostic criteria.10 Small numbers of low-positive MOG-IgG1, CSF MOG-IgG positive, and MS/MOGAD overlap cases limited our ability to evaluate the diagnostic criteria in these difficult clinical scenarios. Further validation studies including these challenging presentations, particularly in a population with a larger number of patients with MS, using different testing centers and in pediatric cohorts warrants further study.

We recognize that the evaluation of the presence of supportive features is influenced by the lack of specific required investigations in some patients as per criteria. This reflects application of the criteria on a retrospective cohort, but, nevertheless, only 2/127 (1%) patients with MOGAD did not
fulfill criteria because of this occurrence. We believe this also highlights the importance of performing and documenting specific tests in a timely manner when considering MOGAD diagnosis together with suggesting the need for future prospective studies on application of the criteria.

In this evaluation study, the 2023 MOGAD diagnostic criteria performed exceptionally well in our cohort of consecutive patients referred to a specialist center with atypical demyelinating disease or clinical features that overlap with AQP4-IgG-positive NMOSD. The criteria closely aligned with our historically established cases of MOGAD and improved both the sensitivity and specificity of previously available recommendations. Our findings highlight the impact of assay timing on patient diagnoses and the importance of appropriate assessment in patients, particularly those with optic neuritis to limit missed diagnoses.

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Appendix (continued)

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