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Frequency of myelin oligodendrocyte glycoprotein antibody in multiple sclerosis

A multicenter cross-sectional study

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Abstract

Objective

To address the frequency of myelin oligodendrocyte glycoprotein (MOG) antibody (Ab) in an unselected large cohort of adults with MS.

Methods

This is a cross-sectional study in 2 MS expert centers (Lyon and Strasbourg University Hospitals, France) between December 1, 2017, and June 31, 2018. Patients aged ≥ 18 years with a definite diagnosis of MS according to 2010 McDonald criteria were tested for MOG-Ab by using a cell-based assay (CBA) in Lyon and subsequently included. Positive samples were tested by investigators blinded to the first result with a second assay in a different laboratory (Barcelona, Spain) by using the same plasmid and secondary Ab.

Results

Serum samples from 685 consecutive patients with MS were analyzed for MOG-Ab. Median disease duration at sampling was 11.5 (interquartile range, 5.8–17.7) years, and 72% were women. Two (0.3%) patients resulted to be MOG-Ab-positive. The 2 patients were women aged 42 and 38 at disease onset and were diagnosed with secondary and primary progressive forms of MS, respectively. This positive result was confirmed by the CBA in Barcelona.

Conclusion

Our findings indicate that MOG-Ab are exceptional in MS phenotype, suggesting that the MOG-Ab testing should not be performed in typical MS presentation.

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Glossary

Ab = antibody; **CBA** = cell-based assay; **DMT** = disease-modifying treatment; **EDMUS** = Eugene Devic Foundation against Multiple Sclerosis; **IQR** = interquartile range; **MOG** = myelin oligodendrocyte glycoprotein; **NMO** = neuromyelitis optica; **OFSEP** = Observatoire Français de la Sclérose En Plaques; **ON** = optic neuritis.

In adults, myelin oligodendrocyte glycoprotein (MOG) antibodies (Ab) are mainly found in patients with a neuromyelitis optica clinical phenotype, i.e., optic neuritis (ON) or myelitis isolated or in combination.¹

A recent review pooling patients from all available MOG-Ab studies found that 24 of 1,608 (1.5%) and 105 of 1771 (6%) patients with a confirmed diagnosis of MS had MOG-Ab by using cell-based assays (CBAs) with immunofluorescence or fluorescence-activated cell sorting (FACS), respectively.² However, the sample size of patients with MS included as controls in these studies is limited, patients were usually pre-selected, and most importantly, such studies have not been designed to ascertain the specific value of MOG-Ab in patients with a definite diagnosis of MS.^{3–6} Thus, to draw definitive conclusions about antibody, specificity should be prevented. The only study aimed at determining the frequency of MOG-Ab in MS included 200 selected patients with MS, all primary or secondary progressive forms, and all tested negative.⁷ Therefore, whether MOG-Ab can be present in MS and in what proportion has never been precisely evaluated.

In the present study, we addressed the frequency of MOG-Ab in a large sample of unselected patients with MS using a highly specific assay.

Methods

Study design

We performed a cross-sectional study in 2 MS expert centers (Lyon and Strasbourg University Hospitals, France) between December 1, 2017, and June 31, 2018. All patients aged ≥ 18 years with a definite diagnosis of MS according to 2010 McDonald criteria. Patients included were visited consecutively as part of their routine clinical practice in the day care unit.⁸

Clinical information was provided in specific case report forms by a neurologist with expertise in neuroinflammatory disorders and entered in the Eugene Devic Foundation against Multiple Sclerosis (EDMUS) database.⁹ Demographic data (sex and Caucasian ethnicity) and age at the onset of disease and disease duration at sampling were collected. MS disease subtype (clinically isolated syndrome, relapsing-remitting, secondary or primary progressive MS) was also reported. Relapses within the month before sampling, as well as corticosteroids and disease-modifying treatments (DMTs) at the time of sampling, were collected. Patients on anti-CD20 were considered on-treatment in the 6 months after the last infusion. Medical charts of

MOG-Ab-positive cases were reviewed in detail by expert clinicians (A.C.-C., R.M., and J.D.S.).

Live CBAs

HEK293 cells were transfected with pEGFP-N1-hMOG plasmid. Serum samples were used at a dilution of 1:640. Allophycocyanin-Goat IgG-Fc γ fragment-specific was used as a secondary antibody and signal intensity evaluation was performed with FACS. As recommended,¹⁰ positive samples were tested by investigators blinded to the first result with a second assay in Barcelona by using the same plasmid and secondary antibody⁴ (supplementary data, links.lww.com/NXI/A169).

Standard protocol approvals, registrations, and patient consents

All participants included in the present study belong to the national French registry designated as Observatoire Français de la Sclérose En Plaques⁹ and signed informed consent to have their medical data collected in routine practice used after anonymization and aggregation for research purposes. MOG-Ab were performed as part of the clinical routine evaluation; thus, no other specific consent was required.

Data availability

Anonymized data can be made available on reasonable request to the corresponding author.

Results

Serum samples from 685 patients with MS were analyzed for MOG-Ab during the period of this study. The median age at disease onset was 28.4 (interquartile range [IQR], 22.1–37.2) years, and the median disease duration at sampling was 11.5 (IQR, 5.8–17.7) years. Seventy-two per cent were women, and 80.6% Caucasians (table 1). Fifty (7.3%) patients had relapsed within the month before sampling. Forty-six (6.7%) and 440 (64.2%) had received corticosteroids and DMTs within the month previous to sampling, respectively. Additional characterization of the MS cohort is depicted in table 1 and table e-1, links.lww.com/NXI/A171.

Two (0.3%) female patients, aged 42 and 38 at MS onset, were found MOG-Ab-positive after 26 and 11 years of disease duration, respectively. One patient was diagnosed with a secondary progressive MS and the other with a primary progressive MS, with no history of ON or myelitis. Clinical information of MOG-Ab-positive patients is shown in table 2 and figure e-1, links.lww.com/NXI/A170.

Table 1 Epidemiologic and clinical features of the MS cohort

Demographic and clinical features	Total MS cohort N = 685
Female, n (%)	498 (72.7)
Age at MS onset, y median (range)	28.4 (3.3–77.8)
Disease duration at sampling, y median (range)	11.5 (0–45.7)
Caucasian, n (%)	552 (80.6)
Others	133 (19.4)
Type of MS, n (%)	
Clinically isolated syndrome	35 (5.1)
Relapsing-remitting	421 (61.5)
Secondary progressive	132 (19.2)
Primary progressive	97 (14.1)
Symptom at the onset of disease, n (%)	
Isolated ON ^a	99/635 (15.6)
Isolated brainstem	70/635 (11)
Isolated long tract	320/635 (50.4)
Combination of symptoms	138/635 (21.7)
Other symptoms	8/635 (1.3)
EDSS at sampling, mean (SD)	3.8 (2.3)
Patty criteria at sampling, n (%)	657/660 (99.5)
CSF-OCB, n (%)	443/488 (90.8)
Relapse 30 d before sampling, n (%)	50 (7.3)
IV or oral MTP 30 d before sampling, n (%)	46 (6.7)
Long-term treatment 30 d before sampling, n (%)	440 (64.2)
Immunosuppressants ^b	29 (6.6)
MS-disease-modifying drugs ^c	411 (93.4)
MOG-Ab-positive patients, n (%)	2 (0.29)

Abbreviations: CSF- OCB = oligoclonal bands in CSF; EDSS = expanded disability status scale; MTP = methylprednisolone; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; ON = optic neuritis.

^a The side of the optic nerve involvement was collected in 70 of the 99 patients: 63 (90%) and 7 (10%) presented with unilateral and bilateral involvement, respectively.

^b Immunosuppressants comprised mycophenolate mofetil, azathioprine, cyclophosphamide, and mitoxantrone.

^c MS-disease-modifying drugs comprised beta-interferon, glatiramer acetate, dimethyl fumarate, teriflunomide, natalizumab, alemtuzumab, and biotin. Rituximab and ocrelizumab were included as MS-disease-modifying drugs.

Discussion

In the present cohort of unselected definite patients with MS, only 2 (0.3%) were found MOG-Ab-positive, among 685 patients tested.

Differential diagnosis at the onset of disease in patients with MOG-Ab-positive and in those with MS is challenging

because a proportion may present with overlapping features, i.e., ON involvement, short myelitis, or MS-like brain lesions. Such an overlap raises the question of whether patients with MS should be tested widely for MOG-Ab. The use of accurate antibody assays is highly recommended to discriminate true positive cases. Currently, live CBA using human full-length MOG and restricting with IgG1 or IgG-Fcγ fragment-specific as a secondary antibody is the most accurate detection method.¹⁰ By using these techniques, we achieved full agreement between Lyon and Barcelona laboratories. Both centers used similar approaches except for the antibody lecture: FACS in Lyon and immunocytochemistry in Barcelona.

The present study was conducted by 2 French referral centers for neuroinflammatory disorders that follow internationally well-validated criteria for MS diagnosis and have a recognized expertise in other less frequent CNS demyelinating diseases. Therefore, if we consider this high clinical sensibility to discriminate rare diseases from typical MS and the fulfillment of 2010 McDonald criteria in all the patients included, we could assume that the 2 MOG-Ab-positive patients yielded a false positive result. Indeed, both patients had no typical symptoms of MOG-Ab-associated disease¹ but a genuine progressive phenotype with typical MS features. Our results are in line with those recently obtained by the Oxford and Mayo group displaying 100% and 99.6% of specificity, respectively, although a preselected MS cohort was included in this study.⁶ The only study evaluating the frequency of MOG-Ab in progressive MS did not find any positive result by using a similar method than us.⁷ However, this is the first study focused on different MS subtypes whose major strength lies on the large sample size allowing for a well-powered investigation. Therefore, the absence of a positive result in 99.7% of patients with typical MS together with the agreement of the results between centers in the MOG-Ab-positive cases supports the high specificity of the antibody testing methodology.

Certain limitations must be addressed. MOG-Ab titers may vary depending on the phase of the disease being higher during relapse and lower in the remission phase.¹ This fluctuation over time may underestimate the real frequency of MOG-Ab and increase the risk of false negative result when performing cross-sectional studies. Moreover, corticosteroids or long-term treatment might also have an influence over titers.

In conclusion, the present study revealed low (0.3%) frequency for MOG-Ab positivity in patients with MS by using highly specific assays. Our results have important clinical implications for neurologists in daily clinical practice, and we do not recommend MOG-Ab testing in patients with MS fulfilling 2010 McDonald criteria, with typical features.

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Table 2 Clinical features of patients with MS with positive MOG-Ab

Patient Id	MS subtype	Age at MS onset, y	Sex	Ethnicity	Symptoms at disease onset	Age at the onset of progressive phase, y	EDSS at sampling	CSF-OCB	MTP within 30 days before sampling	Chronic treatment within 30 days before sampling	Other past treatments	^a MS-like brain lesion	Disease duration at sampling, y	^b MOG-Ab titers (1)
Id.1	SP	42	F	Caucasian	1. Right hemiparesis 2. Left hemiparesis	50	6.5	Pos	No	Biotin	AZA Cyc MMF	Pos	26	640
Id.2	PP	38	F	Caucasian	Progressive gait disturbances	38	6.5	Pos	No	RTX	MMF	Pos	11	2,560

Abbreviations: AZA = azathioprine; CSF-OCB = oligoclonal bands in CSF; Cyc = cyclophosphamide; EDSS = expanded disability status scale; MMF = mycophenolate mofetil; MOG-Ab = myelin oligodendrocyte glycoprotein antibodies; MTP = methylprednisolone; Patient Id = Patient identification; Pos = Positive; PP = primary progressive; RTX = rituximab; SP = secondary progressive.
^a Brain MRI from both patients displayed typical demyelinating lesions compatible with MS, and patient Id1 also had a moderate cortical atrophy.
^b Samples analyzed in University Clinic Hospital from Barcelona showed a positive result with the following titers: Patient Id1 = 1:160, and Patient Id2 = 1:320.

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Disclosure

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Hyacintha d’Indy, MSc	Centre de Recherche en Neurosciences de Lyon	Author	Acquisition of data and performed experiments.
Anne Ruiz, MSc	Centre de Recherche en Neurosciences de Lyon	Author	Acquisition of data and performed experiments.
Nicolas Collongues, MD, PhD	Département de Neurologie, Centre Hospitalier Universitaire de Strasbourg	Author	Acquisition of data, interpretation, and critical revision of the manuscript for important intellectual content
Laurent Kremer, MD	Département de Neurologie, Centre Hospitalier Universitaire de Strasbourg	Author	Interpretation and critical revision of the manuscript for important intellectual content
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Appendix (continued)

Name	Location	Role	Contribution
Romain Casey, PhD	Centre de Recherche en Neurosciences de Lyon, Observatoire Français de la Sclérose en Plaques,	Author	Analysis and interpretation and critical revision of the manuscript for important intellectual content
Sandra Vukusic, MD, PhD	Hôpital Neurologique Pierre Wertheimer Hospices Civils de Lyon, Lyon	Author	Study concept and design, interpretation, and critical revision of the manuscript for important intellectual content
Jérôme De Seze, MD, PhD	Département de Neurologie, Centre Hospitalier Universitaire de Strasbourg	Author	Acquisition of data, interpretation and critical revision of the manuscript for important intellectual content
Romain Marignier, MD, PhD	Hôpital Neurologique Pierre Wertheimer Hospices Civils de Lyon, Lyon	Author	Study concept and design, acquisition of data, analysis and interpretation, and writing

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