Antibodies to Aquaporin 4, Myelin-Oligodendrocyte Glycoprotein, and the Glycine Receptor α1 Subunit in Patients With Isolated Optic Neuritis

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IMPORTANCE In patients with isolated optic neuritis (ON), the presence of antibodies to aquaporin 4 (AQP4) has diagnostic and prognostic value. In the same clinical setting, the significance of antibodies to myelin-oligodendrocyte glycoprotein (MOG) or the glycine receptor α1 subunit (GlyR) is unclear.

OBJECTIVES To investigate the frequency of antibodies to AQP4, MOG, and GlyR in patients with unilateral or bilateral, severe, or recurrent isolated ON and to determine their clinical and prognostic correlates.

DESIGN, SETTING, AND PARTICIPANTS Retrospective case-control study from November 1, 2005, through May 30, 2014, with the detection of autoantibodies in a neuroimmunology referral center. We included 51 patients with ON but without clinical and magnetic resonance imaging findings outside the optic nerves and 142 controls (30 healthy individuals, 48 patients with neuromyelitis optica, and 64 patients with multiple sclerosis).

MAIN OUTCOMES AND MEASURES Clinicoimmunologic analysis. We determined the presence of antibodies to AQP4, MOG, and GlyR using cell-based assays.

RESULTS The median age of the patients at the onset of ON symptoms was 28 (range, 5-65) years; 36 patients (71%) were female. Antibodies were identified in 23 patients (45%), including MOG in 10 patients, AQP4 in 6 patients, and GlyR in 7 patients (concurrent with MOG in 3 and concurrent with AQP4 in 1). Patients with AQP4 antibodies (median visual score, 3.5 [range, 1-9]) had a worse visual outcome than patients with MOG antibodies alone (median visual score, 0 [range, 0-5]; P = .007), patients with seronegative findings (n = 28) (median visual score, 1.0 [range, 0-14]; P = .08), and patients with GlyR antibodies alone (n = 3) (median visual score, 0 [range, 0-2]; P = .10). The median age of the 7 patients with GlyR antibodies was 27 (range, 11-38) years; 5 (71%) of these were female. Among the 3 patients with GlyR antibodies alone, 1 patient had monophasic ON, 1 had recurrent isolated ON, and 1 had conversion to multiple sclerosis. The 3 patients with GlyR antibodies concurrent with MOG antibodies had recurrent isolated ON, and the patient with concurrent AQP4 antibodies had conversion to neuromyelitis optica. Of the 48 controls with neuromyelitis optica, 37 (77%) had AQP4 antibodies, 4 (8%) had MOG antibodies, 2 (4%) had AQP4 antibodies concurrent with MOG antibodies, and 5 (10%) were seronegative. Of the 64 controls with multiple sclerosis, 5 (8%) had GlyR antibodies.

CONCLUSIONS AND RELEVANCE Forty-five percent of patients with unilateral or bilateral, severe, or recurrent isolated ON had antibodies to MOG, AQP4, or GlyR. Patients with AQP4 antibodies had the poorest visual outcomes, whereas patients with MOG antibodies had a better outcome that was similar to that of patients with seronegative findings. The significance of GlyR antibodies in the setting of ON is unclear and deserves further study.
Optic neuritis (ON) is often the presenting symptom of multiple sclerosis (MS) or neuromyelitis optica (NMO). However, after extensive diagnostic workup and prolonged follow-up, some patients are diagnosed as having idiopathic monophasic or recurrent isolated ON. The presence of autoantibodies may help to differentiate these disorders. As many as 20% of patients with recurrent ON have antibodies to aquaporin 4 (AQP4), and their presence conveys the risk for developing transverse myelitis and a poor outcome. A subset of patients with NMO or suspected limited forms (including ON) without AQP4 antibodies have antibodies to myelin-oligodendrocyte glycoprotein (MOG). Patients with MOG antibodies seem to have a better outcome than those with AQP4 antibodies.

In a previous study examining the presence of antibodies to the glycerine receptor α1 subunit (GlyR) in patients with stiff person syndrome, McKeon and colleagues found among 100 control individuals a patient with a 2-year history of visual deficits (visual acuity [VA], 20/400) and bilateral optic atrophy in association with GlyR antibodies. Despite the prolonged duration of symptoms, the VA improved after a trial of corticosteroids (20/100 OD and 20/150 OS). Since then, several of us (E.M.-H., M.S., and A.S.) have seen another patient with bilateral progressive inflammatory optic neuropathy and GlyR antibodies, and similar observations have been made by other investigators. These findings suggested that GlyR antibodies may be associated with ON as relevant pathogenically related antibodies or as an epiphenomenon. We report herein our experience with 51 patients who presented with unilateral or bilateral, severe, or recurrent isolated ON, a clinical profile that is usually suspected of being related to AQP4 antibodies. We tested serum or cerebrospinal fluid (CSF) samples from each patient systematically for all 3 antibodies (AQP4, MOG, and GlyR), with the goal of determining their frequency and the clinical and prognostic correlates.

Methods

Patients and Samples
We obtained written informed consent for this study from all patients, and the study was approved by the review board of the Hospital Clinic, University of Barcelona, Barcelona, Spain. We included patients with the following criteria: (1) new onset of unilateral or bilateral, severe (VA, worse than 20/200), or recurrent ON, suspected to be of demyelinating origin, treated by the authors or with serum or CSF samples sent to our laboratory from November 1, 2005, through May 30, 2014, for antibody studies; (2) absence of central nervous system abnormalities outside the optic nerves and normal or nonspecific abnormal magnetic resonance imaging findings that did not fulfill criteria for MS, NMO, or acute disseminated encephalomyelitis at the time the patient or the samples underwent initial assessment; and (3) adequate clinical information with a follow-up of at least 12 months.

Visual acuity was assessed using an ordinal scale as previously reported on which 0 indicates normal; 1, scotoma but with a VA better than 20/30; 2, a VA of 20/30 to 20/59; 3, a VA of 20/60 to 20/199; 4, a VA of 20/200 to 20/800; 5, counting fingers; 6, light perception only; and 7, no light perception. The final visual outcome was the sum of the last assigned visual score for each eye.

Overall, we included 51 patients with isolated ON (36 adults and 15 children). Serum samples were available from all 51 patients, and CSF samples were available from 4 patients. Control samples included serum from 30 healthy individuals, 48 patients with definite NMO according to the criteria of Wingerchuk et al. and 64 patients (including 8 children) with definite MS at the time of sample collection, the clinical phenotypes included clinically isolated syndrome (n = 28), relapsing remitting (n = 17), secondary progressive (n = 9), and primary progressive (n = 10).

Cell-Based Assays
For the detection of GlyR antibodies, we used a live cell–based assay. In brief, HEK293 cells were transfected with a plasmid (pRKs) containing the human GlyR α1 subunit complementary DNA, as reported. The next day, cells were incubated with patients’ serum samples (diluted 1:40 in growth medium containing culture medium [Dulbecco Modified Eagle Medium; Life Technologies], 5% fetal bovine serum, 5% horse serum, 1% penicillin-streptomycin, 1% glutamate, and 1% sodium pyruvate) or patients’ CSF samples (diluted 1:5) for 1 hour at 37°C. After being fixed and permeabilized for 5 minutes (4% paraformaldehyde and 0.3% Triton X-100 [polyethylene glycol tert-octylphenyl ether; Sigma-Aldrich]), the cells were serially incubated with a monoclonal mouse antibody recognizing the GlyR α1 subunit (mAb44, diluted 1:1000 in 1% bovine serum albumin; Synaptic Systems) for 1 hour at room temperature, followed by the secondary goat antihuman and goat antimouse antibodies (A11013 [Alexa Fluor 488] and A11005 [Alexa Fluor 594]; Molecular Probes/Life Technologies), each diluted 1:1000 in 1% bovine serum albumin. Coverslips were then applied with mounting medium (Vectashield H-1200; Vector Laboratories) and examined under a fluorescence microscope using a commercially available imaging system (Axiovision; Zeiss). All positive samples and 11 randomly selected negative samples underwent similar testing with live cells at room temperature and at 4°C to determine whether changes in the temperature of incubation modified the immunostaining results.

Antibodies to AQP4 and MOG were similarly examined using live HEK293 cells transfected with the AQP4-M23 isof orm or the full-length MOG C-terminal fused to enhanced green fluorescent protein, as reported. For detection of AQP4 antibodies, serum samples were used at a dilution of 1:20; and for MOG antibodies, 1:160. Cerebrospinal fluid samples were used at a dilution of 1:2. The titer of GlyR and MOG antibodies was obtained by serial dilutions of samples until the reactivity was no longer visible.

Results

Demographics and General Clinical Features
The median age of the patients at symptom onset was 28 (range, 5-65) years; 36 patients (71%) were female. The initial episode
was severe unilateral ON in 13 patients (25%), severe bilateral ON in 14 patients (27%), nonsevere bilateral ON in 8 patients (16%), and nonsevere unilateral in 16 (31%). The findings of magnetic resonance imaging of the brain at symptom onset were normal in 36 patients (71%) and had nonspecific abnormalities in 15 patients (29%). The CSF studies available in 37 patients showed CSF-specific IgG oligoclonal bands in 3 (8%). Long-term immunosuppressive therapy with azathioprine, prednisone, or rituximab was administered only in adults (14 of 36 [39%]).

At the last follow-up (median, 33.5 months; interquartile range, 22-68 months), 43 patients retained the diagnosis of idiopathic isolated ON (monophasic in 17 [40%] and recurrent in 26 [60%]), 1 patient had conversion to MS (magnetic resonance imaging criteria of dissemination in space and time9 and 2 relapses of ON), and 7 patients had conversion to NMO or NMO spectrum disorder. Of these 7 patients, 3 had recurrent ON, 2 had episodes of transverse myelitis,12 1 had an episode of brainstem dysfunction, and 1 had bilateral and severe monophasic ON.

Antibody Findings

Serum antibodies were detected in 23 patients (45%). Of these, 10 patients had MOG antibodies, 6 patients had AQP4 antibodies, and 7 patients had GlyR antibodies (3 with concurrent MOG antibodies and 1 with concurrent AQP4 antibodies) (Figure). The change of temperature during the incubation with patients' samples did not modify the results. Paired serum and CSF samples were available from 4 patients, of whom 1 had MOG antibodies in serum and CSF and 1 had concurrent MOG and GlyR antibodies only in serum. In the remaining 2 patients, both samples were negative.

Among the 48 controls with NMO, 37 (77%) had AQP4 antibodies, 4 (8%) had MOG antibodies, 2 (4%) had AQP4 antibodies concurrent with MOG antibodies, and 5 (10%) were seronegative. None of the controls with NMO had GlyR antibodies. Among the 64 controls with MS, 5 (8%) had GlyR antibodies, including 3 with relapsing remitting MS, 1 with a clinically isolated syndrome of myelitis, and 1 with primary progressive MS. The CSF samples of 4 of these 5 patients were available for study, and all were negative for GlyR antibodies. All controls with MS were negative for AQP4 and MOG antibodies. None of the 30 healthy individuals had detectable antibodies.

Clinicoimmunologic Correlates

The 4 patients with 2 antibodies were excluded from the analysis, and we compared the seronegative patients (n = 28), the patients with MOG antibodies only (n = 10), those with AQP4 antibodies only (n = 6), and those with GlyR antibodies only (n = 3) (Table 1). The only significant differences found among subgroups were the final visual scores (P = .04, Kruskal-Wallis test) and the use of long-term immunosuppressive therapy (P < .001, χ² test). Patients with AQP4 antibodies had a worse visual outcome (median visual score, 3.5 [range 1-9]) than patients with MOG antibodies (median visual score, 0 [range, 0-5]; P = .007), seronegative patients (median visual score, 1.0 [range, 0-14]; P = .08), and patients with GlyR antibodies (median visual score, 0 [range, 0-2]; P = .10) (all comparisons, Mann-Whitney test) (Table 1). Patients with AQP4 antibodies also received long-term immunosuppressive therapy more frequently (6 of 6 patients [100%]) compared with patients with MOG antibodies (2 of 10 [20%]), seronegative patients (3 of 28 [11%]), and patients with GlyR antibodies (0 of 3).
Other differences did not reach statistical significance on multiple comparisons, probably owing to the low number of patients in each subgroup. However, compared with the patients with AQP4 antibodies, those with MOG antibodies were less frequently female (5 of 10 [50%] vs 6 of 6 [100%]) and were younger (median age, 18 vs 44 years). No differences were found in the frequency of severe or bilateral first episodes of ON or recurrent ON. The AQP4 antibodies were not detected in children.

The clinical features of the 7 patients with GlyR antibodies are shown in Table 2. Median age was 27 (range, 11-38) years; 5 of these (71%) were female. Among the 3 patients with GlyR antibodies alone, 2 had idiopathic isolated ON (recurrent in one and monophasic bilateral in the other) and 1 experienced conversion to MS.9 The 3 patients with GlyR antibodies concurrent with MOG antibodies had idiopathic recurrent isolated ON, and the patient with concurrent AQP4 antibodies experienced conversion to definite NMO.12 At the last follow-up for the 7 patients with GlyR antibodies (median, 41 months; interquartile range, 33-72 months), the 5 patients with idiopathic isolated ON (excluding those with conversion to NMO and MS) achieved normal VA. The frequency of GlyR antibodies alone in patients with ON was not different from that observed in controls with MS (3 of 47 [6%] vs 5 of 64 [8%]; P > .99). The follow-up of serum GlyR antibody titers was available from 5 patients with ON; in 4 patients the titers remained unchanged, and in 1 patient the antibodies were no longer detectable.

### Discussion

This study shows that 45% of patients with new-onset unilateral or bilateral, severe, or recurrent ON, in the absence of clinical and magnetic resonance imaging findings outside the optic nerves, had antibodies to MOG, AQP4, or GlyR. Moreover, when one considers the patients who at the last follow-up retained the diagnosis of idiopathic isolated ON, 15 of 43 (35%) had MOG, GlyR, or both antibodies. The identification of autoantibodies was important for 2 reasons. First, it showed the presence of specific autoimmune mechanisms, and second, it had clinical and prognostic implications. Indeed, compared with patients with AQP4 antibodies, those with MOG antibodies were younger and, despite the similar frequency of severe or bilateral first episodes of ON or recurrent ON, had a better visual outcome. Some of these antibody-associated features are similar to those reported in the context of NMO or NMO-related syndromes. For example, in patients with NMO or limited forms of NMO, the presence of MOG antibodies has been shown to be associated with a better outcome than the presence of AQP4 antibodies.5,6 In another study examining the presence and prognostic value of AQP4 antibodies in patients with recurrent ON, seropositive patients had a worse final visual score than that of seronegative patients, similar to our study.3 The more frequent use of long-term immunosuppressive therapy in patients with AQP4 antibodies likely is explained by the availability of this antibody in routine clinical
Isolated Optic Neuritis

Original Investigation Research

of the adults.16 However, our study focused on isolated ON, ingisin contrast to that of the studies of children with NMO, ingsbeyond the optic nerves.17 leading to the exclusion of patients with AQP4 antibodies that elitis with rigidity and myoclonus. The GlyR antibodies are toms of stiff person syndrome or progressive encephalomy-

cal phenotypes of MS, and none of them developed symp-

toms of stiff person syndrome or progressive encephalomy-
elitis with rigidity and myoclonus. The GlyR antibodies are abundantly expressed in inhibitory synapses of the brain-

tem, spinal cord, and retina, and the association with demy-
elinating diseases has been suggested in other reports, including 2 patients with NMO18 and a child with transverse myelitis and deep brain white matter abnormalities.19 A pathogenic link among GlyR antibodies, ON, and demyelinating disorders has not been established, but these antibodies can occur in sev-

eral different disorders. Indeed, in a recent study of patients with cerebellar ataxia and glutamic acid decarboxylase 65 antibodies,20 GlyR antibodies were identified in 4 of 34 pa-

Table 2. Clinical Features of Patients With Antibodies

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age at Onset, y</th>
<th>Initial Episode</th>
<th>CSF WBC, No./mm³ (OCB)</th>
<th>Brain MRI Finding</th>
<th>History of Autoimmune Disease</th>
<th>No. of Recurrences</th>
<th>Follow-up, mo</th>
<th>Long-term Immunosuppressive Therapy</th>
<th>Final Diagnosis</th>
<th>Outcome, EDSS Score (Snellen VA)</th>
<th>Antibody (Titer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/27</td>
<td>Severe ON</td>
<td>0 (Negative)</td>
<td>Normal; optic nerve increased T2 signal, Gd+</td>
<td>Psoriasis</td>
<td>2 ON</td>
<td>33</td>
<td>None</td>
<td>Recurrent isolated ON</td>
<td>0 (20/20 OU)</td>
<td>GlyR (1:1280); MOG (1:1280)</td>
</tr>
<tr>
<td>2/F/27</td>
<td>Severe ON</td>
<td>0 (Negative)</td>
<td>Normal; optic nerve increased T2 signal</td>
<td>Rheumatoid arthritis; autoimmune thyroiditis</td>
<td>1 ON</td>
<td>133</td>
<td>Methotrexate</td>
<td>Recurrent isolated ON</td>
<td>0 (20/20 OU)</td>
<td>GlyR (1:160); MOG (1:320)</td>
</tr>
<tr>
<td>3/F/38</td>
<td>Nonsevere ON</td>
<td>4 (Positive)</td>
<td>Nonspecific WML</td>
<td>None</td>
<td>2 ON</td>
<td>41</td>
<td>Glatiramer acetate</td>
<td>RRMS</td>
<td>2.5 (20/30 OD; 20/25 OS)</td>
<td>GlyR (1:80)</td>
</tr>
<tr>
<td>4/F/33</td>
<td>Bilateral ON</td>
<td>0 (Negative)</td>
<td>Normal</td>
<td>None</td>
<td>None</td>
<td>41</td>
<td>None</td>
<td>Monophasic isolated ON</td>
<td>0 (20/20 OU)</td>
<td>GlyR (1:80)</td>
</tr>
<tr>
<td>5/F/22</td>
<td>Severe and bilateral ON</td>
<td>0 (Negative)</td>
<td>Nonspecific WML; optic nerve chiasm increased T2 signal</td>
<td>Small joint arthritis (HLA-B51+); anti-SSB</td>
<td>1 ON; 2 myelitis</td>
<td>72</td>
<td>Azathioprine; rituximab</td>
<td>NMO</td>
<td>2 (20/25 OD; 20/25 OS)</td>
<td>GlyR (1:640); AQPR (1:640)</td>
</tr>
<tr>
<td>6/F/13</td>
<td>Nonsevere ON</td>
<td>7 (Positive)</td>
<td>Normal</td>
<td>None</td>
<td>1 ON</td>
<td>24</td>
<td>None</td>
<td>Recurrent isolated ON</td>
<td>0 (20/20 OU)</td>
<td>GlyR (1:320)</td>
</tr>
<tr>
<td>7/M/11</td>
<td>Nonsevere ON</td>
<td>1 (Negative)</td>
<td>Normal; optic nerve increased T2 signal, Gd+</td>
<td>None</td>
<td>4 ON</td>
<td>36</td>
<td>None</td>
<td>Recurrent isolated ON</td>
<td>0 (20/20 OU)</td>
<td>GlyR (1:160); MOG (1:2560)</td>
</tr>
<tr>
<td>8/M/59</td>
<td>Severe and bilateral ON</td>
<td>NA (Negative)</td>
<td>Nonspecific WML; bilateral optic nerve Gd+</td>
<td>None</td>
<td>None</td>
<td>13</td>
<td>None</td>
<td>Monophasic isolated ON</td>
<td>1 (20/25 OD; 20/20 OS)</td>
<td>MOG (1:1280)</td>
</tr>
<tr>
<td>9/F/22</td>
<td>Nonsevere ON</td>
<td>2 (Negative)</td>
<td>Normal</td>
<td>None</td>
<td>2 ON</td>
<td>215</td>
<td>None</td>
<td>Recurrent isolated ON</td>
<td>1 (20/20 OD; 20/25 OS)</td>
<td>MOG (1:640)</td>
</tr>
<tr>
<td>10/F/29</td>
<td>Severe ON</td>
<td>NA (Negative)</td>
<td>Normal</td>
<td>None</td>
<td>5 ON</td>
<td>96</td>
<td>None</td>
<td>Recurrent isolated ON</td>
<td>4 (20/200 OD; 20/25 OS)</td>
<td>MOG (1:2560)</td>
</tr>
<tr>
<td>11/M/45</td>
<td>Nonsevere ON</td>
<td>0 (Negative)</td>
<td>Normal; optic nerve increased T2 signal, Gd+</td>
<td>None</td>
<td>4 ON</td>
<td>67</td>
<td>Azathioprine; prednisone</td>
<td>Recurrent isolated ON</td>
<td>1 (20/25 OU)</td>
<td>MOG (1:10240)</td>
</tr>
<tr>
<td>12/F/25</td>
<td>Nonsevere ON</td>
<td>NA (Negative)</td>
<td>Normal</td>
<td>None</td>
<td>14 ON</td>
<td>147</td>
<td>IV Ig; azathioprine</td>
<td>Recurrent isolated ON</td>
<td>1 (20/20 OD; 20/25 OS)</td>
<td>MOG (1:1280)</td>
</tr>
<tr>
<td>13/M/14</td>
<td>Severe and bilateral ON</td>
<td>1 (Negative)</td>
<td>Normal</td>
<td>None</td>
<td>None</td>
<td>28</td>
<td>None</td>
<td>Monophasic isolated ON</td>
<td>0 (20/20 OU)</td>
<td>MOG (1:640)</td>
</tr>
<tr>
<td>14/F/9</td>
<td>Severe ON</td>
<td>3 (Negative)</td>
<td>Nonspecific WML</td>
<td>None</td>
<td>None</td>
<td>26</td>
<td>None</td>
<td>Monophasic isolated ON</td>
<td>0 (20/20 OU)</td>
<td>MOG (1:1280)</td>
</tr>
</tbody>
</table>

To our knowledge, the presence of GlyR antibodies has not been investigated previously in patients with isolated ON. In the present study, 7 patients with ON (14%) had GlyR antibodies, and these were associated with other antibodies in 4 patients (57%). Moreover, GlyR antibodies were identified in 5 controls with MS (8%). These patients represented all the clinical phenotypes of MS, and none of them developed symp-
toms of stiff person syndrome or progressive encephalomy-
elitis with rigidity and myoclonus. The GlyR antibodies are (continued)
Table 2. Clinical Features of Patients With Antibodies (continued)

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age at Onset, y</th>
<th>Initial Episode</th>
<th>CSF WBC, No./mm³ (OCC)</th>
<th>Brain MRI Finding</th>
<th>History of Autoimmune Disease</th>
<th>No. of Recurrences</th>
<th>Follow-up, mo</th>
<th>Long-Term Immunosuppressive Therapy</th>
<th>Final Diagnosis</th>
<th>Outcome, EDSS Score (Snellen VA)</th>
<th>Antibody (Titer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15/F/9 Nonsevere ON</td>
<td>9 (Negative)</td>
<td>Normal</td>
<td>None</td>
<td>2 ON</td>
<td>48</td>
<td>None</td>
<td>Recurrent isolated ON</td>
<td>0 (20/20 OU)</td>
<td>MOG (1:320)</td>
<td></td>
</tr>
<tr>
<td>16/M/5 Bilateral ON</td>
<td>1 (Negative)</td>
<td>Nonspecific WML</td>
<td>None</td>
<td>None</td>
<td>12</td>
<td>None</td>
<td>Monophasic isolated ON</td>
<td>0 (20/20 OU)</td>
<td>MOG (1:320)</td>
<td></td>
</tr>
<tr>
<td>17/M/13 Nonsevere ON</td>
<td>117 (Negative)</td>
<td>Nonspecific WML</td>
<td>None</td>
<td>3 ON</td>
<td>15</td>
<td>None</td>
<td>Recurrent isolated ON</td>
<td>0 (20/20 OU)</td>
<td>MOG (1:2560)</td>
<td></td>
</tr>
<tr>
<td>18/F/26 Severe and bilateral ON</td>
<td>NA (Negative)</td>
<td>Normal</td>
<td>None</td>
<td>1 ON</td>
<td>90</td>
<td></td>
<td>Cyclophosphamide</td>
<td></td>
<td>NMO spectrum disorder</td>
<td>AQP4 (NA)</td>
</tr>
<tr>
<td>19/F/50 Severe ON</td>
<td>2 (Negative)</td>
<td>Nonspecific WML</td>
<td>None</td>
<td>2 ON; 1 brainstem relapse</td>
<td>49</td>
<td>Rituaximab</td>
<td>NMO spectrum disorder</td>
<td>2 (20/20 OD; 20/30 OS)</td>
<td>AQP4 (NA)</td>
<td></td>
</tr>
<tr>
<td>20/F/42 Nonsevere ON</td>
<td>8 (Positive)</td>
<td>Nonspecific WML</td>
<td>None</td>
<td>1 ON</td>
<td>14</td>
<td>Azathioprine</td>
<td>NMO spectrum disorder</td>
<td>1 (20/25 OD; 20/20 OS)</td>
<td>AQP4 (NA)</td>
<td></td>
</tr>
<tr>
<td>21/F/27 Severe and bilateral ON</td>
<td>0 (Negative)</td>
<td>Normal</td>
<td>None</td>
<td>5 ON</td>
<td>224</td>
<td>Azathioprine</td>
<td>NMO spectrum disorder</td>
<td>5 (20/200 OD)</td>
<td>AQP4 (NA)</td>
<td></td>
</tr>
<tr>
<td>22/F/65 Severe and bilateral ON</td>
<td>NA Normal</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>34</td>
<td>Azathioprine</td>
<td>NMO spectrum disorder</td>
<td>5 (20/200 OU)</td>
<td>AQP4 (NA)</td>
<td></td>
</tr>
<tr>
<td>23/F/45 Severe ON</td>
<td>NA Nonspecific WML</td>
<td>Lupus and antiphospholipid syndrome ANA*</td>
<td>1 ON; 1 LETM</td>
<td>25</td>
<td>Prednisone; cyclophosphamide; rituximab</td>
<td>NMO</td>
<td>5 (20/20 OD)</td>
<td>AQP4 (NA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ANA+, positive for antinuclear antibodies; CF, counting fingers; CSF, cerebrospinal fluid; EDSS, Expanded Disability Status Scale; Gd+, gadolinium enhancement; IV Ig, intravenous immunoglobulin; LETM, longitudinally extensive transverse myelitis; NA, not available; NMO, neuromyelitis optica; OCB, oligoclonal bands; ON, optic neuritis; RRMS, relapsing-remitting multiple sclerosis; VA, visual acuity; WBC, white blood cell count; WML, white matter lesions.

Su conversion factor: To convert WBC to x10⁹ per liter, multiply by 0.001.

Conclusions

Overall, this study indicates that a substantial number of patients with unilateral or bilateral, severe, or recurrent isolated ON have autoantibodies and that their significance varies with the type of autoantibody. Patients with AQP4 antibodies had the poorest visual outcome, whereas patients with MOG antibodies had a more favorable outcome that was similar to that of seronegative patients. The GlyR antibodies can occur in patients with ON, but their significance in this clinical setting is unclear. Studies with more patients should determine whether GlyR antibodies have a role as biomarkers of immune-mediated ON. In addition, future studies should determine whether patients with milder forms of ON have similar antibody findings.

ARTICLE INFORMATION

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Author Contributions: Drs Saiz and Dalmau had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Martinez-Hernandez, Dalmau. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Martinez-Hernandez, Sepulveda, Rostásy, Höftberger, Graus, Saiz, Dalmau. Critical revision of the manuscript for important intellectual content: Rostásy, Graus, Harvey, Saiz, Dalmau. Statistical analysis: Martinez-Hernandez, Sepulveda. Obtained funding: Martinez-Hernandez, Dalmau. Administrative, technical, or material support: Harvey. Study supervision: Graus, Saiz, Dalmau.

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**REFERENCES**


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