Elevated Intrathecal Myelin Oligodendrocyte Glycoprotein Antibodies in Multiple Sclerosis

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Objective: To evaluate antibodies to myelin oligodendrocyte glycoprotein (MOG) in the serum and cerebrospinal fluid (CSF) of patients with multiple sclerosis (MS) and control individuals.

Design: Prospective case-control series.

Setting: Academic referral center.

Patients: Twenty-six controls with noninflammatory neurologic disease and 35 patients with MS donated serum and CSF for recombinant MOG (rMOG) antibody determination.

Main Outcome Measures: Serum and CSF rMOG antibody and albumin levels were used to calculate an rMOG index. Clinical disability, CSF markers, and magnetic resonance metrics were correlated with the rMOG index.

Results: The rMOG index was elevated in MS patients compared with controls (P = .01). Patients with progressive MS exhibited elevated rMOG indexes compared with patients with relapsing-remitting MS (P = .04). The rMOG index was inferior to the IgG index in differentiating MS patients from controls. However, 7 of 16 patients with MS who had normal immunoglobulin G indexes had an elevated rMOG index. The rMOG index did not correlate with clinical disability, other CSF markers, or radiographic outcome measures.

Conclusions: The rMOG index, a marker of intrathecal MOG antibody production, may provide complementary information to routine CSF testing in the diagnosis of MS. Furthermore, intrathecal anti-MOG antibody production may be more pronounced in progressive than in relapsing forms of MS.

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Multiple sclerosis (MS) is a demyelinating neurologic disorder of the central nervous system (CNS) with a hypothesized autoimmune origin and a clinical course that is often unpredictable at disease onset.1 Discovering a pathologic biomarker to help accurately make the MS diagnosis or predict disease activity and progression would be useful. Humoral immunity may play a role in MS pathogenesis as suggested by cerebrospinal fluid (CSF) oligoclonal IgG and by the presence of antibodies and complement in association with myelin damage in MS plaques.3,4 Various antigens have been proposed as targets of the autoantibody response.3,6 Myelin oligodendrocyte glycoprotein (MOG) is a candidate target self-antigen. This protein is a small component of myelin exclusive to the CNS located on the outer surface of the myelin sheath and hence accessible to antibody attack.7,8 Myelin oligodendrocyte glycoprotein is used to induce experimental autoimmune encephalomyelitis in many species.9,10 Although anti-MOG antibodies alone cannot induce experimental autoimmune encephalomyelitis, they enhance demyelination in some rodent and primate experimental autoimmune encephalomyelitis models.10,11 In humans, the pathogenic role of anti-MOG antibodies is less clear. The potential of anti-MOG antibodies as diagnostic and/or prognostic biomarkers is also unknown. Myelin oligodendrocyte glycoprotein–specific antibodies and T cells are present in healthy control individuals and patients with MS,12 suggesting that the presence of serum anti-MOG antibodies will not be useful to diagnose MS. However, the level and specific target of serum antibodies to MOG may be important.13-18 For example, serum auto-antibodies that targeted extracellular MOG in its native conformation were shown to be lytic in vitro, supporting a potential pathogenic role of these antibodies in MS.19 Controversy surrounds whether serum antibodies against recombinant MOG (rMOG) may predict a second MS relapse in patients with clinically isolated syndrome (CIS).20-23 Some of the contradictory evidence to date is likely the result of methodologic differences among studies. In another CIS study, antmyelin antibodies were
associated with intrathecal IgG production, CSF pleocytosis, and T2 lesion load.26,28 Other studies suggest that MOG antibody levels are elevated in the CSF of patients with MS compared with controls with noninflammatory neurologic disease.27,28

The present study was undertaken to further explore the relationship between serum and CSF anti-MOG antibodies and MS diagnosis, clinical course, and activity. Antibody levels were quantified by enzyme-linked immunosorbent assay (ELISA) using human extracellular rMOG that adopted the native conformation and was glycosylated. To determine whether intrathecal production of anti-MOG antibodies (eg, in CSF) might be important, an rMOG index was calculated.

STUDY PARTICIPANTS

This study was performed at Washington University (St Louis, Missouri) with institutional review board approval. Written consent was obtained from all participants. Serum and CSF samples were collected concurrently during diagnostic procedures from 26 controls with noninflammatory neurologic disease and 35 patients with MS (Table 1). The noninflammatory neurologic disease group included individuals with headache, seizure disorder, and stroke or small vessel disease. All noninflammatory neurologic disease controls had normal brain magnetic resonance imaging results or evidence of small vessel disease or stroke and CSF analyses without evidence of CNS inflammation. All patients with MS fulfilled the McDonald criteria for MS diagnosis.29 Patients were classified by their MS specialist physician based on previously published criteria for MS clinical subtypes.30 Of the patients with MS, 22 had relapsing-remitting MS (RRMS), 5 had secondary progressive MS (SPMS), and 8 had primary progressive MS (PPMS). Routine CSF studies, IgG index, and oligoclonal bands were determined for each study participant. All CSF analyses were performed at Barnes-Jewish Hospital in St Louis, Missouri, except oligoclonal band determination, which was determined by isoelectric focusing with IgG immunoblotting at Mayo Medical Laboratories in Rochester, Minnesota.31 Relapse or remission status was determined at the time of lumbar puncture, before performing the rMOG assays. The Expanded Disability Status Scale32 score and the Multiple Sclerosis Severity Score33 were determined at the time of CSF analyses. Seventeen MS patients had magnetic resonance determination of gadolinium enhancement number and volume, T1 hypointensity number and volume, and T2 hyperintensity number and volume as part of a separate study,34 performed at the time of CSF analysis.

HUMAN rMOG

The rMOG protein, consisting of the 120–amino acid extracellular domain of MOG, was produced using a baculovirus and insect cell–mediated expression system, then purified as previously described.35 The recombinant protein was partially glycosylated. To determine whether intrathecal production of anti-MOG antibodies (eg, in CSF) might be important, an rMOG index was calculated.

ELISAS TO MEASURE ANTIBODIES TO HUMAN MOG

Immunoglobulin levels (all isotypes) to rMOG in serum and CSF samples were semiquantitatively measured by ELISA, as previously described.37 Briefly, rMOG was coated at 10 µg/mL in bicarbonate buffer overnight. Standards of human γ-globulin (Jackson ImmunoResearch Laboratories Inc, West Grove, Pennsylvania) at varying concentrations (from 9 to 570 ng/mL) in duplicate wells were included in each assay. Next, plates were washed with phosphate-buffered saline 4 times and phosphate-buffered saline with 3% bovine serum albumin was added for 2 hours at 22°C. Plates were then washed, after which diluted serum samples (1:250 and 1:500) were added to the wells in duplicate for 1 hour at 22°C. In contrast to serum samples, CSF samples were assayed undiluted and incubated overnight at 4°C. Known positive and known negative samples were included with each assay to confirm interassay consistency. After incubation of the serum and CSF samples, plates were washed and goat anti-human polyvalent immunoglobulin horseradish peroxidase (1:3500; Sigma-Aldrich Co) was applied for 1 hour at 22°C. Plates were then washed 4 times, and 100 µL of freshly prepared tetramethylbenzidine substrate (BD Biosciences, San Diego, California) was added per well for 30 minutes at 22°C, protected from light. The reaction was stopped by addition of 100 µL of 2.5M sulfuric acid (LabChem Inc, Pittsburgh, Pennsylvania). Absorbance was read within 30 minutes at 450 nm on a BioTek ELX800 ELISA plate reader and data analyzed with KC junior software (BioTek Instruments Inc, Winooski, Vermont). To consider a serum sample to be positive, 2 criteria were required: a dilution effect (ie, absorbance at 1:500 must be approximately half of that at 1:250) and absorbance of 0.1 or higher.

Table 1. Demographic Characteristics of Control Individuals and Patients With MS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (n=26)</th>
<th>Patients With MS (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS subtype, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RRMS</td>
<td>NA</td>
<td>22</td>
</tr>
<tr>
<td>SPMS</td>
<td>NA</td>
<td>5</td>
</tr>
<tr>
<td>PPMS</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>43.5 (14.4)</td>
<td>44.0 (8.7)</td>
</tr>
<tr>
<td>Female/male</td>
<td>20/6</td>
<td>20/15</td>
</tr>
<tr>
<td>White/African American</td>
<td>23/3</td>
<td>32/3</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>NA</td>
<td>9.7 (7.3)</td>
</tr>
<tr>
<td>Disease-modifying therapy, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>Interferon beta-1a IM</td>
<td>NA</td>
<td>5</td>
</tr>
<tr>
<td>Interferon beta-1a SC</td>
<td>NA</td>
<td>4</td>
</tr>
<tr>
<td>Interferon beta-1b SC</td>
<td>NA</td>
<td>9</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>NA</td>
<td>4</td>
</tr>
<tr>
<td>EDSS score, median (range)</td>
<td>6.0 (1.0-7.0)</td>
<td></td>
</tr>
<tr>
<td>MSSS, median (range)</td>
<td>6.74 (2.56-9.59)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EDSS, Expanded Disability Status Scale; IM, intramuscular; MS, multiple sclerosis; MSSS, Multiple Sclerosis Severity Score; NA, not applicable; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SC, subcutaneous; SPMS, secondary progressive MS.
The rMOG index is a formula that accounts for blood-brain barrier integrity and indicates the level of antibody to rMOG made within the CNS. This formula is similar to the method of IgG index calculation but uses the rMOG absorbances in place of IgG concentrations. The rMOG index was calculated by the following formula: (CSF rMOG antibody/serum rMOG antibody)/(CSF albumin/serum albumin) = rMOG index.

### STATISTICAL ANALYSIS

The rMOG indexes of 2 independent samples were compared using the t test or Mann-Whitney test based on sample size and distribution. Correlation of rMOG indexes with CSF indexes, disability level, and magnetic resonance metrics were made with Pearson or Spearman correlation as appropriate. Receiver operating characteristic curves were generated using the statistical program SPSS, version 16.0 (SPSS Inc, Chicago, Illinois).

### RESULTS

Antibodies to rMOG were assayed in 35 patients with MS and 26 controls with similar demographics (Table 1). No statistical differences existed between controls and MS patients for serum rMOG antibodies (mean [SD] absorbance, 0.443 [0.383] vs 0.341 [0.309]; \(P = .44\)) or CSF rMOG antibody (0.194 [0.222] vs 0.264 [0.262]; \(P = .27\)). However, the rMOG index showed a significant difference between controls and patients with MS (mean [SD] absorbance, 0.376 [0.247] vs 0.696 [0.663]; \(P = .01\)) (Figure 1). The range of the rMOG index for controls was 0.073 to 0.973, whereas the range for patients with MS was 0.147 to 3.051. A total of 25.7% of patients with MS had rMOG indexes more than 2 SDs above the normal control mean rMOG index.

An rMOG index positive threshold of 0.7 yielded the optimal sensitivity and specificity as a diagnostic test, displaying a sensitivity of 0.37, a specificity of 0.92, a positive predictive value of 0.87, and a negative predictive value of 0.52 for MS. To further assess the usefulness of the rMOG index in the diagnosis of MS, sensitivity and specificity values for rMOG index and IgG index were compared. Area under the receiver operating characteristic curve for the IgG index was 0.891, whereas it was 0.685 for the rMOG index (Figure 2). Thus, the IgG index was superior for differentiating controls vs patients with MS in this cohort. Nonetheless, 7 patients with a normal IgG index had an elevated rMOG index greater than 0.7.

Antibodies to rMOG were compared among different MS clinical subtypes. Because of small sample sizes, the SPMS and PPMS groups were combined into a single progressive MS group for statistical comparison to the RRMS group. When comparing serum and CSF anti-MOG antibodies between patients with RRMS and those with progressive MS (SPMS and PPMS), no statistical difference was observed (\(P = .86\) and \(P = .12\), respectively). However, a higher mean rMOG index was found in patients with progressive MS (\(n = 13\)) compared with those with RRMS (\(n = 22\)) (mean, 0.899 vs 0.576; \(P = .04\)) (Figure 3). On the other hand, no difference in the IgG index between RRMS and progressive MS was observed (0.988 vs 0.901; \(P = .44\)).

Interestingly, no correlations between the rMOG index and other CSF markers were found in this cohort. The rMOG index and IgG index correlated poorly with one another (\(R^2 = .014\)). The rMOG index did not differ between patients with MS with or without oligoclonal bands (\(P = .11\)). The CSF white blood cell count did not correlate with serum rMOG antibodies (\(P = .51\)), CSF rMOG antibodies (\(P = .84\)), or the rMOG index (\(P = .81\)).

There was no clear correlation of the rMOG index with other clinical and radiographic outcomes. No significant difference in the rMOG index in patients in the midst of a relapse or in remission was observed, although the comparison was limited in that only 5 participants were in a relapse at the time of lumbar puncture. Level of disability at the time of lumbar puncture as measured by the Expanded Disability Status Scale or Multiple Sclerosis...
The present study expands on prior studies by calculating the rMOG index as a reflection of the intrathecal synthesis of antibodies to rMOG. Interestingly, the rMOG index was higher in patients with MS than controls, whereas CSF anti-MOG antibodies showed no difference. Moreover, serum anti-MOG antibodies did not differentiate controls from patients with MS in the present study, corroborating the results of several other published studies.

The present study also adds to the existing literature by examining a different cohort of patients with MS, including several with advanced disease and some with progressive clinical subtypes of MS. Progression can be defined as accumulation or advancement of disability in the absence of an acute clinical relapse. In the present cohort, the rMOG index was higher in patients with SPMS and PPMS when compared with those with RRMS, whereas serum and CSF anti-MOG antibodies individually demonstrated no difference. A previous study examining MS subtypes did not detect differences in CSF anti-MOG antibody levels between patients with RRMS and those with PPMS, whereas those with SPMS were not included. In another study, higher levels of anti-MOG antibodies in patients with SPMS compared with those with RRMS were reported. Ectopic B-cell follicles have been detected in the meninges of patients with SPMS and were associated with an aggressive clinical course. These ectopic lymphoid follicles may be a source of MOG antibody production within the CNS. Antibodies directed against conformational epitopes of extracellular MOG are known to have demyelinating potential and might be implicated in degenerative changes characteristic of the progressive clinical subtypes of the disease. One might hypothesize that the rMOG index elevation suggests the degree of CNS damage (as opposed to the IgG index, which is not antigen specific). More study is needed to determine whether the rMOG index may predict progression of disability outside relapses. In addition, longitudinal studies would help determine whether rMOG antibody status changes over time within individual patients and in relation to changing disease phase.

The present study indicates that the rMOG index was inferior to the IgG index for diagnosis of MS. However, using the positive rMOG index threshold of 0.7, we identified an additional 7 of the 16 patients with MS who had a normal IgG index. Moreover, the 2 indexes did not correlate with one another. Sampling error may explain why the number of patients with MS who had normal IgG indexes is greater than previously published sensitivities of the test in isolation. Using the rMOG index increased the sensitivity of CSF testing from 80.0% to 91.4%. This may indicate that the rMOG index can provide important information distinct from that provided by total IgG intrathecal production (Table 2 and Table 3).
previous report48 found that patients with MS had serum reduce demyelination. Natural MOG is glycosylated. A pre-
denatured protein or short synthetic peptides fail to in-
put into rMOG index revealed a potential role for anti-
autoimmune encephalomyelitis models have shown that
activity against a synthetic glycosylated MOG fragment
were antibodies that bind to
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several published studies20,21 have examined the sig-
ificance of antibodies to MOG in the populations with
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rum antibodies to rMOG predicted shortened time to sec-
ond attack. In another study of 133 patients with CIS,20
it was reported that serum anti-MOG and antimyelin ba-
sic protein antibodies correlated with intrathecal IgG
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predict future development of clinically definite MS. On
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index or serum rMOG antibody levels and other CSF and
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populations and methodologic differences.

Limitations of this study include small sample size,
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addition, quantitative brain magnetic resonance
imaging was conducted on only approximately half the
patients with MS, limiting the power to make correla-
tions. The control group of this study did not include
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The rMOG index has the potential to serve as an addi-
tional diagnostic tool for MS because it identified 7 pa-
tients with MS in this cohort who had normal IgG in-
dexes. Although inferior to the established diagnostic IgG
index test, the rMOG index may complement markers of
intrathecal immunoglobulin production. Moreover, the
rMOG index was associated with progressive disease sub-
types in our small cohort. Thus, further studies are needed
to evaluate the diagnostic and prognostic use of the rMOG
index, including its usefulness in predicting evolution
from CIS to clinically definite MS, and to confirm its pre-
dictive value for progressive subtypes of MS.

Table 3. IgG Index, IgG Synthesis Rate, Oligoclonal Band,
and rMOG Index Status of Multiple Sclerosis Patients*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>IgG Index (&lt;0.69)b</th>
<th>IgG Synthesis Rate (&lt;2.9)b</th>
<th>Oligoclonal Bands (0-3)b</th>
<th>rMOG Index</th>
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<tbody>
<tr>
<td>1</td>
<td>0.44</td>
<td>&lt;0.0</td>
<td>Negative</td>
<td>0.87</td>
</tr>
<tr>
<td>2</td>
<td>0.47</td>
<td>&lt;0.0</td>
<td>Positive</td>
<td>0.24</td>
</tr>
<tr>
<td>3</td>
<td>0.52</td>
<td>&lt;0.0</td>
<td>Negative</td>
<td>1.13</td>
</tr>
<tr>
<td>4</td>
<td>0.52</td>
<td>&lt;0.0</td>
<td>Negative</td>
<td>1.22</td>
</tr>
<tr>
<td>5</td>
<td>0.54</td>
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<td>Positive</td>
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</tr>
<tr>
<td>6</td>
<td>0.57</td>
<td>0.3</td>
<td>Negative</td>
<td>0.48</td>
</tr>
<tr>
<td>7</td>
<td>0.58</td>
<td>&lt;0.0</td>
<td>Negative</td>
<td>0.88</td>
</tr>
<tr>
<td>8</td>
<td>0.59</td>
<td>2.7</td>
<td>Positive</td>
<td>0.45</td>
</tr>
<tr>
<td>9</td>
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<td>1.7</td>
<td>Positive</td>
<td>0.98</td>
</tr>
<tr>
<td>10</td>
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<td>0.7</td>
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<tr>
<td>30</td>
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<td>25.9</td>
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<td>Positive</td>
<td>0.73</td>
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<tr>
<td>35</td>
<td>2.60</td>
<td>60.9</td>
<td>Positive</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; rMOG, recombinant myelin oligodendrocyte glycoprotein.

* Elevated levels are set in bold.

b Normal values are given in parentheses.

other study39 also demonstrated that intrathecal synthe-
sems of anti-MOG antibodies was occurring in patients with
MS when total IgG intrathecal synthesis was not

The clinical role (diagnostic and prognostic) of anti-
MOG antibodies in MS remains controversial. Differences
reported in the literature could be because of the
varied techniques used to detect MOG antibodies (ELISA,
immunoblot, immunohistochemical analysis, radioim-
umoassay, and fluorescence-activated cell sorter-
based assays) and different MOG protein preparations
used as antigens. Extensive studies45-47 in experimental
autoimmune encephalomyelitis models have shown that
only antibodies that recognize native extracellular MOG
protein are pathogenic, whereas antibodies that bind to
denatured protein or short synthetic peptides fail to in-
duce demyelination. Natural MOG is glycosylated. A pre-
vious report46 found that patients with MS had serum re-
activity against a synthetic glycosylated MOG fragment
but not against nonglycosylated fragments. In the present
study, a recombinant human MOG extracellular por-
tion was produced in insect cells, resulting in a prepar-
ation that is partially glycosylated (data not shown) with
the conformational structure of native mammalian ex-
tracellular MOG protein.

Several published studies20,21 have examined the sig-
ificance of antibodies to MOG in the populations with
CIS and MS. Several of these studies examined the abili-
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