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Real-Life Evaluation of the MOGAD Diagnostic Criteria

Application Challenges and Discrepancies

Sara Carta,[1] Elia Sechi,[2] Alessandro Dinoto,[1] Chiara Mancinelli,[3] Giacomo Greco,[4,5] Giorgia Teresa Maniscalco,[6] Sara Cornacchini,[7] Maria Pia Giannoccaro,[8,9] Francesca Calabria,[10] Alessandro Marziali,[11,12] Stefano Masciocchi,[13] Mario Risi,[13] Alberto Cossu,[14,15] Irene Volonghi,[16] Gaetano Cantalupo,[14,15] Marco Zoccarato,[17] Riccardo Orlandi,[1] Elisabetta Del Zotto,[18] Diana Ferraro,[19] Milena Trentinaglia,[1] Stefano De Biase,[20] Luisa Grazian,[21] Francesca Caleri,[22] Maria Rachele Bianchi,[23] Patrizia Rossi,[24] Eleonora Virgilio,[25] Marco Capobianco,[25] Rosa Cortese,[26] Carla Tortorella,[27] Francesca Rossi,[28] Giovanna De Luca,[29] Anna Perelli,[30] Silvia Bozzetti,[31] Luigi Zuliani,[32] Margherita Nosadini,[33] Stefano Sartori,[33] Laura Brambilla,[34] Alberto Gajofatto,[1] Alberto Vogrig,[12,11] Luca Massacesi,[7] Valentina Damato,[7] Matteo Gastaldi,[13] and Sara Mariotto[1]

Correspondence
Dr. Mariotto
sara.mariotto@gmail.com

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Abstract

Background and Objectives

Myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD) international panel criteria have been recently proposed to guide MOGAD diagnosis. The aim of this study was to evaluate the criteria performance and assess the discrepancies in their application in the clinical practice in an Italian multicenter cohort and to discuss some challenging aspects.

Methods

We applied the 2023 MOGAD criteria to patients who tested MOG-Abs positive on cell-based assays and were retrospectively recruited from 29 centers. Detailed clinical and paraclinical data were collected. Patients were classified as true positive/negative (TP/TN) in case of concordance between MOGAD criteria application and enrolling center final diagnosis, as false positive (FP) when MOGAD criteria were fulfilled but final diagnosis was different from MOGAD, and as false negative (FN) when MOGAD criteria were not fulfilled and final diagnosis of MOGAD was confirmed. Central revision of FN and FP cases was performed.

Results

We included 214 patients (median age at onset 38.2 years [interquartile range 25.2–50.7], 60.3% female, 23 pediatric patients). Of these, 168 (78.5%) were classified as TP, 9 (4.2%) as FP, 23 (10.7%) as FN, and 14 (6.5%) as TN. The sensitivity of MOGAD criteria was 87.96% (CI 82.5%–92.2%), specificity 60.9% (CI 38.5%–80.3%), positive predictive value 94.9% (CI 91.8%–96.9%), negative predictive value 37.8% (CI 26.7%–50.2%), and accuracy 85.1% (CI 79.6%–89.5%). In 11 of 32 revised cases, available information did not allow a proper diagnosis.

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Supplementary Material

[1]Neurology Unit, Department of Neurosciences, Biomedicine, and Movement Sciences, University of Verona, Italy; [2]Neurology Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Italy; [3]Multiple Sclerosis Centre, Spedali Civili di Brescia, Italy; [4]Department of Brain and Behavioural Sciences, University of Pavia, Italy; [5]Multiple Sclerosis Center, IRCCS Mondino Foundation, Pavia, Italy; [6]Neurological Clinic and Stroke Unit and Multiple Sclerosis Center "A. Cardarelli" Hospital, Napoli, Italy; [7]Department of Neurosciences, Drugs and Child Health, University of Firenze, Italy; [8]IRCCS Istituto delle Scienze Neurologiche di Bologna, Italy; [9]Dipartimento di Scienze Biomediche e Neuromotorie, University of Bologna, Italy; [10]Neurology Unit, AOUI Verona, Italy; [11]Clinical Neurology, Department of Head-Neck and Neuroscience, Azienda Sanitaria Universitaria Friuli Centrale (ASU FC), Udine, Italy; [12]Department of Medicine (DMED), University of Udine, Italy; [13]Neuroimmunology Research Section, IRCCS Mondino Foundation, Pavia; [14]Child Neuropsychiatry Unit, Department of Children and Maternal Health, AOUI Verona, Full Member of European Reference Network EpiCARE, Verona, Italy; [15]Department of Innovation Medicine and Engineering, University of Verona, Italy; [16]Department of Continuity of Care and Frailty, Neurology Unit, ASST-Spedali Civili, Brescia, Italy; [17]Neurology Unit O.S.A., Azienda Ospedale-Università di Padova, Italy; [18]Neurology Unit, Istituto Clinico Fondazione Poliambulanza, Brescia, Italy; [19]Department of Neurosciences, Ospedale Civile di Baggiovara, Azienda Ospedaliero-Universitaria di Modena; [20]Neurology Unit, Ospedale dell'Angelo, Venezia Mestre, Italy; [21]Pediatric Unit, ULSS 2 Marca Trevigiana, Ca' Foncello Hospital, Treviso, Italy; [22]MS Center, Department of Neurology, F. Tappeiner Hospital Meran (BZ), Italy; [23]Neurology Unit, IRCSS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG); [24]Neurology Unit, AULSS7 Pedemontana, St Bassiano Hospital, Bassano del Grappa, Vicenza, Italy; [25]Department of Neurology, S. Croce e Carle Hospital, Cuneo, Italy; [26]Department of Medicine, Surgery and Neuroscience, University of Siena, Italy; [27]Department of Neurosciences, San Camillo-Forlanini Hospital, Rome, Italy; [28]Neurology Unit, Mater Salutis Hospital, Legnago, Verona, Italy; [29]Neurology Unit, Multiple Sclerosis Centre, SS Annunziata University Hospital, Chieti, Italy; [30]Department of Neurology AULSS 6 Euganea Cittadella Hospital, Padova, Italy; [31]Department of Neurology/Stroke Unit, San Maurizio Hospital, Bolzano, Italy; [32]Neurology Unit, AULSS8 Berica, Vicenza, Italy; [33]Paediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padova. Neuroimmunology Group, Paediatric Research Institute "Città della Speranza", Italy; [34]Centro Sclerosi Multipla IRCCS Istituto Neurologico Carlo Besta, Milano, Italy.

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Glossary

ADEM = acute disseminated encephalomyelitis; **CBA** = cell-based assay; **FN** = false negative; **FP** = false positive; **IQR** = interquartile range; **MOG** = myelin oligodendrocyte glycoprotein; **MOGAD** = MOG antibody–associated disease; **MS** = multiple sclerosis; **NPV** = negative predictive value; **PPV** = positive predictive value; **TN** = true negative; **TP** = true positive.

Independent revision changed the diagnosis in 17 of 21 remaining cases, increasing the performance of the MOGAD criteria. Of note, in 3 cases, diagnostic criteria were satisfied only at follow-up. The sensitivity and specificity after independent revision were 98.9% (CI 96%–99.9%) and 91.7% (CI 73%–98.9%), respectively. Moreover, 29 of 214 patients (13.6%) had 1 or more asymptomatic radiologic supportive features, and in 50% (3/6) of FP cases, independent revision did not confirm the presence of supportive features. Patients with clear positive serum titer or CSF-only MOG-Abs were those who received more commonly a MOGAD diagnosis.

Discussion

MOGAD criteria demonstrate a good performance across different centers; however, controversial cases might benefit from collegial discussion and reassessment of MOGAD criteria during the follow-up. Main challenges include availability of proper radiologic data and interpretation of radiologic supportive features.

Introduction

Myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD) is an autoimmune disease that can occur in both adults and pediatric patients with either a monophasic or relapsing course.[1-4] Clinical manifestations are heterogeneous and age-dependent, with adults presenting more often with severe optic neuritis and transverse myelitis and children with acute disseminated encephalomyelitis (ADEM). Other clinical manifestations such as isolated brainstem syndrome or cortical encephalitis with seizures can occur.[5,6]

Peculiar radiologic features help discriminating MOGAD from multiple sclerosis (MS) and neuromyelitis optica spectrum disorder, but some overlaps make the diagnostic process extremely challenging.[7,8]

The main distinctive feature of MOGAD is the presence of serum and/or CSF MOG antibodies (MOG-Abs), which should be tested using cell-based assays (CBAs) based on full-length human MOG. Either fixed commercial or live CBA can be used, although commercial fixed CBA has shown a lower sensitivity and specificity and has not been validated for CSF testing.[9-12] False-positive (FP) results can occur, especially in patients with low-titer MOG-Abs or when testing patients with a low pretest probability.[13]

After expert recommendations proposals,[14,15] the MOGAD international panel criteria have been published in January 2023.[16]

Subsequent studies have validated these criteria on different cohorts, finding a good specificity and sensitivity overall.[17,18] However, variability in applying the MOGAD diagnostic criteria, which may provide important insights into their use in routine clinical practice, has not been specifically investigated.

The aim of this study was to evaluate the real-life performance of the proposed MOGAD diagnostic criteria in an Italian multicenter cohort of MOG-Abs–positive patients and to highlight the challenges and discrepancies in their application.

Methods

Study Design

Patients with positive serum or CSF MOG-Abs results obtained from January 1, 2014, to December 31, 2024, were retrospectively included from 29 Italian centers. The 2023 MOGAD criteria were applied to each case by different neurologists at each participating center. Four groups were identified: true positive ([TP]: MOGAD criteria fulfilled, final diagnosis of MOGAD provided by the enrolling center), true negative ([TN]: MOGAD criteria not fulfilled, final diagnosis different from MOGAD), FP (MOGAD criteria fulfilled, final diagnosis different from MOGAD), and false negative ([FN]: MOGAD criteria not fulfilled, final diagnosis of MOGAD confirmed). Clinical records and MRI scans of FN and FP cases were independently revised by 3 neurologists with experience in MOGAD (S.C., E.S., and S.M.) to evaluate potential discrepancies in the criteria application and to verify the exclusion of better diagnosis, including MS. Consensus was reached after discussion in case of disagreement.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was part of the research protocol approved by the Ethics Committees of the enrolling centers: BIOB-NEU-DNA-2014 and prog. 1052CESC Verona-Rovigo approved by the Ethics Committee of Verona University Hospital (Italy); protocol

n. 16601_oss, approved by Area Vasta Centro—Regione Toscana (Florence, Italy); project code: 0020308/23 approved on April 14, 2023 by the Institutional Review Board of the IRCCS Policlinico San Matteo, Pavia.

MOG-Abs Testing

MOG-Abs testing was performed using live CBAs in 5 laboratories (Verona, Pavia, Florence, Bologna, Orbassano) and fixed CBAs in 8 local laboratories (Modena, Firenze, Siena, Udine, Padova, Siena, Roma, Milano). Clear positive serum MOG-Abs titers were defined according to the proposed diagnostic criteria.[16] For samples tested with fixed CBAs, a clear positive result was defined as a titer of ≥1:100. For live CBAs, clear positive samples had an antibody titer that was at least twice the threshold considered positive by the referring laboratory.

Demographic and Clinical Information

Clinical and paraclinical data were retrospectively collected in a dedicated database by the referring physician from each involved center. Information included the following: (1) demographic data (sex and age at onset, being adult-onset defined as age 18 years and older); (2) dates of disease onset; (3) antibody testing information (date of sampling and type of MOG-Abs assay performed, MOG Abs titers in serum and CSF, AQP4-Abs testing results); (4) clinical phenotype at onset; (5) CSF data (protein concentration, cell count, oligoclonal bands); (6) presence of supportive criteria for MOGAD diagnosis[16]; (7) final diagnosis reported by the referring center. Only in patients who were labeled as FN and FP, additional data such as details of relapses (if any) and MRI records for re-evaluation including axial MRI sequences for the spinal cord and orbital sequences for the optic nerve were requested.

Statistical Analysis

For descriptive statistics, quantitative variables are expressed as median (interquartile ranges [IQRs]) or mean (SD) and categorical variables as percentages. Group comparisons were assessed using nonparametric tests (χ^2 and Mann-Whitney tests), as appropriate.

Sensitivity was calculated as the percentage of patients who met the 2023 criteria and had definite MOGAD as determined by referring physicians (sensitivity = TP/TP + FN) with 95% CI. Specificity was calculated as the percentage of patients who did not meet the 2023 criteria and had FP MOG-Abs according to the treating physicians (specificity = TN/FP + TN) with 95% CI.

Positive predictive value (PPV) of the criteria was calculated as the percentage of true positive divided by total positive (TP/TP + FP) with 95% CI. Negative predictive value (NPV) was calculated as the percentage of true negative divided by total negative (TN/TN + FN) with 95% CI. Accuracy was calculated as the proportion of TP and TN in the whole tested cohort (TP + TN/TP + TN + FP + FN).

Data Availability

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

Results

A total of 214 patients were included. The median age at onset was 38.2 (IQR 25.2–50.7) years, and 129 (60.3%) were female (Table 1). 23 patients (10.7%) were children (median age at onset 12.4 years [IQR 6.4–14.4], 13%–56.5% female).

Types of Assays Used for MOG-IgG Detection

Live CBA was the most common assay used for MOG-Abs detection (n = 170, 79.4% of total cohort; n = 18, 78.4% of the pediatric cohort). CSF was tested in 84 patients (39.3%): of these, 39 (46.4%) were positive in serum only, 32 (42.9%) were positive in both serum and CSF, and 9 (10.7%) were positive in CSF only.

Of the whole cohort, 89 patients (41.6%) had serum clear positive titers, 86 (40.2%) had serum low-positive titers, 30 (14%) had an unknown titer, and 9 (4.2%) were CSF-only positive MOG-Abs. Among the pediatric cohort, most patients (12/23, 52.2%) had a clear positive MOG-Abs result while 11 of 23 (47.8%) had unknown/low-positive titer. CSF was tested in 12 pediatric patients and resulted positive in 9 of 12 patients while we did not observe any isolated CSF positivity in this cohort.

Clinical Phenotypes

Optic neuritis was the predominant phenotype at disease presentation (n = 106, 49.5%), followed by myelitis (n = 79, 36.9%), brainstem or cerebellar deficit (n = 22, 10.3%), ADEM (n = 15, 7%), cerebral monofocal/polyfocal deficit (n = 12, 5.6%), and cortical encephalitis (n = 9, 4.2%). A multifocal clinical presentation was reported in 26 patients (12.2%), including 9 patients with a concomitant myelitis and optic neuritis and 7 patients with brainstem/cerebellar deficit in association with myelitis. In the pediatric cohort, the clinical presentation at onset was ON in 10 patients (43.5%), ADEM in 7 (30%), myelitis in 4 (17.4%), cortical encephalitis in 3 (13%), cerebral monofocal/polyfocal deficit in 1 (4.3%), and vomiting and seizure in 1 (4.3%). Of note, 3 patients presented a multifocal presentation (1 optic neuritis associated with myelitis, 1 ADEM associated with optic neuritis, 1 ADEM with a concomitant cortical encephalitis).

In CSF-only positive patients, the most common clinical presentation was myelitis (n = 8%, 88.9%) while 1 patient had a bilateral optic neuritis.

Detailed clinical presentation classified according to MOG-Abs positivity is provided in Table 1.

Application of the 2023 MOGAD Diagnostic Criteria

MOGAD diagnostic criteria were applied at the time of the first available MOG-Abs testing result, which was at onset in 180

Table 1 Demographic and Clinical Data of Included Patients According to MOG-Abs Positivity

	Whole cohort, n = 214	Clear positive serum MOG-Abs, n = 89	Low-positive/positive with unknown titer serum MOG-Abs/CSF-only positive, n = 125	*p* Value
Age, median (IQR)	38.2 (25.2–50.7)	37.1 (23–50.9)	39 (26.6–50.8)	0.324
Female sex, n (%)	129 (60.3)	55 (61.8)	74 (59.2)	0.702
Live MOG-Abs CBA analysis	170 (79.4)	78 (87.6)	92 (73.6)	0.027
Clinical presentation and radiologic compatible supportive features, n (%)				
Optic neuritis	106 (49.5)	51 (58)	55 (44)	0.055
Bilateral optic neuritis	30 (28.3)	17 (33.3)	13 (29.5)	0.210
Longitudinal optic nerve involvement	32 (30.2)	15 (29.4)	17 (30.1)	0.874
Perineural optic sheath enhancement	28 (26.4)	15 (29.4)	13 (23.6)	0.207
Optic disk edema	38 (35.8)	22 (43.1)	16 (29.1)	0.184
Presence of any supportive feature	70 (66)	34 (66.7)	36 (65.5)	0.895
Myelitis	79 (36.9)	32 (36)	47 (37.6)	0.806
Longitudinally extensive myelitis	43 (54.4)	15 (46.8)	28 (59.6)	0.409
Central cord lesion or H-sign	34 (43)	8 (25)	26 (55.3)	0.016
Conus lesion	33 (41.8)	14 (51.9)	19 (40.4)	0.554
Presence of any supportive feature	52 (65.8)	16 (50)	36 (76.6)	0.057
Brainstem or cerebellar deficit	22 (10.3)	6 (6.7)	16 (12.8)	0.150
ADEM	15 (7)	8 (9)	7 (5.6)	0.339
Cerebral monofocal or polyfocal deficit	12 (5.6)	3 (3.4)	9 (7.2)	0.230
Cerebral cortical encephalitis often with seizures	9 (4.2)	4 (4.5)	5 (4)	0.859
Multiple ill-defined T2 hyperintense lesions in supratentorial and often infratentorial white matter	32 (55.2)	12 (57.1)	20 (36.4)	0.747
Deep gray matter involvement	15 (27.3)	6 (30)	9 (25.7)	0.731
Ill-defined T2-hyperintensity involving pons, middle cerebellar peduncle, or medulla	28 (48.3)	11 (52.4)	17 (45.9)	0.577
Cortical lesions with or without lesional and overlying meningeal enhancement	15 (25.9)	6 (28.6)	9 (25.7)	0.731
Presence of any supportive feature	44 (75.86)	19 (90.5)	25 (67.6)	0.026
Other clinical presentations	5 (2.3)	3 (3.4)	2 (1.7)	0.398
Multifocal presentations	26 (12.2)	13 (14.6)	13 (10.4)	0.365
Presence of any supportive feature (according to clinical presentation)	155 (72.4)	65 (73)	90 (72)	0.839
Presence of any supportive feature (according to MRI asymptomatic lesions)	29 (15)	13 (14.6)	16 (12.8)	0.647
CSF analysis	N = 180	N = 74	N = 106	
Cell count, n/uL, median (IQR)	7 (1–24.3)	5.5 (1–27.5)	8 (1.8–24.3)	0.851
Protein concentration, g/dL, median (IQR)	41.8 (26–57)	40 (21–66.5)	42 (29.7–56.6)	0.371
CSF-restricted oligoclonal bands, n (%)	75/189 (39.7)	23/78 (29.5)	52/111 (46.8)	0.016

Continued

Table 1 Demographic and Clinical Data of Included Patients According to MOG-Abs Positivity *(continued)*

	Whole cohort, n = 214	Clear positive serum MOG-Abs, n = 89	Low-positive/positive with unknown titer serum MOG-Abs/CSF-only positive, n = 125	*p* Value
Final diagnosis				
MOGAD, n (%)	179 (83.6)	85 (95.5)	94 (74.4)	<0.001
True-positive cases classified after revision, n (%)	177 (82.7)	85 (95.5)	92 (73.6)	<0.001
True-negative cases classified after revision, n (%)	22 (10.3)	2 (2.2)	20 (16)	0.001
False-positive cases classified after revision, n (%)	2 (0.9)	2 (2.2)	0	0.092
False-negative cases classified after revision, n (%)	2 (0.9)	0	2 (1.6)	0.233
Patients unclassified after revision, n (%)	11 (5.1)	0	11 (8.8)	0.004

Abbreviations: ADEM = acute disseminated encephalomyelitis; IQR = interquartile range; MOG = myelin oligodendrocyte glycoprotein.

patients (84.9%, median time from onset to testing 0.5 months [IQR 0.3–2.6]), while 34 patients (15.9%) were tested after a median of 56 months from onset ([IQR 54.4–123.7])

Supportive criteria were present in 155 of 214 patients (72.4%), in particular in 65 of 89 patients with a clear positive result (73%) and in 90 of 125 patients with serum unknown/low-positive MOG-Abs titer or isolated CSF MOG-Abs positivity (72%).

Final diagnoses provided by the referring centers were MOGAD in 191 patients (89.3%), MS in 13 (6.1%), and other inflammatory diseases in 10 (4.7%). When applying MOGAD diagnostic criteria according to the final diagnosis, 168 patients (78.5%) were classified as TP, 9 (4.2%) as FP, 23 (10.7%) as FN, and 14 (6.5%) as TN. Accordingly, MOGAD criteria had a sensitivity of 87.96% (CI 82.5%–92.2%) and a specificity of 60.9% (CI 38.5%–80.3%). The PPV was 94.9% (CI 91.8%–96.9%), NPV was 37.8% (CI 26.7%–50.2%), and accuracy was 85.1% (CI 79.6%–89.5%).

Independent Review of FP and FN Cases

As per the study protocol, FP and FN cases (n = 32) were independently reviewed to reassess the diagnosis of MOGAD, as shown in Figure 1. Representative neuroimaging findings of this subgroup are illustrated in Figure 2.

In 11 of 32 cases (34.4%), clinical/radiologic information was believed to be insufficient to establish a definite diagnosis. Of note, in 5 cases, MRI scans were not available for review; 4 patients with ON did not undergo orbital MRI; and 2 patients with myelitis did not undergo axial MRI. Two patients fulfilled MOGAD diagnostic criteria only at relapse and an additional one at follow-up (i.e., MOG-Abs with unknown titer at onset and clearly positive at follow-up, therefore reclassified as TP). After excluding patients with insufficient information, the final diagnosis was changed after central revision in 17 of 21 (81%). In particular, 8 cases (5 FP and 3 FN) were reclassified as TP and 9 (2 FP and 7 FN) were reclassified as TN (eTable 1).

Therefore, 177 of 214 patients (82.7%) were considered as TP, 2 of 214 (0.9%) as FP, 2 of 214 (0.9%) as FN, 22 of 214 (10.3%) as TN, and 11 of 214 (5.1%) as unclassified for insufficient clinical/radiologic information. After revision, MOGAD diagnostic criteria had a sensitivity of 98.9% (CI 96%–99.9%) and a specificity of 91.7% (CI 73%–98.9%). The PPV of MOGAD diagnostic criteria after central revision was 98.9% (CI 95.9%–99.7%) and the NPV was 91.7% (CI 73.4%–99.5%), with an accuracy of 98% (CI 95%–99.5%).

MOGAD diagnosis was more common in patients with clear positive MOG-Abs (85/89, 95.5%) and in isolated CSF positive patients (8/9, 88.9%) than in low-positive ones (n = 61/86, 70.9%, $p < 0.001$).

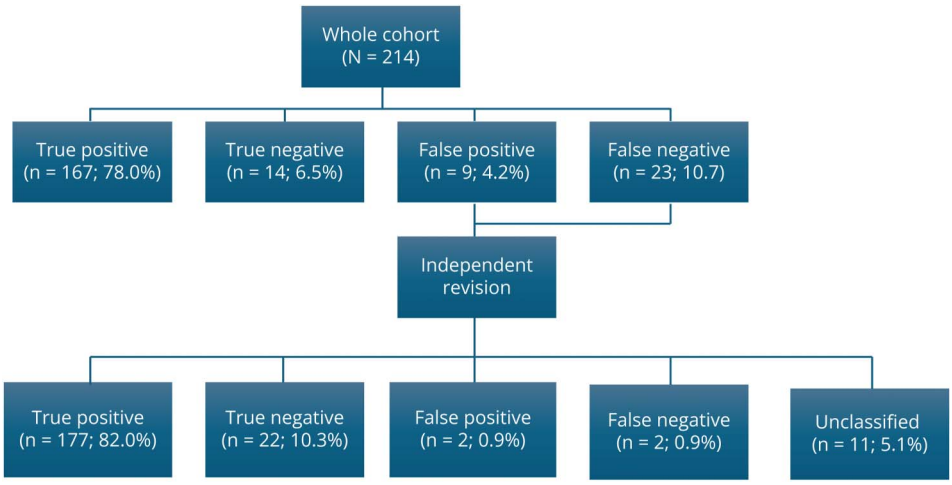
Final diagnosis of MOGAD, TP, TN, FN, and FP did not differ significantly according to the type of assay used (live vs fixed CBA, MOGAD diagnosis $p = 0.852$, TP $p = 0.998$, TN $p = 0.530$, FN $p = 0.484$, and FP $p = 0.485$, respectively).

When including only patients tested in both matrix (i.e., serum and CSF, n = 84), serum/CSF status did not influence final diagnosis/classification (only seropositive patients vs serum and CSF positive patients vs CSF-only positive patients: MOGAD diagnosis $p = 0.459$, TP $p = 0.494$, TN $p = 0.331$, FN $p = 0.883$ and FP $p = 0.558$).

Of note, 3 patients with a clear positive MOG-Abs titer in the live CBA did not receive a final diagnosis of MOGAD (1 with MS, 1 with herpes simplex virus encephalitis, 1 with leukopathy of unknown etiology, Case 1), and 1 patient with longitudinally extended transverse myelitis tested positive for both low-titer MOG-Abs and AQP4-Abs, therefore, was classified as TN.

Moreover, 29 of 214 patients had 1 or more asymptomatic radiologic supportive features (i.e., 20 patients presented with multiple ill-defined T2 hyperintense lesions in supratentorial and

Figure 1 Application of the 2023 MOGAD Diagnostic Criteria in Our Cohort



MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease.

infratentorial white matter; 8 had ill-defined lesion involving the pons, middle cerebellar peduncle, or medulla; 2 presented with cortical lesions; 2 had deep gray matter involvement; and 6 presented with radiologic supportive features for myelitis).

Among these, 4 of 29 patients did not have any radiologic supportive feature for the presenting clinical symptoms despite clear positive MOG-Abs and were, therefore, diagnosed as MOGAD and considered TP. One patient with low MOG-Abs titer was diagnosed as MS (TN).

Supportive clinical/radiologic features were reported in 6 patients (4 with low MOG-Abs titer, 1 with unknown titer, and 1 with high MOG-Abs titer) who received a final diagnosis different from MOGAD, including MS, but in 50% of cases, these were not confirmed at independent revision.

The final diagnosis was MOGAD in 22 of 23 pediatric patients. One patient with serum high-titer MOG-Abs and paired CSF positivity presenting with nausea, vomiting, and seizures received a final diagnosis of herpetic encephalitis. Supportive criteria were present in 22 of 23 patients (95.7%). The sensitivity and specificity of MOGAD criteria applied in the pediatric cohort were 100% (CI 85%–100%) and 100% (CI 21%–100%), respectively.

Among patients with CSF-only positive MOG-Abs, 8 of 9 (88.9%) met the supportive criteria and received a final diagnosis of MOGAD. However, 1 patient, initially diagnosed with MOGAD but lacking supportive criteria, had insufficient records for clinical review.

Challenges encountered when applying MOGAD diagnostic criteria are presented further in illustrative clinical cases.

Description of Clinical Cases

Case 1 (FP)

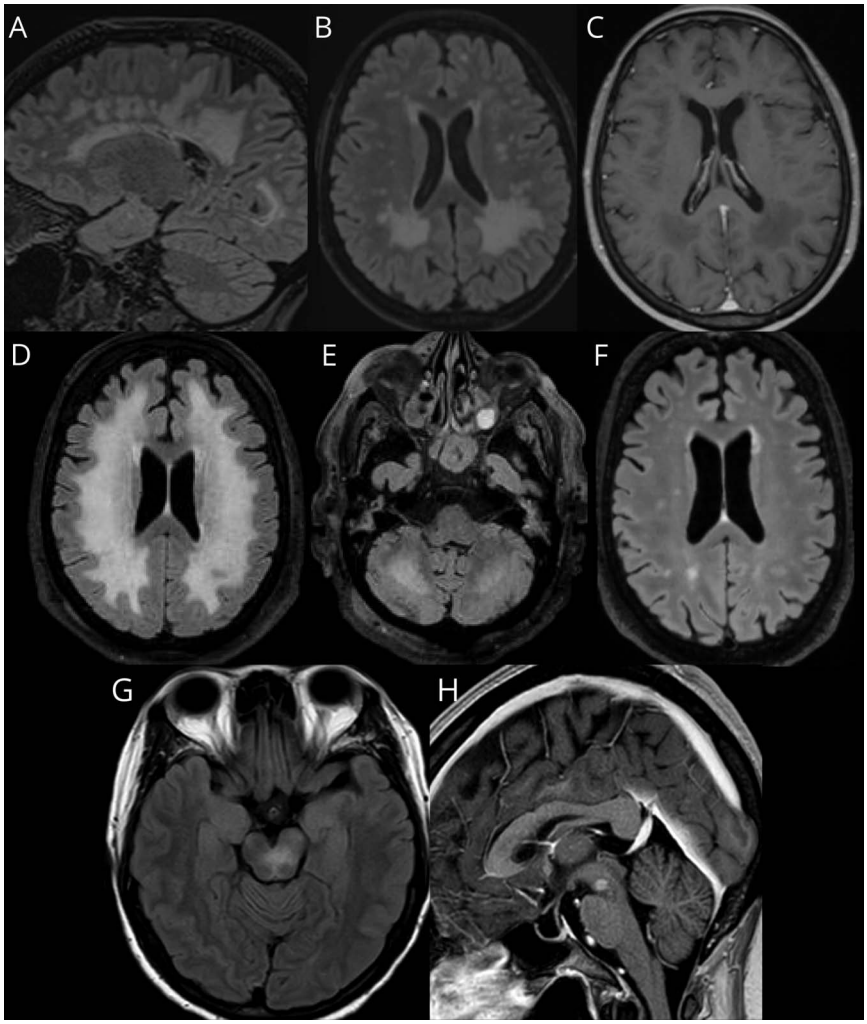
An adult patient presented to the emergency unit with sudden onset of hypoesthesia affecting the second and third branches of the left trigeminal nerve. Two weeks after, symptoms worsened, affecting the contralateral side. Neurologic examination was otherwise unremarkable. The patient reported no relevant medical history, and routine laboratory analyses were within normal limits.

Brain MRI revealed diffuse supratentorial leukodystrophy, which appeared hypointense on T1-weighted images without gadolinium enhancement (Figure 2). CSF analysis was normal, with the exception of a single CSF band detected through isoelectric focusing. A comprehensive vascular workup including echocardiography, carotid duplex ultrasonography, Holter electrocardiography, and thrombophilia screening yielded negative results.

Testing for MOG-Abs using a live cell-based assay was clearly positive in serum but negative in CSF. Given MOG-Abs positivity and the absence of other identifiable causes, the patient was treated with IV methylprednisolone (1 g daily for 5 days). However, no clinical improvement was observed. MOG-Abs were retested 4 times over the following year, consistently yielding clear positive results. Follow-up brain MRI scans performed 1 and 2 years after symptom onset were stable.

While the presence of clear positive MOG-Abs with a core clinical feature (i.e., brainstem deficit) fulfills MOGAD diagnostic criteria, the overall clinical presentation, lack of response to corticosteroids, and disease course are atypical. Given these discrepancies, this case was classified as FP.

Figure 2 MRI Scans of MOG-Abs–Positive Patients



Case 1: T2/fluid-attenuated inversion recovery (FLAIR)-weighted sequences showed diffuse, symmetrical, supratentorial white matter hyperintensity (A and B), hypointense in T1-weighted sequences with no contrast enhancement (C). Case 2: Diffuse and symmetrical white matter hyperintensity involving supratentorial (D) and infratentorial regions (E) is shown in T2/FLAIR-weighted sequences. Follow-up brain MRI performed 4 months later showed an almost complete lesion resolution (F). Case 3: Brain MRI revealed an ill-defined T2/FLAIR hyperintense lesion located in the midbrain (G) with associated gadolinium enhancement (H). MOG-Abs = MOG antibodies.

Case 2 (FN)

We previously reported the case of an adult patient who was hospitalized for pneumonia and acute kidney failure and afterward developed subacute consciousness decline requiring orotracheal intubation.[19] Neurologic examination revealed a comatose state with no response to painful stimuli and right-sided pyramidal signs. Brain MRI showed diffuse T2/fluid-attenuated inversion recovery (FLAIR) leukodystrophy-like hyperintense lesions in both the supratentorial and infratentorial white matter, including the brainstem (Figure 2). EEG demonstrated generalized theta and delta slowing without epileptic abnormalities. CSF analysis revealed mild pleocytosis (10 cells/mm^3).

A comprehensive evaluation for CNS infections, autoimmune and paraneoplastic encephalitis, metabolic encephalopathy, and uremic hemolytic syndrome was unremarkable, except for the detection of serum low-titer MOG-Abs using a live CBA. Based on these findings, the patient was treated with high-dose IV steroids, followed by oral tapering, leading to significant improvement. During clinical examination, a skin lesion on the right hemithorax was noted, raising suspicion of malignancy. A biopsy was performed, and histologic analysis confirmed a locally invasive melanoma. Four months later, the patient was asymptomatic with a normal neurologic examination. MOG-Abs titer decreased, and follow-up MRI demonstrated near-complete resolution of previously detected lesions. After 2 years, no relapse occurred.

This patient had serum low-titer MOG-Abs and a clinical presentation compatible with ADEM, but the radiologic profile was atypical for MOGAD. The involvement of the white matter was widespread and symmetrical, not consistent with multifocal T2 bright lesions, which represent the supportive radiologic feature for this core clinical MOGAD presentation. However, the clinical and radiologic evolution and the prompt response to corticosteroids support MOGAD diagnosis, suggesting in this case a FN result.

Case 3 (TP)

An adult patient presented to the emergency department with subacute onset of generalized weakness and dysarthria. Medical history was notable only for diabetes. Neurologic examination showed dysarthria and was otherwise unremarkable. Routine laboratory tests were normal. Brain MRI revealed a 5-mm T2 hyperintense lesion in the midbrain, with postgadolinium enhancement (Figure 2). CSF analysis was negative. The live MOG-Abs CBA was clearly positive in serum with paired CSF positivity. The patient was treated with methylprednisolone 1 g for 5 days, followed by short steroid tapering due to diabetes. After treatment, clinical symptoms fully recovered, and a follow-up MRI scan 1 year later showed partial lesion resolution.

The patient had a core clinical feature (brainstem deficit) with a lesion located in the midbrain, which did not fulfill MOGAD supportive features. However, because this patient had a clear positive MOG-Abs result, no additional supportive criteria were needed for MOGAD diagnosis.

Discussion

In this study, we evaluated the performance of the 2023 MOGAD diagnostic criteria in a multicenter cohort of MOG-Abs–positive patients and explored the discrepancies in their application in challenging cases.

In particular, we observed the following: (1) an independent case-based revision can improve the performance of the MOGAD diagnostic criteria, in particular in more challenging presentations; (2) the main challenging aspects in the application of the MOGAD criteria are the availability of adequate MRI data and the interpretation of radiologic findings; (3) patients with MOGAD can sometimes satisfy diagnostic criteria only at follow-up; (4) patients with serum high-titer or CSF-only MOG-Abs are those who receive more commonly a MOGAD diagnosis.

Our study confirms that MOGAD diagnostic criteria perform well in clinical practice.[17,18,20-24] Similar to other studies, we observed that the performance is better in the pediatric population, which shows more commonly supportive features.[18] However, sensitivity/specificity and accuracy were similar to those previously reported only when challenging cases (FNs and FPs) were independently re-evaluated, thus suggesting that misinterpretation of criteria might occur. This underlines the relevance of discussing challenging cases, as the illustrative ones reported here, and the importance of reassessing MOGAD criteria during subsequent relapses and of obtaining appropriate neuroimaging including spinal cord axial sequences and dedicated imaging of the optic nerve.

Indeed, a critical point in the application of the MOGAD criteria is the availability of adequate radiologic imaging/sequences and the interpretation of radiologic supportive features, which can hinder the correct evaluation of supportive criteria.

Furthermore, the role of asymptomatic lesions, which do not align with radiologic supportive features according to the proposed MOGAD criteria,[16] was not negligible in our cohort. The inclusion of suggestive asymptomatic lesions among the supportive features of the diagnostic criteria could enhance their sensitivity. Further evaluation is needed because this might compromise specificity, given that MS, one of the primary differential diagnoses, is typically characterized by silent radiologic lesions.[25]

Finally, as illustrated in Case 3 and already reported,[26,27] midbrain involvement can occur in patients with MOGAD, even in isolation, although this feature is not included among the supportive criteria. Incorporating this location and valuing radiologic lesion evolution over time might further increase diagnostic sensitivity and could be considered for future iterations of diagnostic criteria.

These results highlight the relevance of proper complementary examinations and the need to apply standard MRI protocols, as already proposed.[21,23,28] Of note, supportive clinical/radiologic features were equally distributed across patients with different antibody status and absent in around 30% of cases. In these cases, MOG-Abs titration or antibody testing performed with more sensitive live CBAs might help achieve a correct diagnosis.[29]

Similar to other studies,[20,21] we observed that few patients satisfy the diagnostic criteria only at follow-up. This observation suggests re-evaluating patients who do not fulfill the criteria at first analysis over the follow-up, particularly in cases with remote attacks or inadequate information.

Finally, although diagnoses different than MOGAD can occur with clear positive results, we confirm, in line with the correlation of MOG-Abs titers with their PPV, that they are more frequent when low-positive MOG-Abs results are encountered.[11,13,21] Of note, similar to clear positive cases, CSF-only positive patients were usually properly diagnosed with MOGAD. Although MOG-Abs CSF testing is still debated, our data reinforce the utility of this analysis in clinical practice.

Our study has limitations related to the retrospective design, including selection bias, incomplete data collection, and the lack of standardized imaging protocols, and the main inclusion of adult patients. In addition, only cases showing discrepancy between clinical evaluation and criteria application were centrally revised, partially limiting the accuracy of our results. Of note, we observed in our cohort a high frequency of clear positive results and most samples were tested with live CBAs, which are not broadly available worldwide; these findings may have influenced criteria interpretation and

may hinder the reproducibility of our findings in different cohorts.[23] Unintentional selection and referral bias may have also influenced cohort characteristics and results.

In addition, independent clinical case revision was applied only to FP and FN cases and not systematically, although typical clinical manifestations of MOGAD are more easily recognized in clinical practice than atypical ones. Finally, similar to previous studies,[18] the performance of MOGAD diagnostic criteria was evaluated using clinicians' assessment as the gold standard, despite its susceptibility to subjective biases and interpretation.

Nevertheless, our data provide robust examination of the performance of the MOGAD proposed criteria in clinical practice and provide some relevant issues that need to be further evaluated in prospective studies and potentially considered in future MOGAD criteria revision.

Author Contributions

S. Carta: 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. E. Sechi: 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. Dinoto: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. C. Mancinelli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Greco: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G.T. Maniscalco: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Cornacchini: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.P. Giannoccaro: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Calabria: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Marziali: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Masciocchi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Risi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Cossu: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. I. Volonghi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Cantalupo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Zoccarato: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R. Orlandi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Del Zotto: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Ferraro: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Trentinaglia: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. De Biase: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L Grazian: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Caleri: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M.R. Bianchi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Rossi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E. Virgilio: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Capobianco: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R. Cortese: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Tortorella: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Rossi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. De Luca: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Perelli: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Bozzetti: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Zuliani: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Nosadini: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Sartori: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Brambilla: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Gajofatto: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Vogrig: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Massacesi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. V. Damato: drafting/revision of

the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Gastaldi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. 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.

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