



HAL
open science

Frequency of myelin oligodendrocyte glycoprotein antibody in multiple sclerosis: A multicenter cross-sectional study

Alvaro Cobo-Calvo, Hyacintha d'Indy, Anne Ruiz, Nicolas Collongues, Laurent Kremer, Françoise Durand-Dubief, Fabien Rollot, Romain Casey, Sandra Vukusic, Jérôme de Sèze, et al.

► To cite this version:

Alvaro Cobo-Calvo, Hyacintha d'Indy, Anne Ruiz, Nicolas Collongues, Laurent Kremer, et al.. Frequency of myelin oligodendrocyte glycoprotein antibody in multiple sclerosis: A multicenter cross-sectional study. *Neurology Neuroimmunology & Neuroinflammation*, 2020, 7 (2), 10.1212/NXI.0000000000000649 . hal-03791044

HAL Id: hal-03791044

<https://hal.science/hal-03791044v1>

Submitted on 28 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Frequency of myelin oligodendrocyte glycoprotein antibody in multiple sclerosis

A multicenter cross-sectional study

Álvaro Cobo-Calvo, MD, PhD, Hyacintha d'Indy, MSc, Anne Ruiz, MSc, Nicolas Collongues, MD, PhD, Laurent Kremer, MD, Françoise Durand-Dubief, MD, PhD, Fabien Rollot, MSc, Romain Casey, PhD, Sandra Vukusic, MD, PhD, Jérôme De Seze, MD, PhD, and Romain Marignier, MD, PhD

Correspondence

Dr. Marignier
romain.marignier@chu-lyon.fr

Neurol Neuroimmunol Neuroinflamm 2020;7:e649. doi:10.1212/NXI.0000000000000649

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.

From the Service de Neurologie (Á.C.-C., F.D.-D., S.V., R.M.), Sclérose en Plaques, Pathologies de La Myéline et Neuro-inflammation, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, France; Centre de Référence pour Les Maladies Inflammatoires Rares Du Cerveau et de La Moelle (MIRCEM) (Á.C.-C., F.D.-D., S.V., R.M.), Hôpital Neurologique Pierre Wertheimer Hospices Civils de Lyon, Lyon, France; Centre de Recherche en Neurosciences de Lyon (Á.C.-C., H.I., A.R., R.M.), U1028 INSERM, UMR5292 CNRS, Lyon, France; Département de Neurologie (N.C., L.K., J.D.S.), Centre Hospitalier Universitaire de Strasbourg, France; Biopathologie de La Myéline (N.C., J.D.S.), Neuroprotection et Stratégies Thérapeutiques, INSERM U1119, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, France; Centre D'investigation Clinique (N.C., J.D.S.), INSERM U1434, Centre Hospitalier Universitaire de Strasbourg, France; Centre de Recherche en Neurosciences de Lyon (F.R., R.C., S.V.), Observatoire Français de La Sclérose en Plaques, INSERM 1028 et CNRS UMR5292, Lyon, France; and Université Claude Bernard Lyon 1 (F.R., R.C., S.V.), F-69000 Lyon, France; Hospices Civils de Lyon, Lyon, France.

Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures. Funding information is provided at the end of the article

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

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.

Acknowledgment

The authors thank Dr. Albert Saiz (Center of Neuroimmunology, Hospital Clinic, Barcelona, Spain) for having performed different antibody testing. The authors thank the group of NeuroBioTec from Hôpital Civils de Lyon for supporting this study.

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.

Study funding

This work was conducted using data from the Observatoire Français de la Sclérose en Plaques (OFSEP), which is supported by a grant provided by the French State and handled by the “Agence Nationale de la Recherche,” within the framework of the “Investments for the Future” program, under the reference ANR-10-COHO-002 Observatoire Français de la Sclérose en Plaques (OFSEP), the EDMUS Foundation, and Déchaine Ton Coeur.

Disclosure

F. Durand-Dubief serves on a scientific advisory board for Merck Serono and has received funding for travel and honoraria from Biogen, Idec, Merck Serono, Novartis, Sanofi Genzyme, Roche, and Teva Pharm. S. Vukusic has received consulting and lecturing fees, travel grants, and research support from Biogen, GeNeuro, Genzyme, Novartis, Merck Serono, Roche, Sanofi-Aventis and Teva Pharm. R. Marignier has received consulting and lecturing fees, travel grants, and research support from Bayer-Schering, Biogen, Idec, Genzyme, Novartis, Merck Serono, Roche, Sanofi-Aventis, and Teva Pharma. Go to Neurology.org/NN for full disclosures

Publication history

Received by *Neurology: Neuroimmunology & Neuroinflammation* September 30, 2019. Accepted in final form November 5, 2019.

Appendix Authors

Name	Location	Role	Contribution
Alvaro Cobo-Calvo, MD, PhD	Hôpital Neurologique Pierre Wertheimer Hospices Civils de Lyon, Lyon	Author	Study concept and design, acquisition of data, analysis and interpretation, and writing
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
Françoise Durand-Dubief, MD, PhD	Hôpital Neurologique Pierre Wertheimer Hospices Civils de Lyon, Lyon	Author	Interpretation and critical revision of the manuscript for important intellectual content
Fabien Rollot, MSc	Centre de Recherche en Neurosciences de Lyon, Observatoire Français de la Sclérose en Plaques,	Author	Analysis, interpretation and critical revision of the manuscript for important intellectual content

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

References

1. Cobo-Calvo A, Ruiz A, Maillart E, et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: the MOGADOR study. *Neurology* 2018;90:e1858–e1869.
2. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. *Nat Rev Neurol* 2019;15:89–102.
3. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. *J Neuroinflammation* 2016;13:279.
4. Höftberger R, Sepulveda M, Armangue T, et al. Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease. *Mult Scler* 2015;21:866–874.
5. Hachohen Y, Absoud M, Deiva K, et al. Myelin oligodendrocyte glycoprotein antibodies are associated with a non-MS course in children. *Neuro Neuroimmunol Neuroinflamm* 2015;2:e81. doi: 10.1212/NXI.0000000000000081.
6. Waters PJ, Komorowski L, Woodhall M, et al. A multicenter comparison of MOG-IgG cell-based assays. *Neurology* 2019;92:e1250–e1255.
7. Jarius S, Ruprecht K, Stellmann JP, et al. MOG-IgG in primary and secondary chronic progressive multiple sclerosis: a multicenter study of 200 patients and review of the literature. *J Neuroinflammation* 2018;15:88.
8. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011;69:292–302.
9. Vukusic S, Casey R, Rollot F, et al. Observatoire Français de la Sclérose en Plaques (OFSEP): A unique multimodal nationwide MS registry in France. *Mult Scler Epub* 2018 Dec 13.
10. Jarius S, Paul F, Aktas O, et al. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. *J Neuroinflammation* 2018; 15:134.

Neurology[®] Neuroimmunology & Neuroinflammation

Frequency of myelin oligodendrocyte glycoprotein antibody in multiple sclerosis: A multicenter cross-sectional study

Álvaro Cobo-Calvo, Hyacintha d'Indy, Anne Ruiz, et al.
Neurol Neuroimmunol Neuroinflamm 2020;7;
DOI 10.1212/NXI.0000000000000649

This information is current as of December 13, 2019

Updated Information & Services	including high resolution figures, can be found at: http://nn.neurology.org/content/7/2/e649.full.html
References	This article cites 9 articles, 1 of which you can access for free at: http://nn.neurology.org/content/7/2/e649.full.html##ref-list-1
Citations	This article has been cited by 1 HighWire-hosted articles: http://nn.neurology.org/content/7/2/e649.full.html##otherarticles
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Devic's syndrome http://nn.neurology.org/cgi/collection/devics_syndrome Multiple sclerosis http://nn.neurology.org/cgi/collection/multiple_sclerosis
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://nn.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://nn.neurology.org/misc/addir.xhtml#reprintsus

Neurol Neuroimmunol Neuroinflamm is an official journal of the American Academy of Neurology. Published since April 2014, it is an open-access, online-only, continuous publication journal. Copyright Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.. All rights reserved. Online ISSN: 2332-7812.

