Neuromyelitis Optica IgG Status in Acute Partial Transverse Myelitis

Thomas F. Scott, MD; Salima L. Kassab, MD; Sean J. Pittock, MD

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.

Arch Neurol. 2006;63:1398-1400

O 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-
tive medical record reviews, and all met the criteria described later. These patients have been followed up prospectively following performance of the assay for NMO antibodies.

We categorized our patients into 3 groups as follows. In group 1, APTM was defined according to the criteria published previously that included patients exhibiting mild symmetrical sensori- and/or motor symptoms or marked asymmetrical motor and/or sensory symptoms. All of these 22 patients had a normal cerebral MRI. All but 1 patient (with a normal spinal MRI) had small focal (n=13) or multifocal (n=8) spinal MRI lesions extending over 2 or fewer spinal cord segments. Patients with LETM at presentation were excluded. The mean follow-up at the time of NMO antibody testing was 5 years (range, 12-120 months). In patients with a lengthy follow-up, repeat cerebral MRIs were obtained every 12 to 24 months and remained negative. Group 2 patients had NMO and fulfilled previously published criteria. The mean follow-up in these 4 NMO patients at the time of testing was 36 months (range, 12-105 months). In group 3, there were 6 patients with MS fulfilling the criteria of Poser et al. These patients had multiple cerebral lesions on MRI and relapsing-remitting features; signs and symptoms of severe myelopathy (n=2), severe recurrent optic neuritis (n=3), or both (n=1); and no other prominent symptoms indicating involvement of other components of the central nervous system. All group 3 patients had signs of spinal and optic nerve demyelination on neurologi- cal examination and spinal cord lesions demonstrated by MRI (always ≤2 vertebral segments). The mean follow-up was 45 months (range, 42-48 months). Patient characteristics, including disability score after stabilization or recovery, are given in the Table. Expanded Disability Status Scale (EDSS) measurements are routinely recorded in our MS clinic and were all performed by a single experienced examiner (T.F.S.). Patients were considered stable for a final EDSS determination if the EDSS score was unchanged over at least 2 examinations performed at least 3 months apart.

### RESULTS

In group 1, 21 (95%) of the 22 patients with APTM were seronegative for NMO antibodies. These 21 patients with APTM presented with low levels of disability and sometimes experienced mild relapses (n=10) before NMO-IgG testing. One seronegative patient developed a mild relapse during the brief follow-up since NMO-IgG testing (average clinical course, 5.5 months; range, 4-7 months).

Most group 1 patients were not taking immunosuppressants or corticosteroids at the time of NMO-IgG testing (20 [91%] of 22 patients), with a notable exception being the sole patient testing seropositive for NMO-IgG. This patient had a severe course compared with the others. She presented initially with an episode of mild APTM. The MRI obtained 10 days after the first attack of APTM showed a faint small area of increased signal at C7. Another attack occurred 14 months later, with the appearance of a longitudinally extensive lesion on MRI (from C7 to T4). This patient developed a severe relapse 5 months later, with worsening of the longitudinally extensive lesion by MRI; her EDSS score reached 8.0. After treatment with high-dose corticosteroids, plasmapheresis, and methotrexate, 7.5 mg/wk, the EDSS score improved slowly over 3 months to 6.0. The patient continued to improve slowly over the next year after additional low-dose methotrexate therapy (20 mg/wk), reaching an EDSS score of 5.5. The NMO-IgG test was performed during methotrexate treatment. The average EDSS score in the remaining patients was 2.5 (range, 0-5.0). In group 2, NMO-IgG was detected in 3 of the 4 patients with definite NMO (mean EDSS score, 6; range, 2-10). All 4 patients were being treated with long-term immunosuppressive agents at the time of testing. In group 3, none of the patients with MS tested positive for NMO-IgG (mean EDSS score, 3.5; range, 1.0-6.0).

### COMMENT

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. 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. Unfortunately, the working defi- nition 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. Important differences in prognosis in patients with APTM compared with patients with LETM were recently described. 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.

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 con- trast 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 consid- ered to have clinically definite MS given the limitation of pathological features (both clinically and radiographi- cally) to the spinal cord only.
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.

Accepted for Publication: June 13, 2006.
Correspondence: Thomas F. Scott, MD, 420 E North Ave, East Wing Office Bldg, Suite 200, Pittsburgh, PA 15212 (tscott@wpahs.org).

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