RESEARCH ARTICLE

Significance of Myelin Oligodendrocyte Glycoprotein Antibodies in CSF

A Retrospective Multicenter Study

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Abstract

Background and Objectives

Although the diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is based on serum MOG antibodies (MOG-Abs) positivity, patients with coexisting or restricted MOG-Abs in the CSF have been reported. The aim of this study is to characterize the relevance of CSF MOG-Abs positivity in clinical practice.

Methods

Eleven medical centers retrospectively collected clinical and laboratory data of adult and pediatric patients with suspected inflammatory CNS disease and MOG-Abs positivity in serum and/or CSF using live cell-based assays. Comparisons were performed using parametric or nonparametric tests, as appropriate. Potential factors of unfavorable outcomes were explored by Cox proportional hazard models and logistic regression.

Results

The cohort included 255 patients: 139 (55%) women and 132 (52%) children (i.e., <18-year-old). Among them, 145 patients (56.8%) had MOG-Abs in both serum and CSF (MOG-Abs seropositive and CSF positive), 79 (31%) only in serum (MOG-Abs seropositive and CSF negative), and 31 (12%) only in CSF (MOG-Abs seronegative and CSF positive). MOG-Abs seronegative and CSF positive predominated in adults (22% vs 3% of children), presented more commonly with motor (n = 14, 45%) and sensory symptoms (n = 13, 42%), and all but 4 (2 multiple sclerosis, 1 polyradiculoneuritis, and 1 Susac syndrome) had a final diagnosis compatible with MOGAD. When comparing seropositive patients according to MOG-Abs CSF status, MOG-Abs seropositive and CSF positive patients had a higher Expanded Disability Status Scale (EDSS) at nadir during the index event (median 4.5, interquartile range [IQR] 3.0–7.5 vs

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Glossary

Abs = antibodies; **ADEM** = acute disseminated encephalomyelitis; **ARR** = annualized relapse rate; **CBA** = cell-based assays; **CNS** = central nervous system; **CI** = confidence interval; **DMD** = disease-modifying drug; **EDSS** = Expanded Disability Status Scale; **IF** = immunofluorescence; **IQR** = interquartile range; **MOG** = myelin oligodendrocyte glycoprotein; **MOG-Abs** = MOG antibodies; **MOGAD** = myelin oligodendrocyte glycoprotein antibody associated disease; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **OR** = odds ratio.

3.0, IQR 2.0–6.8, $p = 0.007$) and presented more commonly with sensory (45.5% vs 24%, $p = 0.002$), motor (33.6% vs 19%, $p = 0.021$), and sphincter symptoms (26.9% vs 7.8%, $p = 0.001$) than MOG-Abs seropositive and CSF negative. At the last follow-up, MOG-Abs seropositive and CSF positive cases had more often persistent sphincter dysfunction (17.3% vs 4.3%, $p = 0.008$). Compared with seropositive patients, those MOG-Abs seronegative and CSF positive had higher disability at the last follow-up ($p \leq 0.001$), and MOG-Abs seronegative and CSF positive status were independently associated with an EDSS ≥3.0.

Discussion

Paired serum and CSF MOG-Abs positivity are common in MOGAD and are associated with a more severe clinical presentation. CSF-only MOG-Abs positivity can occur in patients with a phenotype suggestive of MOGAD and is associated with a worse outcome. Taken together, these data suggest a clinical interest in assessing CSF MOG-Abs in patients with a phenotype suggestive of MOGAD, regardless of the MOG-Abs serostatus.

Myelin oligodendrocyte glycoprotein (MOG) has been identified as a target of circulating serum antibodies (Abs) in patients with a distinctive demyelinating CNS condition named MOG antibodies (MOG-Abs)-associated disease (MOGAD). The development of highly sensitive live cell-based assays (CBAs), displaying a very good interassay agreement,[1] has allowed the clinical-MRI spectrum of this disorder to be defined and differentiated from multiple sclerosis (MS) and aquaporin-4-antibody-positive neuromyelitis optica spectrum disorder (NMOSD).[2] MOGAD can have a monophasic or relapsing course, manifesting most often with optic neuritis and/or myelitis in adults and acute disseminated encephalomyelitis (ADEM) or optic neuritis in children. Non-ADEM encephalitis, brainstem, or cerebellar syndromes can also occur.[3-15] The prognosis is usually good, but moderate-severe disability has been reported, emphasizing the need to identify predictors of long-term outcome.[16-18]

Currently, a diagnosis of MOGAD requires the presence of MOG-Abs in the serum of patients with a compatible clinical-MRI phenotype.[2,3,19] Accordingly, MOG-Abs are thought to be primarily produced in the periphery and may mediate their pathogenic effect in the CNS after crossing the blood–brain barrier in concomitance with T cell activation.[20-23] However, recent studies reported paired serum and CSF positivity in 41%–61% of patients[23,24] and also some cases with isolated CSF MOG-Abs positivity,[7,25-28] suggesting intrathecal MOG-Abs production. Isolated CSF MOG-Abs cases are rare and have clinical and pathologic findings similar to seropositive patients. However, there are some reports of CSF isolated positivity in patients with MS in both adults and in children.[7,27]

The aim of our study was to evaluate the frequency and the clinical utility of CSF MOG-Abs positivity in both adults and children with suspected inflammatory CNS disorders.

Methods

Study Subjects

This study includes patients with suspected inflammatory demyelinating diseases of the CNS and MOG-Abs positivity in serum and/or CSF retrospectively enrolled from 11 centers (Italy, Spain, France, Austria, Germany, Switzerland, Australia, and the United States, eTable 1, links.lww.com/WNL/C527). Only patients with available paired serum and CSF obtained within a month interval from each other were included.

To determine the specificity of CSF-only MOG-Abs in relation to MOGAD, a control group of patients with a final diagnosis of MS according to the updated diagnostic criteria[29] and with available paired serum and CSF samples was also included.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was part of the research protocol approved by the Ethics Committees of the enrolling centers: prog. 1052CESC Verona-Rovigo approved by the Ethics Committee of Verona University Hospital (Italy), COOLIN-BRAIN CER-VD—approval number: 2018-01622 for Lausanne University Hospital (Switzerland), EK 1123/2015 for the Medical University of Vienna (Austria), AN4095 approved by the Ethics Committee of the Medical University of Innsbruck (Austria), 12/CHW/295 approved by the human research ethics committee at the Sydney Children's Hospitals Network (Australia), protocol approved by the institutional review board at Mayo Clinic College of Medicine, Rochester (MN, USA), PR(AG)398/2020 for Cemcat, Barcelona (Spain), and HCB/2014/0297 approved by the Ethic Committee of the Hospital Clinic of Barcelona (Spain). Samples from the Hospital Clinic of Barcelona are deposited in the registered biobank of Institut d'Investigació Biomèdica August Pi I Sunyer

Table 1 Demographic and Clinical Data of CSF-Only MOG-Abs Positive Patients

CSF-restricted MOG-Abs positive patients (n = 31)		
Demographic data	Pediatric patients, n (%)	4 (12.9)
	M:F ratio	1:1.8
	Age at onset (y), median [range]	32 (6–85)
	Acute treatment before MOG-Abs sampling, n (%)	12 (37.2)
	Time from onset to sampling (d), median (range)	2.4 (0–406)
Clinical data	Time from onset to symptoms nadir (d), median (range)	7 (1–90)
	EDSS at nadir of attack, median (range)	3.5 (2–10)
	Visual symptoms at onset, n (%)	10 (32.5)
	Visual acuity ≤0.2 (20/100), n/tot (%)	1/8 (12.5)
	Motor symptoms, n (%)	14 (45.2)
	Sensory symptoms, n (%)	13 (41.9)
	Sphincter dysfunction, n (%)	7 (22.6)
	Encephalopathy, n (%)	5 (16.1)
	Brainstem symptoms, n (%)	8 (25.8)
CSF data	Pleocytosis, n (%)	19 (61.3)
	Protein concentration, median (range)	0.6 (0.1–5.16)
	Increased IgG index, n/tot (%)	6/20 (30)
	Oligoclonal bands, n/tot (%)	14/27 (51.9)
Disease course and outcome	Follow-up (mo), median (range)	9 (0.3–416.4)
	Relapsing disease, n (%)	9 (29.0)
	Annualized relapse rate, mean (SD)	0.4 (0.9)
	EDSS at the last follow-up, median (range)	2.0 (0.0–10.0)
	EDSS ≥3, n (%)	13 (41.9)
	Visual acuity at the last follow-up, median (range)	1 (0.4–1) 20/20 (20/50-20/20)
	Pyramidal FS ≥ 3 at last follow-up, n/tot (%)	6/28 (21.4)
	Sphincter dysfunction at the last follow-up, n/tot (%)	8/29 (27.6)
	Patients under chronic treatment at the last follow-up, n (%)	18 (58.1)
	Classic immunosuppressants	9 (29%)
	MS disease-modifying drugs	1 (3.2%)
	Other immunosuppressants	8 (25.8%)
Final diagnosis, n (%)	Seronegative NMOSD	8 (25.8)
	Encephalitis	6 (13.3)
	Encephalitis + myelitis	3 (9.7)
	Myelitis	4 (12.9)
	Optic neuritis	4 (12.9)
	Optic neuritis + myelitis	2 (6.5)
	MS	2 (6.5)
	Susac syndrome	1 (3.2)
	Acute polyradiculoneuritis	1 (3.2)

Abbreviations: % = percentage; CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; FS = Functional System; IQR = interquartile range; MS = multiple sclerosis; N = number; NMOSD = neuromyelitis optica spectrum disorders.
Visual acuity was measured through the Snellen Chart and reported in decimals; the 20/20 scale is also displayed. Acute treatment includes intravenous corticosteroids, plasma exchange, and intravenous immunoglobulins.

(IDIBAPS). Informed consent for storage and use of these samples for research purposes was obtained from all patients.

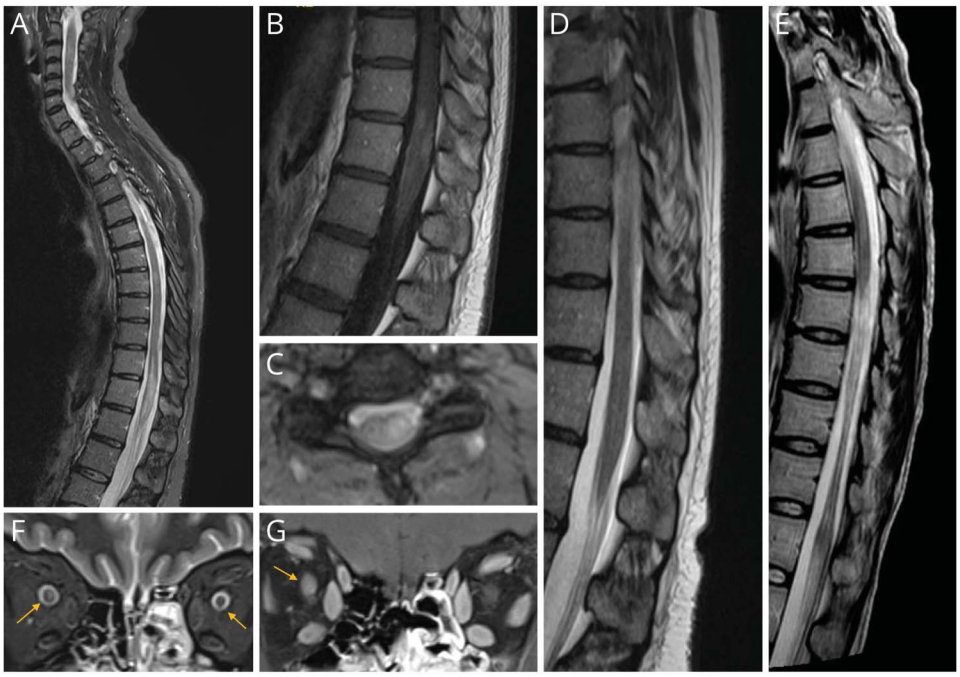
MOG-Abs Testing

Serum and CSF samples were tested for MOG-Abs through live CBA quantified by either flow cytometry (FACS) or microscopic visual score evaluation in immunofluorescence in the reference laboratory for each recruiting center. When a live CBA was not available, a reference center (the Neuropathology and Neuroimmunology Laboratory, University of Verona, Italy) performed the analysis. MOG-Abs positivity in serum and CSF was defined according to the cut-off previously established in each reference laboratory (eTable 1, links.lww.com/WNL/C527). Patients were classified according to paired serum/CSF MOG-Abs results into (1) isolated CSF positive (MOG-Abs seronegative and CSF positive), (2) isolated serum positive (MOG-Abs seropositive and CSF negative), and (3) paired serum and CSF positive (MOG-Abs seropositive and CSF positive). All MOG-Abs seronegative and CSF positive samples were independently retested in a blinded manner in a second expert laboratory (Neurologic Research Laboratory, Medical University of Innsbruck, Austria) for confirmation.[1]

Demographic and Clinical Information

Clinical and paraclinical data were retrospectively collected in a dedicated database by different referring physicians from the involved centers. Information comprised (1) demographic data (sex and age at onset, defining 2 groups: adults ≥18-year-old and children <18-year-old); (2) dates of different clinical episodes; (3) visual acuity (collected through the Snellen Chart, in case of bilateral visual loss the value of the worst eye was considered) and disability at nadir of the clinical episode

Figure 1 Radiologic Findings of MOG-Abs Seronegative and CSF Positive Patients



Spinal cord MRI displayed short T2-hyperintense lesions in the cervical and thoracic spinal cord (C2-C3, C6, T8) and a longitudinally extensive lesion (T11-L1) involving conus medullaris (A) that had patchy postcontrast enhancement (B). Transversal section on the cervical spinal cord showed T2-hyperintensity, more evident on the left (C). The follow-up MRI performed 7 months after the clinical episode and intravenous steroids treatment showed an almost complete normalization (D). A follow up MRI of a MOG-Abs seronegative and CSF positive patient who had a LETM showing marked spinal cord atrophy of the thoracic segment (E). Orbital MRI of a patient with bilateral optic neuritis showed bilateral anterior optic nerve thickening (F) and postcontrast enhancement (bilateral, left optic nerve enhancement not shown, G).

and at the last follow-up (Expanded Disability Status Scale [EDSS], or Pyramidal Functional System Score); (4) CSF information (protein concentration, cell count, oligoclonal bands presence, and IgG index); (5) acute treatment including intravenous corticosteroids, plasma exchange, and intravenous immunoglobulins (IVIg); and (6) maintenance therapy including azathioprine, mycophenolate mofetil, rituximab, other MS-disease-modifying drugs, and other treatments (cyclophosphamide, methotrexate, mitoxantrone, IVIG, tocilizumab).

A clinical attack was defined as the occurrence of new symptoms or exacerbation of existing symptoms persisting for at least 24 hours in the absence of fever and infection.

Statistical Analysis

For descriptive statistics, quantitative variables are expressed as median (interquartile ranges [IQRs]) or mean (SD) and categorical variables as percentages. For group comparisons (MOG-Abs seropositive and CSF positive/MOG-Abs seropositive and CSF negative/MOG-Abs seronegative and CSF positive), parametric (t-test or χ^2) or nonparametric (Kruskal-Wallis, Wilcoxon, or exact Fisher) tests were performed, as appropriate.

To evaluate time to first relapse and the risk of disability MOG-Abs seropositive and CSF positive or MOG-Abs seropositive and CSF negative patients were both considered seropositive and compared with MOG-Abs seronegative and CSF positive cases. First, to evaluate time to first relapse, a Kaplan-Meier curve was performed. Second, to assess disability (defined as reaching EDSS ≥3.0 at the last follow-up), univariate binary logistic regression models were performed according to baseline covariates (age at onset, sex, disability at onset measured by EDSS, oligoclonal bands, and CSF pleocytosis), and treatment received over the follow-up. Variables resulting from the univariate analysis with a p-value ≤ 0.20 were included in a multivariate binary regression model. The model was adjusted by time of follow-up. The results were expressed as odds ratio (OR) with 95% of CI. A p-value of 0.05 was considered statistically significant. All statistical analyses were performed with STATA-12 software (64-bit, StataCorpi, College Station, TX).

Data Availability

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

Results

Demographic Data and Cohort Subdivision

The study included 255 patients: 139 (54.5%) were women, median age at onset was 16 years old [IQR 6–39], and 132 (51.8%) were pediatric patients. Most patients were tested within 3 months from onset or relapse (69.6% and 11.3%, respectively), and 59.6% received acute treatment before sampling. Among them, 145 cases (56.8%) were MOG-Abs seropositive and CSF positive, 79 (31%) MOG-Abs seropositive and CSF negative, and 31 (12.2%) MOG-Abs seronegative and CSF positive. MOG-Abs seronegative and CSF positive status was more common in adults than in children (27/123, 22% vs 4/132, 3.1%, $p < 0.001$), and MOG-Abs

Table 2 Comparison of Demographic and Clinical Data Between MOG-Abs Seropositive and CSF Negative, and MOG-Abs Seropositive and CSF Positive Patients

	Whole group n = 224	MOG-Abs seropositive and CSF negative n = 79	MOG-Abs seropositive and CSF positive n = 145	*p* Value
Pediatric patients, n (%)	128 (57.1)	39 (49.4)	89 (61.4)	
Acute treatment before sampling, n (%)	140 (63.4)	56 (70.9)	84 (59.1)	**0.019**
Time from onset to sampling (d), median (range)	0.5 (0.0–277.7)	0.4 (0.0–146.5)	0.5 (0.0–277.7)	0.521
Age at onset (y), median (range)				
Whole cohort	13 (0–74)	18 (1–67)	12 (0–74)	0.174
Adult patients	43 (18–74)	41 (18–67)	43.5 (18–74)	0.741
Pediatric patients	6.1 (0–17.9)	6.7 (1.0–16)	6 (0–17.9)	0.944
Male:Female ratio				
Whole cohort	1:1.1	1:1.1	1:1.1	0.993
Adult patients	1:1.3	1:1	1:1.5	0.297
Pediatric patients	1:1	1:0.9	1:1.3	0.399
Time from onset to symptoms nadir (d), median (range)				
Whole cohort	7 (0–120)	5 (0–90)	7 (0–120)	0.061
Adult patients	7 (0–90)	7 (0–90)	7 (1–60)	0.257
Pediatric patients	5 (0–120)	4 (1–15)	7 (0–120)	0.123
EDSS at attack nadir, median (range)				
Whole cohort	4.0 (0.0–10.0) (n = 178)	3.0 (0.0–10.0) (n = 64)	4.5 (0.0–9.5) (n = 114)	**0.007**
Adult patients	3.5 (0.0–10.0) (n = 79)	3.0 (0–10) (n = 33)	4.0 (0–9.5) (n = 46)	**0.002**
Pediatric patients	5.0 (0.0–9.5) (n = 99)	5.0 (0–9.5) (n = 31)	5.0 (1–9.5) (n = 68)	0.635
Visual symptoms at onset, n/tot (%)				
Whole cohort	98/224 (43.7)	41/79 (51.9)	57/145 (39.3)	0.070
Adult patients	52/96 (54.2)	27/40 (67.5)	25/56 (44.6)	**0.027**
Pediatric patients	46/128 (35.9)	14/39 (35.9)	32/89 (36.0)	0.995
Visual acuity ≤0.2 (20/100) at attack nadir (in patients with optic neuritis at onset), n/tot (%)				
Whole cohort	39/72 (54.2)	16/31 (51.6)	23/41 (56.1)	0.705
Adult patients	21/45 (46.7)	10/23 (43.5)	11/22 (50.0)	0.661
Pediatric patients	18/27 (66.7)	6/8 (75.0)	12/19 (63.2)	0.551
Motor symptoms, n/tot (%)				
Whole cohort	84/222 (37.8)	19/79 (24.1)	65/143 (45.5)	**0.002**
Adult patients	31/95 (32.6)	8/40 (20.0)	23/55 (41.8)	**0.025**
Pediatric patients	53/127 (41.7)	42/88 (47.7)	11/39 (28.2)	**0.040**
Sensory symptoms, n/tot (%)				
Whole cohort	63/222 (28.4)	15/79 (19.0)	48/143 (33.6)	**0.021**
Adult patients	42/95 (44.2)	13/40 (32.5)	29/55 (52.7)	**0.050**

Continued

Table 2 Comparison of Demographic and Clinical Data Between MOG-Abs Seropositive and CSF Negative, and MOG-Abs Seropositive and CSF Positive Patients *(continued)*

	Whole group n = 224	MOG-Abs seropositive and CSF negative n = 79	MOG-Abs seropositive and CSF positive n = 145	*p* Value
Pediatric patients	21/127 (16.5)	2/39 (5.1)	19/88 (21.6)	**0.021**
Sphincter dysfunction, n/tot (%)				
Whole cohort	45/224 (20.1)	6/79 (7.8)	39/145 (26.9)	**0.001**
Adult patients	34/96 (35.4)	5/40 (12.5)	29/56 (51.8)	**≤0.001**
Pediatric patients	11/128 (8.6)	1/39 (2.6)	10/89 (11.2)	0.107
Encephalopathy, n/tot (%)				
Whole cohort	83/222 (37.4)	23/79 (29.1)	60/143 (42)	0.058
Adult patients	10/95 (10.5)	0/40 (0)	10/55 (18.2)	**0.004**
Pediatric patients	73/127 (57.5)	23/39 (59.0)	50/88 (56.8)	0.821
Brainstem dysfunction, n/tot (%)				
Whole cohort	45/222 (20.3)	18/79 (22.8)	27/143 (18.9)	0.489
Adult patients	15/95 (15.8)	9/55 (16.4)	6/40 (15.0)	0.857
Pediatric patients	30/127 (23.6)	12/39 (30.8)	18/88 (20.5)	0.207
Pleocytosis n/tot (%)				
Whole cohort	137/203 (67.5)	38/74 (51.4)	99/129 (76.7)	**≤0.001**
Adult patients	52/91 (57.1)	14/38 (36.8)	38/53 (71.7)	**0.001**
Pediatric patients	85/112 (75.9)	24/36 (66.7)	61/76 (80.3)	0.116
Protein concentration, median (range)				
Whole cohort	0.36 (0.1–2.8)	0.3 (0.1–1.8)	0.4 (0.1–2.8)	**0.001**
Adult patients	0.4 (0.1–2.8)	0.4 (0.2–1.8)	0.5 (0.1–2.8)	**0.026**
Pediatric patients	0.3 (0.1–1.6)	0.3 (0.1–1.0)	0.3 (0.1–1.6)	**≤0.001**
Increased IgG index n/tot (%)				
Whole cohort	16/100 (16.0)	8/38 (21.1)	8/62 (12.9)	0.281
Adult patients	9/65 (13.9)	5/28 (17.9)	4/37 (10.8)	0.415
Pediatric patients	7/35 (20.0)	3/10 (30.0)	4/21 (16.0)	0.350
Oligoclonal bands n/tot (%)				
Whole cohort	25/161 (15.5)	6/58 (10.3)	19/103 (18.5)	0.173
Adult patients	17/85 (20.0)	6/37 (16.2)	11/48 (22.9)	0.444
Pediatric patients	8/76 (10.5)	0/21 (0.0)	8/55 (14.6)	0.065

Abbreviations: % = percentage; EDSS = Expanded Disability Status Scale; MOG-Abs = MOG antibodies; N = number.
Results with statistically significant difference are marked in bold**.** Visual acuity was measured through the Snellen Chart and reported in decimals; the 20/20 scale is also displayed. Acute treatment includes intravenous corticosteroids, plasma exchange, and intravenous immunoglobulins.

seronegative and CSF positive cases were older at onset (median age 32, IQR [19.0–50.0 vs 13 [IQR 5.3–36]) in comparison to seropositive patients ($p \leq 0.001$). None in the consecutive control cohort of 90 adult patients with MS referred to the Verona Neurology Unit tested positive for MOG-Abs in serum or CSF.

Description of MOG-Abs Seronegative and CSF Positive Cases

MOG-Abs were detected in CSF only in 31 patients, with no discordant results on confirmatory analysis. Of these, 20 (64.5%) were women, median age at onset was 32 years old [IQR 19–47], and 4 (12.9%) were children. Detailed clinical

Table 3 Outcome Comparison Between MOG-Abs Seropositive and CSF Negative, and MOG-Abs Seropositive and CSF Positive Patients

	Whole group n = 224	MOG-abs seropositive and CSF negative n = 79	MOG-abs seropositive and CSF positive n = 145	*p* Value
Follow-up (mo) median, (range)				
Whole cohort	25.3 (0.4–395.4)	20.8 (0.4–155.2)	27.4 (1.2–395.4)	0.056
Adult patients	20.9 (1.2–348.1)	14 (1.6–142.0)	27.9 (1.2–348.1)	**0.015**
Pediatric patients	29.1 (0.4–395.4)	31.9 (0.4–155.2)	27.0 (2.0–395.4)	0.862
Annualized relapse rate, mean, SD				
Whole cohort	0.3 (1.1)	0.4 (1.6)	0.3 (0.6)	0.665
Adult patients	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.488
Pediatric patients	0.4 (1.3)	0.5 (2.2)	0.3 (0.6)	0.981
EDSS at the last follow-up, median, (range)				
Whole cohort	0 (0–10) (n = 220)	1.0 (0–10) (n = 75)	0 (0–9.5) (n = 145)	0.562
Adult patients	1.5 (0–10) (n = 96)	1.0 (0–10) (n = 40)	2.0 (0–9.5) (n = 56)	0.378
Pediatric patients	0 (0–9) (n = 124)	0 (0–9) (n = 35)	0 (0–7) (n = 89)	0.744
EDSS ≥3.0 at the last follow up, n/tot (%)				
Whole cohort	39/220 (17.7)	14/75 (18.7)	25/145 (17.2)	0.793
Adult patients	26/96 (27.1)	10/40 (25.0)	16/56 (28.6)	0.698
Pediatric patients	13/124 (10.5)	4/35 (11.4)	9/89 (10.1)	0.829
Visual acuity at the last follow-up (in patients with visual loss at onset), median, range				
Whole cohort	1.0 (0.0–1.0) 20/20 (0–20/20) (n = 72)	0.8 (0.0–1.0) 20/25 (0–20/20) (n = 30)	1.0 (0.0–1.0) 20/20 (0–20/20) (n = 42)	**0.049**
Adult patients	0.8 (0.0–1.0) 20/25 (0–20/20) (n = 40)	0.8 (0.0–1.0) 20/25 (0–20/20) (n = 21)	1 (0.0–1.0) 20/20 (0–20/20) (n = 19)	0.500
Pediatric patients	1.0 (0.1–1) 20/20 (20/200–20/20) (n = 32)	1.0 (0.1–1) 20/20 (20/200–20/20) (n = 9)	1.0 (0.3–1) 20/20 (20/63–20/20) (n = 23)	0.267
Pyramidal FS ≥ 3 at the last follow-up, n/tot (%)				
Whole cohort	17/207 (8.2)	5/69 (7.3)	12/138 (8.7)	0.720
Adult patients	13/88 (14.8)	4/36 (11.1)	9/52 (17.3)	0.421
Pediatric patients	4/119 (3.4)	1/33 (3.0)	3/86 (3.5)	0.901
Sphincter dysfunction at the last follow-up, n/tot (%)				
Whole cohort	27/209 (12.9)	3/70 (4.3)	24/139 (17.3)	**0.008**
Adult patients	22/88 (25.0)	3/36 (8.3)	19/52 (35.5)	**0.003**
Pediatric patients	5/121 (4.1)	0/34 (0)	5/87 (5.8)	0.153
Maintenance therapy at the last follow up, n/tot (%)				
Not treated	143/222 (64.4)	93/145 (64.1)	50/77 (64.9)	0.969

Continued

Table 3 Outcome Comparison Between MOG-Abs Seropositive and CSF Negative, and MOG-Abs Seropositive and CSF Positive Patients *(continued)*

	Whole group n = 224	MOG-abs seropositive and CSF negative n = 79	MOG-abs seropositive and CSF positive n = 145	*p* Value
Classic immunosuppressants	45/222 (20.3)	30/145 (20.7)	15/77 (19.5)	
MS disease-modifying therapy	2/222 (0.9)	1/145 (0.7)	1/77 (1.3)	
Other immunosuppressants	32/222 (14.5)	21/145 (14.5)	11/77 (14.3)	

Abbreviations: % = percentage; EDSS = Expanded Disability Status Scale; FS = Functional system; MOG-Abs = MOG antibodies; MS: multiple sclerosis; N = number.
Results with statistically significant difference are marked in bold**.** Visual acuity was measured through the Snellen Chart and reported in decimals; the 20/20 scale is also displayed.

and paraclinical data are reported in Table 1, whereas representative radiologic findings are described in Figure 1. At the index event, patients presented more commonly with motor (n = 14, 45.2%) and sensory symptoms (n = 13, 41.9%), suggestive for myelitis or visual symptoms (n = 10, 32.5%), with a median EDSS at nadir of 3.5 [IQR 3.0–5.0]. None of adult patients displayed MRI findings suggestive of MS. On CSF analysis, 19 (61.3%) patients displayed pleocytosis (>5 white blood cells) and 14 (51.9%) had CSF restricted oligoclonal bands. After a median follow-up of 9 months [IQR 2–18], 10 (32.3%) patients experienced relapses. Median EDSS at the last evaluation was 2.0 [IQR 1.0–4.0], but 13 (41.9%) patients had an EDSS ≥3.0, and 8/29 (27.6%) patients had residual bladder/bowel dysfunction.

The final diagnoses were compatible with MOGAD in 27/31 cases (87.1%). Phenotypes at the last follow-up were seronegative NMOSD (n = 8, 25.8%), encephalitis (n = 9, 23.0%, in 3 cases in association with myelitis), isolated optic neuritis (n = 4, 12.9%), isolated myelitis (n = 4, 12.9%), and combined optic neuritis and myelitis (n = 2, 6.5%). %). In addition, 1 adult had Susac syndrome (3.2%), 1 pediatric patient acute polyradiculoneuritis (n = 1, 3.2%), and 2 pediatric patients with MS (n = 2, 6.5%).

Comparison of Seropositive Patients According to MOG-Abs CSF Status (MOG-Abs Seropositive and CSF Negative/MOG-Abs Seropositive and CSF Positive)

Among 224 MOG-Abs seropositive patients, 119 (53.1%) were women, median age at onset was 13 years old [IQR 5.3–36], and 128 cases (57.1%) were children. Of these, 145 (64.7%) patients were MOG-Abs seropositive and CSF positive and 79 (35.3%) MOG-Abs seropositive and CSF negative, being MOG-Abs seropositive and CSF positive the most common profile in both adults and children. Acute treatment before sampling was more frequently administered in MOG-Abs seropositive and CSF negative (70.9% vs 59.1%). When comparing demographic data between MOG-Abs seropositive and CSF negative and MOG-Abs seropositive and CSF positive patients, no significant differences emerged (for more details see Table 2).

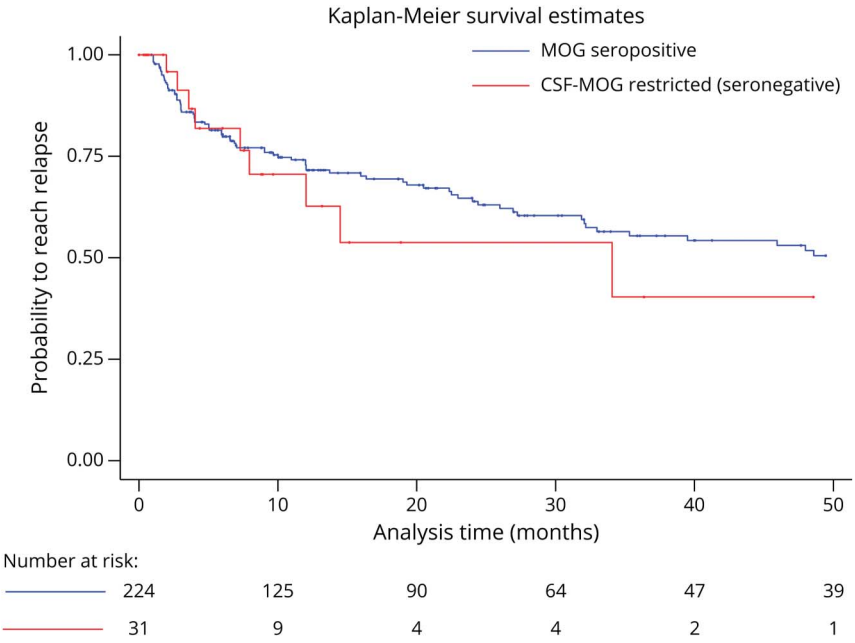
Compared with MOG-Abs seropositive and CSF negative cases, MOG-Abs seropositive and CSF positive patients had a more severe disability at nadir during their index event ($p = 0.007$) and more commonly motor and sensory symptoms ($p = 0.002$ and 0.021, respectively) consistent with myelitis. The whole MOG-Abs seropositive and CSF positive group, and in particular adults, presented more commonly with sphincter dysfunction ($p = 0.001$ and $p \leq 0.001$, respectively). MOG-Abs seropositive and CSF positive adults also had less commonly visual symptoms ($p = 0.027$) and more commonly encephalopathy ($p = 0.004$). On CSF analysis, MOG-Abs seropositive and CSF positive subjects showed an increased protein concentration ($p = 0.001$) and CSF cell count ($p \leq 0.001$), whereas no difference emerged for IgG index and oligoclonal bands (Table 2).

At the last follow-up (median 25.3 months [IQR 9.9–59.3]), MOG-Abs seropositive and CSF negative cases showed worse visual acuity ($p = 0.049$), and MOG-Abs seropositive and CSF positive patients had more commonly persistent sphincter dysfunction ($p = 0.008$). However, no difference emerged in annualized relapse rate (ARR) and final EDSS ≥3.0, Table 3. On univariate and multivariate analyses, the presence of CSF MOG-Abs was not related with increased relapse risk or EDSS≥3.0 at the last follow-up (eTable 2, links.lww.com/WNL/C527).

Disease Course Comparison Between Seropositive (MOG-Abs Seropositive and CSF Negative, and MOG-Abs Seropositive and CSF Positive) and Seronegative (MOG-Abs Seronegative and CSF Positive) Patients

Mean (SD) ARR was 0.3 (1.2), with no differences between the 2 groups. Median EDSS at the last follow-up was higher in MOG-Abs seronegative and CSF positive patients (2.0, [IQR 1.0–4.0]) compared with seropositive patients (0, [IQR 0–2.0], $p \leq 0.001$). EDSS ≥3.0 and sphincter dysfunction were more frequently observed in MOG-Abs seronegative and CSF positive patients than in seropositive patients (21.4% vs 8.2%, $p = 0.027$ and 27.6% vs 12.9%, $p = 0.037$, respectively). Visual acuity at the last follow-up did not differ between the 2 groups (for more details see eTable 3, links.lww.com/WNL/C527).

Figure 2 Kaplan-Meier Analysis Estimation of Time to Reach a First Relapse Between MOG Abs Seropositive (MOG-Abs Seropositive and CSF Negative, and MOG-Abs Seropositive and CSF Positive) and CSF MOGAbs Restricted (MOG-Abs Seronegative and CSF Positive) Patients



Median Time to Reach the First Relapse was 6.6 months (Range 1.0–177.0) for seropositive patients and 7.3 months (Range 2.0–34.1) for seronegative patients (p = 0.970). Abbreviation: MOG-Abs = myelin oligodendrocyte glycoprotein antibodies.

When assessing time to relapse with the Kaplan-Meier analysis, no difference was observed (Figure 2). The univariate analysis showed that MOG-Abs seronegative and CSF positive status (OR 3.35; 95% CI 1.52–7.41), older age at disease onset (OR 1.03; 95% CI 1.02–1.05), higher EDSS at nadir (OR 1.31; 95% CI 1.14–1.49), longer follow-up (OR 1.01; 95% CI 1.00–1.01), administration of classical immunosuppressants (OR 10.06; 95% CI 4.53–22.29), and other immunosuppressants (OR 6.28; 95% CI 2.61–15.10) were related to a higher risk of reaching an EDSS ≥3.0 at the last follow-up. The multivariate analysis showed that being MOG-Abs seronegative and CSF positive was an independent risk factor for reaching an EDSS ≥3.0 (OR 4.80; 95% CI 1.26–18.26). Age at onset (OR 1.03; 95% CI 1.00–1.06), EDSS at nadir (OR 1.66; 95% CI 1.30–2.11), and therapy with classical immunosuppressants (OR 6.23; 95%CI 1.87–20.79) were also independent risk factors for reaching an EDSS ≥3.0 (Table 4).

Discussion

In this retrospective, multicenter study analyzing paired serum and CSF MOG-Abs in a large cohort of adult and pediatric patients, we observed that (1) CSF-restricted MOG-Abs can be found (12.2% in our cohort), particularly in adults with a phenotype suggestive of MOGAD; (2) paired serum and CSF MOG-Abs positivity occurs in more than half (56.8%) of MOGAD patients; (3) among MOG-Abs seropositive cases, patients with a paired CSF positivity have a more severe clinical presentation, more frequently symptoms compatible with myelitis, and displayed more commonly CSF pleocytosis and increased protein content; (4) compared with seropositive patients, MOG-Abs seronegative and CSF positive cases have higher risk of reaching EDSS 3.0, in particular in relation to symptoms compatible with myelitis, but display the same relapse rate.

The pathophysiology of MOGAD is not fully elucidated. The hypothesis is that an unknown trigger might elicit an immune response in the periphery with the subsequent production of MOG-Abs. The presence of intrathecal CSF MOG-Abs is thought to derive from the passive transfer of antibodies through a damaged blood–brain barrier.[23,30] However, the description of cases with CSF-restricted MOG-Abs,[24,27,28] which is herein confirmed, questions this model.

A possible explanation could be that activated peripheral B and T cells cross the blood–brain barrier early in the disease in a subgroup of patients, thus generating an immune response and antibody production within the CNS compartment. The pathogenic role of intrathecal plasma cells is well established in other CNS inflammatory diseases, such as MS[31] or AQP4-Abs-seropositive NMOSD, where a fraction of CSF antibodies is produced by intrathecal B cells.[32,33] Similarly, in other antibody-mediated CNS disorders such as anti-NMDAR encephalitis, intrathecal antibody production has a relevant pathogenic role and is associated with disease activity.[34-38] In addition, MOG-Abs intrathecal synthesis has recently been reported in different groups of MOG-Abs

Table 4 Univariate and Multivariate Logistic Regression Analysis for Reaching EDSS≥3 at the Last Follow-up in MOG-Abs Seropositive (MOG-Abs Seropositive and CSF Negative, and MOG-Abs Seropositive and CSF Positive) vs Seronegative (MOG-Abs Seronegative and CSF Positive) Cases

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Age at onset	1.03	1.02 to 1.05	**<0.001**	1.03	1.00–1.06	**0.021**
Female sex	0.71	0.39 to 1.33	0.291			
EDSS at nadir	1.31	1.141.49	**<0.001**	1.66	1.30–2.11	**<0.001**
Pleocytosis	0.39	−0.31-1.10	0.176			
Oligoclonal bands	2.00	0.92 to 4.36	0.082	1.05	0.27–3.98	0.948
Maintenance treatment, classic immunosuppressant	10.06	4.54 to 22.29	**<0.001**	6.23	1.87–20.79	**0.003**
Maintenance therapy, MS DM	5.83	0.49 to 69.09	0.162	14.33	0.73–282.79	0.080
Maintenance therapy, other[a]	6.28	2.61 to 15.10	**<0.001**	3.00	0.79–11.52	0.108
MOG-Abs seronegative and CSF positive[b]	3.35	1.52 to 7.41	**0.003**	4.80	1.26–18.26	**0.022**
Follow-up, mo	1.01	1.00 to 1.01	**0.003**	1.01	1.00–1.01	0.194

Abbreviations: EDSS = Expanded Disability Status Scale; MS DMD = Multiple sclerosis-modifying drugs; MOG-Abs = MOG antibodies; OR = odds ratio.
[a] Other immunosuppressants: cyclophosphamide, methotrexate, mitoxantrone, IVIG, tocilizumab.
[b] Seropositive cases (MOG-Abs seropositive and CSF negative, and MOG-Abs seropositive and CSF positive) as reference.
Results with statistically significant difference are marked in bold.

seropositive and seronegative patients, supported by an increased CSF/serum MOG-IgG index in the former group and by the absence of serum MOG-Abs in the latter.[26,27] Accordingly, CSF oligoclonal bands were detected in more than half of patients with CSF-restricted MOG-Abs, in agreement with previously data.[27] Although oligoclonal bands generally support MS diagnosis, several studies have shown that they can be detected in a broad spectrum of neurologic diseases, including autoimmune encephalitis and other inflammatory diseases.[39] Further studies are needed to assess the significance and possible persistence over time of oligoclonal bands in patients with CSF-restricted MOG-Abs. Finally, the few available pathologic studies of patients with CSF isolated MOG-Abs showed a neuropathologic phenotype compatible with MOGAD, with a minority of B cells and plasma-cells detected in the perivascular space.[27,28] Taken together, these findings favor the occurrence of MOG-Abs intrathecal synthesis in a subgroup of patients.

Among patients with CSF-restricted MOG-Abs, the most common manifestations in our cohort were encephalopathy and myelitis, in accordance with a recent study.[27] Of note, the clinical phenotype of MOG-Abs seronegative and CSF positive adults was compatible with MOGAD, but 2 pediatric patients had a diagnosis of MS. This finding was not unexpected because low titer MOG-Abs have already been reported in both serum and CSF of patients with MS, particularly in children,[7] and serum MOG-Abs have been observed in 1% of patients with other neurologic diseases.[40,41] In a recent study analyzing CSF and serum MOG-Abs in 105 patients with MS, 2 were positive in the CSF.[42] Consequently, MOG-Abs CSF positivity has to be interpreted according to the clinical context and only cases with a compatible phenotype should be analyzed, as already recommended for serum MOG-Abs testing.[2]

Our results also confirm that CSF MOG-Abs are common in MOG-Abs seropositive patients, in agreement with previous data showing paired serum and CSF MOG-Abs positivity in 50%–70% of MOGAD.[7,23,24,27] These findings are consistent with previous observations on AQP4-Abs-seropositive NMOSD, where CSF AQP4-Abs can be detected in 57%–68% of cases.[23,30]

According to our data, testing MOG-Abs in CSF might be of relevance also in seropositive patients and could help to identify severe cases presenting with myelitis or encephalitis. The relationship between the certain clinical phenotypes and the presence of MOG-Abs within the CSF observed in this study reinforces previous data.[27] In other antibody-mediated disorders, as those associated with CASPR2-Abs, a similar phenomenon has been described, with the presence of CSF-Abs associated with limbic encephalitis and the presence of serum-Abs with neuromyotonia or Morvan syndrome.[43] This observation might be explained by the susceptibility of the optic nerve to serum MOG-Abs because of the presence of a leakage in the blood–brain barrier at the level of the optic disc.[44] Another proposed explanation is linked to the one-way flow from the intracranial subarachnoid space to the orbital subarachnoid space, which makes the identification of CSF antibodies in patients with isolated optic neuritis difficult.[45]

Of note, CSF-restricted MOG-Abs positive patients present an increased risk of reaching an EDSS 3.0 at the follow-up

when compared with seropositive patients. This could reflect the association between CSF only MOG-Abs and the presence of transverse myelitis with the related tissue damage mediated by intrathecal antibody synthesis. Our results did not display any difference in relapse risk between MOG-Abs seronegative and CSF positive and seropositive patients, indicating that CSF MOG-Abs positivity does not predict a relapsing disease course.

Our study has limitations, particularly related to the retrospective design. This study included tertiary centers with a potential referral bias. Although live CBA methodology is optimal for MOG-Abs detection, this is often only available at reference centers.[1,46] This could explain the higher frequency of MOG-Abs seronegative and CSF positive patients observed in our study in comparison with previous reports.[24,27] Considering the wider availability of fixed CBAs, future studies comparing live and fixed assays should be performed to apply our results on a larger scale.

Moreover, because the referring laboratories used different techniques to quantify MOG-Abs (e.g., live cell-based flow cytometry assay vs live cell-based immunofluorescence assay), we were not able to perform a proper comparison between MOG-Abs titers. Of note, the inclusion of patients with paired CSF sample available potentially selected cases with a more severe phenotype, which might influence the generalization of our results. In addition, the recent introduction of MOG-Abs CSF testing might have affected the characteristics of this cohort and, in particular, the short follow-up, which might have influenced our results. In addition, data regarding MOG-Abs CSF presence in patients with other immunologic and noninflammatory disorders are scarce with few available data related to their presence and titers and should be expanded in future larger cohorts.[27] Another limitation is that we did not include all consecutive patients with demyelinating diseases referred to the participating centers. For this reason, this study could not evaluate the sensitivity and specificity of MOG-Abs CSF testing.

Finally, this study was not designed to evaluate treatment efficacy and treatment was included in the analysis to mitigate bias. Even if in our analysis reaching an EDSS of 3 was associated with the administration of any/some treatments, this result should be interpreted cautiously because more disabled patients probably received more frequently immunosuppressive treatments.

In conclusion, despite the fact that few MOG-Abs seronegative and CSF positive cases did not display a clear MOGAD phenotype, our results support the relevance of MOG-Abs CSF analysis in the clinical practice, which can support, in addition to clinical and radiologic findings, the identification of patients with a more severe clinical phenotype. Future prospective multicenter studies will help to further clarify and expand our findings.

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Appendix *(continued)*

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