Neuromyelitis Optica IgG Status in Acute Partial Transverse Myelitis

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Background: Neuromyelitis optica (NMO) IgG is a specific marker for NMO. Furthermore, a high proportion of patients with longitudinally extensive transverse myelitis (characterized by spinal cord lesions extending 3 vertebral segments or more on magnetic resonance imaging) are seropositive for NMO-IgG and are considered to have a limited form of NMO. The NMO-IgG status in mild cases of acute partial transverse myelitis associated with minimal magnetic resonance imaging abnormalities (spinal cord lesions <2 vertebral segments on magnetic resonance imaging) is unknown.

Objective: To investigate the NMO-IgG status of patients with acute partial transverse myelitis and a normal cerebral magnetic resonance image.

Design: Observational, retrospective consecutive case series with longitudinal follow-up.

Setting: Allegheny Multiple Sclerosis Treatment Center.

Patients: Three groups of patients were tested for NMO-IgG. Group 1 consisted of 22 patients with acute partial transverse myelitis, group 2 consisted of 4 patients with definite NMO (by 1999 criteria of Wingerchuk et al), and group 3 consisted of 6 patients with definite multiple sclerosis.

Main Outcome Measure: NMO-IgG status. A commercially available assay for NMO antibodies was performed at the Mayo Clinic. Testing was performed during the convalescent stage of the illness.

Results: Of the 22 patients with acute partial transverse myelitis, only 1 was seropositive for NMO-IgG at presentation. This patient subsequently developed recurrent episodes of longitudinally extensive transverse myelitis that are typically seen in association with NMO-IgG. Three of the 4 patients meeting criteria for NMO were seropositive. None of the patients with multiple sclerosis had NMO-IgG detected.

Conclusion: NMO-IgG is rarely encountered in patients with acute partial transverse myelitis, which is in sharp contrast to the high frequency of this antibody in patients with NMO and longitudinally extensive transverse myelitis.

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Our knowledge, the clinical significance of newly described neuromyelitis optica (NMO) antibodies (NMO-IgG) has been evaluated only at the Mayo Clinic, where the assay for the detection of NMO antibodies was developed recently. Investigators have described a high rate of NMO antibody positivity in patients fulfilling the criteria for NMO and a low rate of positivity in patients with classic multiple sclerosis (MS). In addition, 40% of patients presenting with longitudinally extensive transverse myelitis (LETM), involving at least 3 vertebral segments on magnetic resonance imaging (MRI), have been positive for NMO-IgG; these patients have a high risk of early relapse. To our knowledge, the rate of NMO positivity in patients presenting with mild symptoms of acute partial transverse myelitis (APTM) involving short asymmetric lesions (<2 vertebral segments) on MRI has not been studied. We tested such a population of patients with APTM for the presence of NMO-IgG to better define the spectrum of demyelinating disease associated with NMO antibody positivity.

Methods

Serum samples were tested at Mayo Clinic’s Neuroimmunology Laboratory. All samples were tested blind to the clinical and radiologic findings. Details of the performance of this assay have been published previously. We considered patients positive for NMO-IgG by immunofluorescence with titers at 1:120 or higher and those negative with titers less than 1:120. Patients chosen for the study were seen consecutively at the Allegheny Multiple Sclerosis Treatment Center, Pittsburgh, having undergone retrospec-
Table. Patient Characteristics by Group

<table>
<thead>
<tr>
<th>Type of Disease</th>
<th>Male-Female Ratio</th>
<th>Disease Duration, mo*</th>
<th>Age, y*</th>
<th>Final EDSS Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTM (n = 22)</td>
<td>7:15</td>
<td>30 (24-36)</td>
<td>37.5 (30-45)</td>
<td>2.8 (0-5.5)</td>
</tr>
<tr>
<td>Devic syndrome (n = 4)</td>
<td>1:3</td>
<td>36 (30-42)</td>
<td>45.0 (35-55)</td>
<td>6.0 (2.0-10.0)</td>
</tr>
<tr>
<td>Spinal-optic multiple sclerosis (n = 6)</td>
<td>1:5</td>
<td>45 (42-48)</td>
<td>48.5 (39-58)</td>
<td>3.5 (1.0-6.0)</td>
</tr>
</tbody>
</table>

Abbreviations: APTM, acute partial transverse myelitis; EDSS, Expanded Disability Status Scale.
*Data are given as average (range).

This study reports that NMO-IgG is rarely present in patients with mild APTM, in sharp contrast to the high frequency in patients with recurrent LETM.¹

This study has implications regarding the way we think about TM. NMO-IgG seems to differentiate some patients with LETM from those with APTM, and has predictive and prognostic significance, suggesting that the length of the lesion in TM is important.² Unfortunately, the working definition for the diagnosis of idiopathic acute TM proposed by the Transverse Myelitis Consortium Working Group does not distinguish between APTM and complete TM or LETM.³ Important differences in prognosis in patients with APTM compared with patients with LETM were recently described.³ Patients with APTM remain at fairly high risk for the development of MS (range, 20%-30%), even when presenting with an initially normal cerebral MRI, in sharp contrast to patients with LETM.⁴⁵

As the relatively low disability scores of our patients with APTM suggest, this syndrome seems to be clinically mild even when relapses occur. This stands in contrast to most patients with demyelinating disease associated with NMO-IgG positivity, wherein patients tend to have more severe relapses and disability long term. Longitudinal experience with patients with relapsing APTM was previously reported; these patients were not considered to have clinically definite MS given the limitation of pathological features (both clinically and radiographically) to the spinal cord only.³
Although the main focus of this report was to examine the utility of NMO-IgG testing in patients with mild APTM, we were also interested in the utility of NMO-IgG in patients with other presentations. We sought to verify the high rate of NMO-IgG positivity in those with NMO, as presented by the Mayo Clinic, and to verify the low rate of NMO-IgG positivity in patients with MS, specifically patients with MS who had severe optic and/or myelopathic features.

Taken together, these data suggest that the length of the lesion in patients with acute idiopathic TM may have important implications and may allow further separation of TM into different diagnostic and pathogenetic categories. Patients with LETM should have NMO-IgG tested, because a positive result likely predicts relapse or development of NMO and supports consideration of those seropositive as having a common underlying pathogenic mechanism. This study suggests that the same is not true for APTM. A recent study reported that NMO-IgG binds selectively to the mercurial-insensitive water channel protein aquaporin 4, which is concentrated in astrocytic foot processes at the blood-brain barrier. Aquaporin 4 is the predominant water channel protein in the central nervous system and has an important role in water homeostasis. The pathogenesis of NMO and related disorders like LETM is incompletely understood, but immunopathological and serological observations, and beneficial responses to plasmapheresis therapy, implicate a circulating autoantibody as the principal effector of the lesions of NMO. Early experience gained through an open-label trial of rituximab showed benefit in terms of relapse rate reduction and further suggests that a B-cell-mediated inflammatory process is involved. Proof of a targeted immune attack directed against aquaporin 4, as a cause for NMO spectrum disorders, including LETM, is awaited.

Our study has several limitations. The optimal timing of serum collection for NMO-IgG testing is yet to be defined. If we had alternatively tested patients during the acute phase of APTM, we might have identified some additional positive cases. Also, our patients with spino-optic predominant MS were tested after significant recovery from severe attacks. Whether disease activity impacts serological status is unclear. However, our patients in the Devic syndrome group were also tested during periods of remission and still had a high rate of positivity. In addition, many seropositive patients with NMO and LETM (either recurrent or single) were tested months or years after an attack or had mild attacks (V. A. Lennon, MD, PhD, S.J.P., and B. G. Weinschenker, MD, unpublished observations). An additional limitation surrounds our use of multiple MRI scanners and imaging protocols. The patients, however, underwent imaging within a few weeks of the onset of symptoms, usually with 1.5-T units, and we are confident that most of our patients with APTM have only small focal or small multifocal lesions by MRI. A notable exception was our single NMO-IgG-positive patient, who initially underwent scanning using a 0.5-T unit (hence, a more extensive lesion could have been missed). Thus, if a distinction is to be made regarding acute TM in respect of the length of the lesion on MRI, the timing of the MRI may be important, because if performed too early or late in the evolution of acute TM, it may miss the active inflammatory lesion when at its maximum length.

In conclusion, this study supports the argument that NMO-IgG is a marker of NMO and related disorders. In adult TM, NMO-IgG seropositivity is more likely found in patients with LETM and seropositivity may predict relapse or development of NMO. This study found a low frequency of NMO-IgG seropositivity in those with idiopathic APTM. A single NMO-IgG-seropositive patient, with initial presentation of APTM, subsequently developed a more severe bout of acute TM associated with a longitudinally extensive lesion. In agreement with initial studies, we also found a high rate of NMO antibody positivity in patients with NMO and did not detect NMO-IgG in a small group of patients with MS with predominantly spinal-optic symptoms.

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Author Contributions: Study concept and design: Scott and Pittock. Acquisition of data: Scott and Kassab. Analysis and interpretation of data: Scott, Kassab, and Pittock. Drafting of the manuscript: Scott, Kassab, and Pittock. Critical revision of the manuscript for important intellectual content: Scott, Kassab, and Pittock. Administrative, technical, and material support: Kassab. Study supervision: Scott and Pittock.

REFERENCES