Anti–Myelin Oligodendrocyte Glycoprotein Antibodies in Pediatric Patients With Optic Neuritis

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Objective: To study the humoral immune response directed at myelin oligodendrocyte glycoprotein (MOG) in pediatric patients with isolated and recurrent optic neuritis (ON).

Design: Observational prospective case series.

Setting: Six pediatric hospitals in Germany and Austria.

Patients: Thirty-seven patients 18 years or younger with single or recurrent episodes of ON were recruited from 6 different hospitals.

Main Outcome Measures: Clinical features, magnetic resonance imaging findings, intrathecal IgG synthesis, and outcome were recorded. A live cell–based immunofluorescence assay was used to measure serum IgG antibodies to MOG and aquaporin 4.

Results: A single episode of ON was observed in 10 patients, and 15 experienced 2 to 12 episodes. The acute episode of ON was part of a clinically isolated syndrome in 12 patients, of whom 8 were subsequently classified as having multiple sclerosis. High-titer serum MOG-IgG antibodies (≥1:160) were detected in 17 patients (46%). In addition, high titers of MOG-IgG antibodies were more frequently observed in 12 of the 15 patients with recurrent episodes of ON (80%; median titer, 1:640) compared with 2 of the 10 patients with monophasic ON (20%; median titer, 0) and 3 of the 12 patients with ON as part of a clinically isolated syndrome (25%; median titer, 0).

Conclusion: High-titer MOG-IgG antibodies are predominantly detected in pediatric patients with recurrent ON, indicating that anti–MOG-specific antibodies may exert a direct role in the pathogenesis of ON in this subgroup.


Optic Neuritis (ON) is an inflammation of the optic nerve, resulting in disturbed visual function heralded or accompanied by retro-orbital/eye movement pain.1 The differential diagnosis is broad and entails metabolic, infectious, toxic, vascular, or space-occupying causes and autoimmune-mediated mechanisms. In the latter group, ON can occur in isolation, as a recurrent condition, or as the initial symptom of an autoimmune-mediated demyelinating disease, such as multiple sclerosis (MS) or neuromyelitis optica (NMO).

An increased risk for the subsequent conversion to clinically definite MS within 2 years was observed in patients with a first episode of ON, especially in those presenting with typical T2-weighted magnetic resonance imaging (MRI) lesions in the white matter.2 However, reliable biomarkers to predict the individual disease course of patients with acute monophasic ON are not available. At present, increasing evidence suggests that B-cell–mediated mechanisms contribute to the pathogenesis in at least a subgroup of patients with demyelinating diseases.3,4 One extensively studied potential target structure for autoantibodies is the myelin oligodendrocyte glycoprotein (MOG), which is localized on the outer surface of myelin sheaths—in particular, of the optic nerves—and oligodendrocytes.5 Several studies have demonstrated that the correct membrane topology and glycosylation are crucial for the pathogenic activity of anti–MOG antibodies, which can induce demyelination in vitro.6,7 Increased serum levels of anti-MOG antibodies in children and, to a lesser degree, in adults with acute disseminating encephalomyelitis (ADEM) and MS could only be detected with cell-based assays.8,12 High-titer MOG-IgG antibody lev-
els in particular were found in pediatric patients with ADEM; the titers drop to undetectable levels in the recovery phase but persist in children with MS.8,9

For the management and prognosis of ON in children, a biomarker to predict the subsequent course of MS or NMO would be of great importance. Therefore, we determined serum antibody levels against native MOG in addition to aquaporin 4 (AQP4)–IgG in pediatric patients with an acute episode of ON.

METHODS

PATIENTS

We enrolled 37 pediatric patients with ON (aged, ≤18 years). All patients were diagnosed, treated, and prospectively followed up from January 1, 2004, through December 31, 2010, at 6 pediatric hospitals in Germany and Austria with experience in the treatment of children with demyelinating diseases. Twenty-two patients presented with a first episode of ON, and 15 had recurrent ON with 2 to 12 relapses. All patients fulfilled the following inclusion criteria for ON: clinical presentation characterized by acute or subacute visual loss without evidence of a metabolic, infectious, toxic, vascular, or space-occupying cause and a relative afferent papillary defect in the affected eye; visual field defect; impaired color vision; and/or pathological visual evoked potentials.

Demographic and clinical data collected for each patient included sex, age at onset, follow-up interval, oligoclonal bands (OCBs), MRI findings, presence of disease-modifying therapies, and results of neurophysiological studies (eTable; http://www.archneur.com). Three patients with recurrent ON were treated with immunomodulatory drugs (2 received azathioprine sodium and 1 received monthly intravenous immunoglobulin). From the group with ON as part of a clinically isolated syndrome (CIS), 8 patients were subsequently diagnosed as having MS. Four of those patients were being treated with immunomodulatory drugs (interferon beta in 3 and glatiramer acetate in 1). All patients were treated with methylprednisolone acetate, 20 to 30 mg/kg/d, for 3 to 5 consecutive days.

Immunofluorescence assay, as previously described.8,15

MOG-IgG and AQP4-IgG

IMMUNOFLUORESCENCE ASSAY

All serum samples were analyzed for the presence of MOG-IgG and AQP4-IgG antibodies by an extracellular live cell–staining immunofluorescence technique using transiently transfected MOG- or AQP4-expressing cells as previously described.8,15 Screening was performed at dilutions of 1:20 and 1:40 by 2 clinically blinded investigators (K.S. and S.M.), and positive serum samples were further diluted to determine the titer levels of antibodies.

RESULTS

In the present study, we examined the clinical manifestation and course of 37 patients (27 girls and 10 boys; median age at first clinical manifestation, 13 [range, 2-18] years) with an acute episode of ON who underwent serum analysis for the presence of MOG-IgG and AQP4-IgG antibodies. Thirty-four patients presented with unilateral and 3 with bilateral ON (see the Table and eTable for details). Twenty-nine patients were diagnosed as having monophasic ON, whereas the remaining patients had their second (n=4), third (n=2), fourth (n=1), or fifth episode (n=1) of ON at the time of blood sampling. Thus, 29 serum samples were taken at baseline and 8 samples at a later point (median, 1.3 years after the first clinical manifestation; range, 0.2-5.0 years; eTable).

As part of the patients' workup, MRI of the brain (cerebral MRI) was available for all patients and MRI of the spinal cord (spinal MRI) was performed in 27. In 36 patients, results of OCB testing in serum and cerebrospinal fluid by means of immunoblot after isoelectric focusing were available. The presence of serum IgG antibodies to MOG and AQP4 was evaluated with a live cell–staining immunofluorescence assay, as previously described.8,15

In contrast to 16 of 37 ON patients with seronegative findings for MOG-IgG, serum MOG-IgG antibodies (median titer, 1:20; titer range, 0-1:5120) were detected in 21 patients (Figure and eTable). Furthermore, high-titer (≥1:160) anti-MOG antibodies were present in 17 patients. In addition, all patients had seronegative findings for AQP4-IgG antibodies.

To further analyze whether patients with recurrent episodes of ON have high-titer antibodies to MOG-IgG, the cohort was divided into 3 subgroups after a median clinical follow-up of 2.1 years (range, 0.9-6.2 years [≥2 years in 25 of 37 patients]) (Figure and eTable).

1. Patients with a single episode of ON and absent white matter lesions on MRI (subgroup 1; 10 patients).

2. Patients with recurrent episodes of ON, absent OCBs, and no MS-like lesions on MRI (subgroup 2; 15 patients).

3. Patients with a single episode of ON (subgroup 3; 12 patients), classified as a CIS owing to MS-like lesions on MRI and/or positive OCBs.

SUBGROUP 1

Ten patients (8 girls and 2 boys; median age, 13 [range, 5-18] years; median follow-up, 2.2 [range, 1.7-4.8] years...
Years in 8 of 10 patients) were diagnosed as having a single episode of unilateral ON (Table and eTable), with normal cerebral MRI findings at the initial workup. Only 1 patient had MRI evidence of swelling of the optic nerve. Spinal MRI was available from 6 patients and revealed no abnormalities. Oligoclonal bands in the cerebrospinal fluid, measured in 9 of 10 patients, were present in 2 patients with a single episode of ON.

Eight patients regained normal visual activity, whereas 2 continued to experience unilateral optic atrophy with marked visual impairment. The MOG-IgG serostatus in patients with a single episode of ON was negative in 6 or low-titer positive in 2, with levels of 1:20 and 1:40. In contrast, high-titer anti-MOG antibodies were present in only 2 patients, with titer levels of 1:640 and 1:5120 (eTable).

As shown in the Table and Figure, median levels of antibodies to native MOG were significantly lower in this group of patients (median, 0 [range, 0 to 1:5120]) compared with patients with recurrent episodes of ON (median, 1:640 [range, 0 to 1:5120]).

### SUBGROUP 2

Fifteen patients (9 girls and 6 boys; median age, 10 [range, 2-16] years; median follow-up, 2.5 [range, 0.9-6.2] years (>2 years in 11 of 15 patients) experienced 2 to 12 episodes of ON, which occurred during a period of 3 months to 5 years (Table and eTable). Bilateral visual impairment was diagnosed in 3 patients with recurrent ON. Six patients had normal cerebral and spinal MRI findings initially. Two patients showed swelling of the affected optic nerve on MRI. Two patients had the first event of ON associated with headache and altered mental status and MRI findings suggestive of ADEM. In addition, 4 patients with ON had MRI lesions in the white matter or basal ganglia. Two of 6 patients with cerebral MRI changes had a lesion in the cervical and thoracic spinal cord extending more than 3 segments and classified as longitudinal extensive transverse myelitis. One patient had only a single T2-weighted lesion in the spinal cord not extending more than 2 segments (patient 14, eTable). All follow-up MRIs showed resolution of the white matter lesions. Additional episodes of ON in these patients were not associated with new lesions in the cerebral MRI.

### Table. Clinical and Immunological Characteristics of Pediatric Patients With ON

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Monophasic ON (n = 10)</th>
<th>Recurrent ON (n = 15)</th>
<th>CIS/MS (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. of patients</td>
<td>Female 8</td>
<td>9</td>
<td>10</td>
<td>.34</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>Male 2</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>At first clinical manifestation</td>
<td>13 (5 to 18)</td>
<td>10 (2 to 16) a</td>
<td>16 (9 to 18)</td>
<td>.02</td>
</tr>
<tr>
<td>At sampling</td>
<td>13 (5 to 18)</td>
<td>12 (2 to 18)</td>
<td>16 (9 to 18)</td>
<td>.07</td>
</tr>
<tr>
<td>Follow-up, median (range), y</td>
<td>2.2 (1.7 to 4.8)</td>
<td>2.5 (0.9 to 6.2)</td>
<td>1.9 (1.7 to 4.7)</td>
<td>.40</td>
</tr>
<tr>
<td>MOG-IgG findings</td>
<td>No. (%) of patients b</td>
<td>2 (20)</td>
<td>12 (80) a,c</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Titer, median (range)</td>
<td>0 (0 to 1:5120)</td>
<td>1.640 (0 to 1:5120) a,c</td>
<td>0 (0 to 1:640)</td>
<td>.007 (.03) d</td>
</tr>
<tr>
<td>No. of patients with UON:BON: ON + ADEM:ON/CIS</td>
<td>10:0:0</td>
<td>10:3:2:0</td>
<td>0:0:12</td>
<td>.001</td>
</tr>
<tr>
<td>OCBs, No. (%) of patients</td>
<td>2 (22) a</td>
<td>0</td>
<td>11 (92)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of patients with cMRI findings normal: ON swelling:ADEM-like:MS-like</td>
<td>9:1:0</td>
<td>7:2:6:0</td>
<td>1:0:11</td>
<td>.001</td>
</tr>
<tr>
<td>No. of patients with sMRI findings normal: MS-like: NMO-like</td>
<td>6:0</td>
<td>12:1:2</td>
<td>6:5:0 e</td>
<td>.04</td>
</tr>
<tr>
<td>Impaired visual outcome, No. (%) of patients</td>
<td>2 (20)</td>
<td>5 (33)</td>
<td>2 (17)</td>
<td>.56</td>
</tr>
</tbody>
</table>

**Abbreviations**: ADEM, acute disseminating encephalomyelitis; BON, bilateral optic neuritis; cMRI, cerebral magnetic resonance imaging; CIS, clinically isolated syndrome; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMO, neuromyelitis optica; OCBs, oligoclonal bands; ON, optic neuritis; sMRI, spinal MRI; UON, unilateral ON.

a Significantly different compared with monophasic ON.
b Indicates patients with high titers (≥1:160).
c Significantly different compared with CIS/MS.
d P value corrected for age at sampling and sex by logistic regression analysis.
e Not analyzed in 1 patient.
f Not analyzed in 4 patients.

Figure. Myelin oligodendrocyte glycoprotein (MOG)–IgG antibody levels were significantly elevated in children with recurrent episodes of optic neuritis (ON) compared with children with an isolated episode or an ON as part of a clinically isolated syndrome (CIS). The dotted line indicates a titer of 1:160; high titers are considered to be those greater than 1:160. MS indicates multiple sclerosis.

[>2 years in 8 of 10 patients] were diagnosed as having a single episode of unilateral ON (Table and eTable), with normal cerebral MRI findings at the initial workup. Only 1 patient had MRI evidence of swelling of the optic nerve. Spinal MRI was available from 6 patients and revealed no abnormalities. Oligoclonal bands in the cerebrospinal fluid, measured in 9 of 10 patients, were present in 2 patients with a single episode of ON.

Eight patients regained normal visual activity, whereas 2 continued to experience unilateral optic atrophy with marked visual impairment. The MOG-IgG serostatus in patients with a single episode of ON was negative in 6 or low-titer positive in 2, with levels of 1:20 and 1:40. In contrast, high-titer anti-MOG antibodies were present in only 2 patients, with titer levels of 1:640 and 1:5120 (eTable).

As shown in the Table and Figure, median levels of antibodies to native MOG were significantly lower in this group of patients (median, 0 [range, 0 to 1:5120]) compared with patients with recurrent episodes of ON (median, 1:640 [range, 0 to 1:5120]).

**SUBGROUP 2**

Fifteen patients (9 girls and 6 boys; median age, 10 [range, 2-16] years; median follow-up, 2.5 [range, 0.9-6.2] years (>2 years in 11 of 15 patients) experienced 2 to 12 episodes of ON, which occurred during a period of 3 months to 5 years (Table and eTable). Bilateral visual impairment was diagnosed in 3 patients with recurrent ON. Six patients had normal cerebral and spinal MRI findings initially. Two patients showed swelling of the affected optic nerve on MRI. Two patients had the first event of ON associated with headache and altered mental status and MRI findings suggestive of ADEM. In addition, 4 patients with ON had MRI lesions in the white matter or basal ganglia. Two of 6 patients with cerebral MRI changes had a lesion in the cervical and thoracic spinal cord extending more than 3 segments and classified as longitudinal extensive transverse myelitis. One patient had only a single T2-weighted lesion in the spinal cord not extending more than 2 segments (patient 14, eTable). All follow-up MRIs showed resolution of the white matter lesions. Additional episodes of ON in these patients were not associated with new lesions in the cerebral MRI.
Only 3 of 15 patients with recurrent ON were seronegative for MOG-IgG antibodies, with no pathological MRI abnormalities and only 2 episodes of ON (Figure and Table). Most patients (12 of 15) with recurrent ON were seropositive for MOG-IgG antibodies with levels of 1:160 or more (median, 1:640 [range, 1:160 to 1:5120]).

To exclude a possible confounding factor of age for anti-MOG seropositivity, we adjusted our analysis for age as a covariate using logistic regression analysis, and MOG-IgG findings remained significant (Table).

Median MOG-IgG titers were significantly higher in this group of patients compared with patients with a single ON episode or ON as part of a CIS \((P = .01)\) (Figure and Table).

**SUBGROUP 3**

Eleven of 12 patients (10 girls and 2 boys; median age, 16 [range, 9-18] years; median follow-up, 1.9 [range, 1.7-4.7] years \([ > 2 \text{ years in } 6 \text{ of } 12 \text{ patients}]\) had a first episode of ON and evidence of dissemination in space with 2 or more T2-weighted MRI white matter lesions. One patient had a single spinal lesion but OCBs in cerebrospinal fluid. Oligoclonal bands were present in the cerebrospinal fluid of 11 of 12 patients. Eight patients with CIS were subsequently diagnosed as having MS owing to a second clinical episode with new symptoms or new lesions on cerebral MRI. Four of the 8 patients with MS receive disease-modifying treatments at present (cTable).

In contrast to 7 of 12 patients with CIS who had undetectable levels of MOG-IgG antibodies at the initial presentation, 2 had low-titer anti-MOG levels (1:20) and 3 had high-titer MOG-IgG antibodies (Figure, Table, and cTable).

**COMMENT**

Anti-MOG antibodies have not been investigated in pediatric patients with ON to date, to our knowledge. Therefore, we assessed the presence of MOG-IgG antibodies in the serum of 37 pediatric patients with an acute episode of ON by using a live cell–staining immunofluorescence assay for the detection of IgG antibodies to natively folded MOG. Overall, MOG-IgG antibodies were detected in 21 of 37 patients with an acute episode of ON. In addition, our results show elevated MOG-IgG antibody levels, particularly in pediatric patients with recurrent episodes of ON who had no clinical and/or MRI evidence of a chronic demyelinating disease process, including MS or NMO. Furthermore, this study confirms recently published results showing low MOG-IgG antibody titers in patients with ON as part of CIS.

Optic neuritis can occur as a single episode or as recurrent episodes affecting 1 or both eyes but can also be associated with other acute or chronic autoimmuned mediated demyelinating diseases, such as ADEM, CIS/MS, or NMO. In clinical practice, different clinical, laboratory, and radiological features are used to differentiate these diseases. For example, children with isolated ON and ADEM are usually younger, have a preceding viral illness, or have other symptoms, such as an encephalopathy, compared with children diagnosed as having CIS. Patients with ON who eventually develop a chronic demyelinating disease often show MRI evidence of previous subclinical demyelinating episodes or exhibit evidence of an intrathecal IgG synthesis. Nevertheless, at the initial presentation of ON, it often remains difficult to predict the future disease course. Therefore, the identification of disease-relevant and individually reliable biomarkers would be highly important.

Our results suggest that pediatric patients with a single episode of ON and normal findings on MRI of the brain combined with low or absent levels of serum MOG-IgG antibodies are less likely to develop recurrent episodes of ON or MS. Moreover, high levels of MOG-IgG antibodies \((\geq 1:160)\) indicate that patients with an initial ON event will not develop a chronic demyelinating disease, such as MS or NMO, offering an additional tool in the differential diagnosis. Our findings further delineate a subgroup of children with recurrent episodes and high MOG-IgG levels, indicating that antibodies to MOG play an important role in the disease process of ON. Nine patients with recurrent ON and high MOG-IgG antibody levels had MRI findings in the brain at the first presentation ranging from swelling of the optic nerves to brain and/or white matter lesions of the spinal cord. All MRI lesions resolved and no new lesions occurred, but patients had subsequent episodes of ON. Levels of MOG-IgG from this initial episode in this subgroup of patients were available from 4 and remained high in 3.

The presence of antibodies directed at MOG and their relevance for the disease pathogenesis of MS or ADEM have been studied extensively. Several animal studies have demonstrated that MOG-IgG antibodies can induce antibody-mediated demyelination and enhance experimental autoimmune encephalomyelitis. If MOG-IgG antibodies are instrumental in the disease process, plasma exchange may be a therapeutic tool for patients with severe disease.

In our cohort, bilateral ON was seen in only 3 patients with recurrent episodes. Therefore, bilateral ON occurred less commonly and was not predictive of MS, as previously reported. However, the range of MRI findings at the initial manifestation of ON and the rate of visual recovery were similar to other reports. White matter lesions on MRI and the presence of OCBs highly predicted the conversion to MS, and most of our patients had full recovery with normal eyesight and normal visual evoked potentials.

One limitation of our study is that serum MOG-IgG antibody levels were measured only at the first episode in 7 of 15 patients with recurrent ON. In the remaining 8 patients, serum MOG-IgG antibody levels were measured at the last episode of ON. Therefore, we do not know whether MOG-IgG antibody levels at previous episodes and, in particular, at the first episode of ON were elevated in these patients. However, serum samples from 6 patients could be obtained from subsequent acute attacks of ON. These patients had elevated MOG-IgG antibody levels at the initial ON event, and titers remained persistently high and positive in 4 of them for up to 7 years.

Another limitation of our study is that in the monophasic and/or recurrent ON groups, a conversion to re-
current ON or CIS/MS is possible. We thus tried to obtain a clinical follow-up longer than 2 years from all patients. Although the median follow-up of both groups was longer than 2 years, 2 patients in the monophasic ON group (with follow-up of 1.7 and 1.9 years) and 4 patients in the recurrent ON group (with follow-up of 0.9, 1.2, 1.6, and 1.8 years) had a follow-up of less than 2 years.

In summary, high MOG-IgG levels were predominately detected in patients with recurrent ON who had no intrathecal IgG synthesis and who had MRI findings ranging from normal to optic nerve swelling and ADEM-like lesions. Therefore, anti-MOG antibody serostatus may be a new tool that can be used in combination with clinical and imaging findings to separate these patients from those who will eventually develop a chronic demyelinating disease, such as MS or NMO. Our results further indicate that MOG-specific antibodies may exert a direct role in the disease pathogenesis in a subgroup of patients with recurrent episodes of ON.

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**REFERENCES**