Immunoglobulin A Antibodies Against Myelin Oligodendrocyte Glycoprotein in a Subgroup of Patients With Central Nervous System Demyelination

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**IMPORTANCE** Differential diagnosis of patients with seronegative demyelinating central nervous system (CNS) disease is challenging. In this regard, evidence suggests that immunoglobulin (Ig) A plays a role in the pathogenesis of different autoimmune diseases. Yet little is known about the presence and clinical relevance of IgA antibodies against myelin oligodendrocyte glycoprotein (MOG) in CNS demyelination.

**OBJECTIVE** To investigate the frequency of MOG-IgA and associated clinical features in patients with demyelinating CNS disease and healthy controls.

**DESIGN, SETTING, AND PARTICIPANTS** This longitudinal study comprised 1 discovery and 1 confirmation cohort derived from 5 centers. Participants included patients with suspected or confirmed demyelinating diseases and healthy controls. MOG-IgA, MOG-IgG, and MOG-IgM were measured in serum samples and cerebrospinal fluid (CSF) of patients, who were assessed from September 2012 to April 2022.

**MAIN OUTCOMES AND MEASURES** Frequency and clinical features of patients who were seropositive for MOG-IgA and double-seronegative for aquaporin 4 (AQP4) IgG and MOG-IgG.

**RESULTS** After the exclusion of 5 participants with coexisting AQP4-IgG and MOG-IgA, MOG-IgG, and/or MOG-IgM, 1339 patients and 110 healthy controls were included; the median follow-up time was 39 months (range, 0-227 months). Of included patients with isolated MOG-IgA, 11 of 18 were female (61%), and the median age was 31.5 years (range, 3-76 years). Among patients double-seronegative for AQP4-IgG and MOG-IgG (1126/1339; 84%), isolated MOG-IgA was identified in 3 of 50 patients (6%) with neuromyelitis optica spectrum disorder, 5 of 228 patients (2%) with other CNS demyelinating diseases, and 10 of 848 patients (1%) with multiple sclerosis but in none of the healthy controls (0/110). The most common disease manifestation in patients seropositive for isolated MOG-IgA was myelitis (11/17 [65%]), followed by more frequent brainstem syndrome (7/16 [44%] vs 14/75 [19%], respectively; P = .048), and infrequent manifestation of optic neuritis (4/15 [27%] vs 46/73 [63%], respectively; P = .02) vs patients with MOG-IgG. Among patients fulfilling 2017 McDonald criteria for multiple sclerosis, MOG-IgA was associated with less frequent CSF-specific oligoclonal bands (4/9 [44%] vs 325/351 [93%], respectively; P < .001) vs patients with multiple sclerosis who were MOG-IgG/IgA seronegative. Further, most patients with isolated MOG-IgA presented clinical attacks after recent infection or vaccination (7/11 [64%]).

**CONCLUSION AND RELEVANCE** In this study, MOG-specific IgA was identified in a subgroup of patients who were double-seronegative for AQP4/MOG-IgG, suggesting that MOG-IgA may be a novel diagnostic biomarker for patients with CNS demyelination.

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The identification of aquaporin 4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG) along with the description of their disease entities has paved the way for serological diagnoses in patients with central nervous system (CNS) demyelination, including neuromyelitis optica spectrum disorder (NMOSD) and MOG antibody–associated disease. Yet the differential diagnosis and management of patients with AQP4-/MOG-IgG double-seronegative disease remains a challenge.

Recent evidence suggests that IgA may play a role in the pathogenesis of inflammatory disorders. However, the role of autoreactive IgA antibodies in CNS demyelination is still unclear. Here, we conducted an observational, retrospective, longitudinal multicenter study to investigate the frequency of MOG-IgA and its association with clinical features in demyelinating CNS syndromes.

### Methods

#### Study Participants
We cross-sectionally screened serum samples from 1344 patients with suspected or confirmed multiple sclerosis (MS), MOG antibody–associated disease, or NMOSD at sampling and 110 healthy controls from 5 centers in a discovery and confirmation setup. Patients were assessed from September 2012 to April 2022 (median follow-up time, 39 months; range, 0-227 months). Both CSF and longitudinal serum samples were measured when available. Five patients were excluded from the study (eMethods in Supplement 1). This study was approved by the institutional review boards of the participating centers. All patients provided written informed consent.

#### Clinical and Imaging Data
Retrieval and analysis of available clinical and other data, magnetic resonance images, and retinal optical coherence tomography are described in the eMethods and eTable 1 in Supplement 1.

#### Live Cell-Based MOG Assay
Serum samples (1:100) and CSF (1:5) were examined for IgA/IgG/IgM reactivity against full-length human MOG using a live cell-based assay as previously described (eMethods in Supplement 1). For each sample, the ratio of the geometric mean channel fluorescence intensity of the control cell line divided by the geometric mean channel fluorescence intensity of the human MOG-transfected cell line divided by the geometric mean channel fluorescence intensity of the control cell line was calculated. Geometric mean channel fluorescence ratio cutoffs were set to 3 SDs and a 25% surplus above the mean values for the healthy controls of the discovery cohort (IgA ≥2.4, IgG ≥3, IgM ≥1.6).

#### Statistical Analysis
We used χ² and Fisher exact tests for categorical variables. For continuous variables, we used unpaired t tests. The significance cutoff was set at P < .05. For optical coherence tomography analyses, we performed linear mixed models at eye level with correction for age and sex (fixed effects) to account for intraparticipant, intereye dependencies. We used Prism 9 version 9.4.1 or R version 4.1.3 (packages: ellipse, pastecs, readxl, ggplot2, car, ImerTest, MuMIn, Matrix, carData and lme4). Further details are described in the eMethods in Supplement 1.

### Results
To assess the frequency of MOG-IgA seropositivity, we investigated MOG-IgA, MOG-IgG, and MOG-IgM in 1339 patients with CNS demyelination (MS, n = 865; NMOSD, n = 196; other demyelinating diseases, n = 278) (Figure 1A-C). Overall, MOG-IgG was present in 81 of 1339 patients (6%) (Figure 1C) of whom 18 of 81 (22%) presented either coexisting MOG-IgA (15/81 [19%]) or MOG-IgM (3/81 [14%]) (eFigure 1 and eTable 2 in Supplement 1). Isolated MOG-IgM was identified in 6 additional patients, and 1 patient presented with coexisting MOG-IgM and MOG-IgA. Isolated serum MOG-IgA was identified in 18 of 1126 patients (1.6%) who were double-seronegative for AQP4-/MOG-IgG (Figure 1C) of whom 18 of 81 (22%) presented either coexisting MOG-IgA (15/81 [19%]) or MOG-IgM (3/81 [14%]) (eFigure 1 and eTable 2 in Supplement 1). Isolated MOG-IgM was identified in 6 additional patients, and 1 patient presented with coexisting MOG-IgM and MOG-IgA. Isolated serum MOG-IgA was identified in 18 of 1126 patients (1.6%) who were double-seronegative for AQP4-/MOG-IgG (Figure 1C) of whom 18 of 81 (22%) presented either coexisting MOG-IgA (15/81 [19%]) or MOG-IgM (3/81 [14%]) (eFigure 1 and eTable 2 in Supplement 1). Demographic and clinical features of patients with isolated MOG-IgM and MOG-IgA are summarized in the Table and eTables 2 and 3 in Supplement 1.

MOG-IgA was positive in 3 of 50 patients (6%) with NMOSD, in 5 of 228 patients (2%) with other demyelinating diseases, and in 10 of 848 patients (1%) with MS who were double-seronegative for AQP4-/MOG-IgG (Figure 1D). Myelitis (11/17 [65%]) was the most frequent disease manifestation, followed by brainstem syndrome (7/16 [44%] vs 14/75 [19%], respectively; P = .048), which occurred at a higher frequency than in patients with MOG-IgG. Optic neuritis was less frequent in the isolated MOG-IgA group (4/15 [27%] vs 46/73 [63%] in the MOG-IgG group; P = .02) (Figure 2A and eFigure 2 in Supplement 1). Peripapillary retinal nerve fiber...
layer and ganglion cell–inner plexiform layer thicknesses in eyes of patients with isolated MOG-IgA and optic neuritis were not different from those of MOG-IgG patients with optic neuritis (eFigure 3 in Supplement 1). Additionally, no significant differences in the frequency of disease manifestations were detected in other MOG-Ig isotype groups (MOG-IgM, MOG-IgG/A, MOG-IgG/M), except for a difference in optic neuritis frequency comparing isolated MOG-IgA with isolated MOG-IgG (35/55 [64%]) (eFigure 2 in Supplement 1).

Interestingly, only 4 of 9 patients (44%) who were seropositive for isolated MOG-IgA and had a diagnosis of MS presented CSF-specific OCBs, clearly less than in those with MOG-IgA/IgG seronegative MS (4/9 [44%] vs 325/351 [93%], respectively; P < .001) (Figure 2B and eTable 3 in Supplement 1).

Overall, patients with isolated MOG-IgA presented at least 1 of the following imaging features: (1) myelitis (short or longitudinally extensive); (2) periventricular lesion; (3) tumefactive deep white matter lesion; and (4) brainstem lesion, resembling NMOSD, atypical MS, and atypical demyelination phenotypes (Figure 2C and D and eFigure 4 in Supplement 1).
Investigating the frequency of patients with records of clinical attacks (onset or relapses) reported within 3 months following infection or vaccination, we observed no significant difference between the isolated MOG-IgA (7/11 [64%]) and MOG-IgG (7/19 [37%]) groups. No association with specific vaccines or pathogens was observed (eTable 3 in Supplement 1). Furthermore, there was no evidence of seroconversion from neither MOG-IgM/-IgG nor MOG-IgA as detected in our cohort, we expand on the existing literature by reporting isolated MOG-IgA seropositivity in patients seronegative for MOG-IgG/IgM and AQP4-IgG.

Unlike IgG, which is mounted systemically, IgA is mainly produced in mucosal tissues where it serves as a first-line barrier against pathogens and commensals, raising questions about the different mechanisms of immune activation that lead to divergent MOG-Ig responses. Although a high frequency of patients who were seropositive for isolated MOG-IgA showed records of attacks preceded by infections or vaccinations, we did not observe associations with specific triggers. An alternative explanation for the occurrence of isolated MOG-IgA could be subsequent seroconversion from MOG-IgM or MOG-IgG induced by the inflammatory milieu. While our longitudinal data of unchanged MOG-Ig isotype patterns over time argue against this, little is known about disease-specific induction of isolated IgA responses. Future studies are required to investigate the clinical relevance of both isolated and coexisting MOG-IgG/IgA seropositivity.

In contrast to IgG, which is known for its proinflammatory role through complement activation, the pathogenic potential of IgA is debated. Yet evidence suggests that IgA may target neuronal and myelin antigens in CNS inflammation, and a proinflammatory role via IgA immune complex formation and subsequent immune activation has been described in several diseases. The distinct clinical syndrome in patients seropositive for isolated MOG-IgA, characterized by frequent inflammation of the brainstem and spinal cord, areas with high blood-brain barrier permeability, further suggests that IgA may have a pathogenic role in CNS inflammation. Prospective studies investigating immune activation mechanisms and transferring MOG-IgA into animals will be important steps to assess pathogenicity and clarify the etiology of MOG-IgA-associated disease.

**Limitations**

Our study has several limitations. First, the clinical data were mostly obtained retrospectively with some unavailable clinical variables; therefore, we cannot exclude the possibility of recollection bias. Second, serum samples were not always collected from untreated patients, possibly underestimating the detected frequency of MOG-IgA/IgG/IgM. Further, the small number of patients seropositive for isolated MOG-IgA may have underpowered the detection of additional clinical and other differences, compromising the generalizability of the findings.

**Conclusions**

In this study, MOG-specific IgA was identified in a subgroup of patients who were double-seronegative for AQP4-/MOG-IgG and presented with distinct clinical features. This finding suggests a potential use of MOG-IgA as a biomarker in AQP4-/MOG-IgG double-seronegative CNS demyelination. Further prospective studies are required to enhance the characterization of the syndrome and decipher underlying pathogenic mechanisms.
Figure 2. Clinical Characterization of Patients Seropositive for Myelin Oligodendrocyte Glycoprotein (MOG) Immunoglobulin (Ig) A

A. Frequency of disease manifestations

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelitis (n = 125)</td>
<td>40</td>
</tr>
<tr>
<td>Brainstem syndrome (n = 63)</td>
<td>20</td>
</tr>
<tr>
<td>Optic neuritis (n = 90)</td>
<td>10</td>
</tr>
<tr>
<td>Encephalopathy (n = 15)</td>
<td>5</td>
</tr>
</tbody>
</table>

B. Frequency of CSF-specific OCBs

<table>
<thead>
<tr>
<th>Type of OCBs</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated MOG-IgA (n = 9)</td>
<td>100</td>
</tr>
<tr>
<td>MOG-IgG (with or without IgA/IgM)</td>
<td>80</td>
</tr>
<tr>
<td>Negative OCBs</td>
<td>60</td>
</tr>
<tr>
<td>Positive OCBs</td>
<td>40</td>
</tr>
</tbody>
</table>

C. MRI of patients with MOG-IgA

<table>
<thead>
<tr>
<th>Disease</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMOsD</td>
<td>Periventricular lesion</td>
</tr>
<tr>
<td>Atypical MS</td>
<td>Periventricular lesion</td>
</tr>
<tr>
<td>Atypical demyelination</td>
<td>Periventricular lesion</td>
</tr>
</tbody>
</table>

D. Typical features of patients with MOG-IgA

- Myelitis
- Brainstem syndrome
- Optic neuritis
- Periventricular lesions
- Deep white matter lesions
- Oligoclonal bands

**Note:**
- A, Frequency of disease manifestations for patients with isolated MOG-IgA and MOG-IgG.
- B, Frequency of positive and negative cerebrospinal fluid (CSF)-specific oligoclonal bands (OCBs) in MOG-IgA seropositive multiple sclerosis (MS) compared with seronegative MS.
- C, Magnetic resonance imaging (MRI) of patients with MOG-IgA highlighting the following disease phenotypes: neuromyelitis optica spectrum disorder (NMO-SD, often presenting with myelitis), atypical MS (often presenting with periventricular lesions), and atypical demyelination (often associated with brainstem syndrome or with tumor-mimic/ atypical demyelination). D, Clinical features frequently observed in isolated MOG-IgA seropositive central nervous system demyelination. Arrows indicate high and low frequencies.

**Statistical Significance:**
- Fisher exact test, P < .05.
- Fisher exact test, P < .001.
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Author Contributions: Dr Pröbstel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Ayzenberg Galvão Ribeiro Gomes and Ms Kulsvehagen contributed equally as co–first authors.

Concept and design: Ayzenberg Galvão Ribeiro Gomes and Ms Kulsvehagen contributed responsibility for the integrity of the data and the conduct of the study. Dr de Moura Brasil Matos reported grants from Hoffmann-La Roche outside the submitted work. Dr Kulsvehagen reported grants from CNPq–Conselho Nacional de Desenvolvimento Científico e Tecnológico (308172/2018-3) during the conduct of the study. Dr Ribeiro Monteiro reported grants from CNPq–Conselho Nacional de Desenvolvimento Científico e Tecnológico during the conduct of the study. Dr Schindler reported nonfinancial support from UCB Pharma outside the submitted work. Dr Chien reported grants from Novartis and Alexion during the conduct of the study and nonfinancial support as a member from the Canadian Institutes of Health Research Standing Committee on Science outside the submitted work. Dr Schwake reported speaker honoraria from Alexion and travel support from Novartis and UCB outside the submitted work. Dr Schindler reported research grant support from Novartis and speaker honoraria from Roche and Alexion outside the submitted work. Dr Akats reported personal fees from Alexion, Almirall, Horizon, Novartis, and Roche outside the submitted work and serving as steering committee member and co-coordinator of the German Neuromyelitis Optica Study Group (NEMOS). Dr Fischer reported grants to their institution from Medtronic, Stryker, Rapid Medical, Penumbra, and Phenex; consultant fees paid to their institution from Medtronic, Stryker, and CSL Behring outside the submitted work; participation in an advisory board for Alexion/Portola, Boehringer Ingelheim, Biogen, and Actera (fees paid to institution); member of a clinical event committee of the COATING study (Phenex); member of the data and safety monitoring committee of the TITAN, LATE-MT, and IN EXTREMIS trials; and vice-presidency of the Swiss Neurology Society during the conduct of the study.

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