Short Myelitis Lesions in Aquaporin-4-IgG–Positive Neuromyelitis Optica Spectrum Disorders

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Importance  Short transverse myelitis (STM; <3 vertebral segments) is considered noncharacteristic of neuromyelitis optica (NMO) spectrum disorders (NMOSDs). Nonappreciation of the potential for STM to occur in NMOSD may lead to increased disability from delay in diagnosis and appropriate treatment.

Objectives  To determine the frequency of short lesions at the initial myelitis manifestation of NMOSD and to compare the demographic, clinical, and radiological characteristics of aquaporin-4-IgG (AQP4-IgG) seropositive and seronegative STM.

Design, Setting, and Participants  We reviewed the records and images of patients at the Mayo Clinic who were identified as AQP4-IgG positive from 1996 to 2014. Inclusion criteria were first STM episode, magnetic resonance imaging performed 90 days or less from symptom onset, spinal cord T2-hyperintense lesion less than 3 vertebral segments, AQP4-IgG seropositivity, and a final diagnosis of NMO or NMOSD. Patients with an initial longitudinally extensive transverse myelitis were excluded (n = 151). Patients with STM who were seronegative for AQP4-IgG among an Olmsted County population–based cohort of inflammatory demyelinating disorders of the central nervous system were used as a control group.

Main Outcomes and Measures  Delay to diagnosis in months, clinical and radiological characteristics, and disability measured by ambulatory status.

Results  Twenty-five patients who were AQP4-IgG seropositive with an initial STM represented 14% of initial myelitis episodes among patients with NMOSD. The STM episode was defined as the first manifestation of NMOSD in 10 patients (40%) preceded by optic neuritis in 13 patients (52%) and preceded by a nausea and vomiting episode in 2 patients (8%). In comparison with the excluded patients with NMOSD who had an initial longitudinally extensive transverse myelitis, delay to diagnosis/treatment was greater when initial lesions were short (P = .02). In AQP4-IgG-positive STM cases, subsequent myelitis episodes were longitudinally extensive in 92%. Attributes more common in patients with AQP4-IgG–positive STM than in 27 population-based patients with AQP4-IgG–negative STM included the following: nonwhite race/ethnicity; tonic spasms; coexisting autoimmunity; magnetic resonance imaging (central cord lesions, T1 hypointensity, and a brain inconsistent with multiple sclerosis); and cerebrospinal fluid (oligoclonal bands lacking).

Conclusions and Relevance  Short transverse myelitis is not uncommon in NMOSD and, when it is present, delays diagnosis and treatment. Clinical and radiological characteristics identified in this study may help select patients with STM who are at the highest risk for an NMOSD. Short transverse myelitis does not exclude consideration of AQP4-IgG testing or NMOSD diagnosis.
ongitudinally extensive transverse myelitis (LETM), defined by magnetic resonance imaging (MRI) as extending 3 or more vertebral segments, is the most specific radiological finding supporting neuromyelitis optica (NMO) diagnosis in adult patients1-2 and has prompted physicians to test for aquaporin-4 (AQP4)-IgG.3 Seropositivity confirms the diagnosis of an NMO spectrum disorder (NMOSD), predicts recurrent myelitis or optic neuritis, and dictates therapeutic options.4 Early and accurate diagnosis of NMO or NMOSD is important to minimize cumulative disability from repeated episodes.5 The goal of diagnosis of NMO or NMOSD is important to minimize disability.6 Short transverse myelitis (STM; lesions defined by MRI as not extending 3 vertebral segments) is far more common in multiple sclerosis (MS)7 than in NMO.8-13 Although AQP4-IgG seropositivity is predicted to be infrequent in STM,8 it is not known how frequent short cord lesions are in patients who are AQP4-IgG positive. The goal of our study was to determine the frequency of short lesions in patients with an initial myelitis manifestation of NMOSD and to compare the demographic, clinical, and radiological characteristics of seropositive and seronegative patients with STM.

Methods

Patient Ascertainment and Inclusion Criteria
This study was approved by the Mayo Clinic institutional review board and all included patients provided written informed consent. We reviewed the medical records and images of 319 patients who were AQP4-IgG seropositive with NMO and NMOSD identified from 1996 to 2014 through our clinical and serological databases at the Mayo Clinic in Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida. Inclusion criteria were a first transverse myelitis episode14; an MRI performed 90 days or less from symptom onset and radiological details available for the first myelitis episode; a spinal cord T2-hyperintense lesion shorter than 3 vertebral segments; AQP4-IgG seropositivity; and a final diagnosis of NMO or NMOSD.1 Twenty-five patients met inclusion criteria.

We excluded 294 patients who were seropositive with NMO or NMOSD who had an initial episode of LETM (n = 151), no MRI spine details at initial myelitis or MRI performed more than 90 days after onset (n = 111), no myelitis episode (n = 28), an asymptomatic spinal cord lesion (n = 3), and a dorsal medullary lesion with slight extension to the cervical cord (n = 1).

Control STM Group
We included as control patients (n = 27) from the Olmsted County population–based cohort of inflammatory demyelinating disease those who met the following criteria: (1) STM was documented by spine MRI performed within 90 days of myelitis onset, (2) serum sample was available, and (3) an AQP4-IgG test result was negative. Final diagnoses at last follow-up (median, 103 months; range, 21-174 months) included 15 patients with relapsing–remitting MS7; 10 patients with monophasic STM; and 2 patients with relapsing STM.

AQP4-IgG Assays
The serostatus of AQP4-IgG was evaluated by 1 or more of the following assays: (1) enzyme-linked immunosorbent, (2) tissue-based indirect immunofluorescence,3 or (3) transfected cell-based (fixed [Euroimmun Inc] or live [fluorescence-activated cell sorting]).6

Radiological Methods
A variety of MRI techniques in multiple different scanners were used during 18 years, reflecting clinical practice at the time; all available sequences were reviewed. All MRIs were reviewed by Mayo Clinic neurologists or neuroradiologists.

Statistical Methods
Descriptive summary statistics were reported as median (range, minimum-maximum) for continuous variables and frequencies and percentages for categorical variables. Comparisons were performed using Wilcoxon rank sum test or Fisher exact test using SAS JMP 8.0 software.

Definitions
Neuromyelitis optica diagnosis was based on Wingerchuk et al7 criteria. An MS diagnosis was based on Polman et al7 criteria. And NMOSDs were defined as AQP4-IgG–seropositive optic neuritis (single/recurrent) or AQP4-IgG–seropositive transverse myelitis (single/recurrent).

Results

Short Transverse Myelitis Not Uncommon in the Initial Myelitis Episode of NMOSD
A short lesion (<3 vertebral segments) was the first transverse myelitis event in 25 of 176 patients (14%); 151 patients (86%) had an initial longitudinally extensive lesion (≥3 vertebral segments).

Comparison of AQP4-IgG–Seropositive and AQP4-IgG–Seronegative STM
The Table compares demographic, clinical, laboratory, and radiological characteristics of the 25 patients who were AQP4-IgG seropositive with STM to the population–based control cohort of 27 patients who were AQP4-IgG seronegative with STM.

Additional Details of AQP4-IgG–Seropositive STM Cases
Figures 1 and 2 demonstrate representative images. Myelitis was the first manifestation of NMOSD in 10 patients (40%); in 13 patients (52%), myelitis was preceded by optic neuritis (77% were severe or associated with poor recovery and 23% were bilateral). In 2 patients (8%), myelitis was preceded by an episode of severe nausea/vomiting. Multiple sclerosis was the initial diagnosis in 10 patients (40%) and 6 received interferon-β treatment for presumed MS. One patient worsened after starting interferon-β and in the remaining 5 patients, no benefit was seen with interferon-β. In 83% of AQP4-IgG–seropositive STM cases, the treating physician questioned the diagnosis of NMOSD because the spinal lesion was short. Three patients (12%) were receiving immunosuppressant therapy at the time.
All patients were seropositive by 1 or more of the following tests for AQP4-IgG: 16 patients with tissue-based immunofluorescence (64%; median titer, 760; range, 480-61440); 11 patients with enzyme-linked immunosorbent assay (44%; median, 160 units; range, 2.2 to >160 [normal, <1.6]); 8 patients (32%) with AQP4-transfected fixed cell–based assay; and 16 patients with AQP4-transfected live cell–based assay (flow cytometry). The median period of follow-up from NMOSD onset was 65 months (range, 3-293 months). The final diagnosis was NMO in 17 patients and NMOSD in 8 patients.

### Table. Clinical, Laboratory, and Radiological Findings of Short Transverse Myelitis in Patients With AQP4-IgG Positivity and in a Population-Based Cohort of Patients With Aquaporin-4-IgG Negativity

<table>
<thead>
<tr>
<th>Demographic</th>
<th>AQP4-IgG, No. (%)</th>
<th>Negative (n = 27)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>18 (72)</td>
<td>21 (78)</td>
<td>.63</td>
</tr>
<tr>
<td>Age at myelitis onset, median (range), y</td>
<td>50 (29-70)</td>
<td>42 (18-67)</td>
<td>.04</td>
</tr>
<tr>
<td>Nonwhite race/ethnicitya</td>
<td>8 of 23 (35)</td>
<td>0 (0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness</td>
<td>24 (96)</td>
<td>26 (96)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Weakness</td>
<td>12 (48)</td>
<td>7 (26)</td>
<td>.1</td>
</tr>
<tr>
<td>Bowel/bladder dysfunction</td>
<td>6 (24)</td>
<td>6 (22)</td>
<td>.88</td>
</tr>
<tr>
<td>Lhermittes</td>
<td>4 (16)</td>
<td>2 (7)</td>
<td>.41</td>
</tr>
<tr>
<td>Tonic spasms</td>
<td>6 (24)</td>
<td>1 (4)</td>
<td>.046</td>
</tr>
<tr>
<td>Concomitant nausea and vomiting</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td>.23</td>
</tr>
<tr>
<td>Need for gait aid at maximal severity</td>
<td>4 (16)</td>
<td>1 (4)</td>
<td>.18</td>
</tr>
<tr>
<td>Personal Hx of autoimmunitya</td>
<td>10 (40)</td>
<td>2 (7)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Family Hx autoimmunity (1st-degree relative)</td>
<td>9 (36)</td>
<td>5 (19)</td>
<td>.21</td>
</tr>
<tr>
<td>Family Hx MS (1st-degree relative)</td>
<td>0 (0)</td>
<td>3 (11)</td>
<td>.24</td>
</tr>
<tr>
<td>Laboratory abnormalities, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>9 of 20 (45)</td>
<td>4 of 22 (18)</td>
<td>.1</td>
</tr>
<tr>
<td>SSA/double-stranded DNA antibodies</td>
<td>5 of 13 (38)</td>
<td>2 of 13 (15)</td>
<td>.38</td>
</tr>
<tr>
<td>Cerebrospinal fluidd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated white blood cell count (&gt;5/μL)d</td>
<td>7 of 11 (64)</td>
<td>10 of 21 (48)</td>
<td>.47</td>
</tr>
<tr>
<td>Elevated protein (&gt;45 mg/dL)</td>
<td>4 of 9 (44)</td>
<td>11 of 21 (52)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Oligoclonal bands (&gt;3)</td>
<td>1 of 11 (9)</td>
<td>11 of 21 (52)</td>
<td>.02</td>
</tr>
<tr>
<td>Spine MRIe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval Sx onset to MRI, median (range), d</td>
<td>15.5 (2-90)</td>
<td>24 (3-90)</td>
<td>.81</td>
</tr>
<tr>
<td>Single lesion</td>
<td>18 (72)</td>
<td>19 (70)</td>
<td>.9</td>
</tr>
<tr>
<td>T2 length, vertebral segments, median (range)</td>
<td>1 (0.5-2.5)</td>
<td>1 (0.5-2.5)</td>
<td>.09</td>
</tr>
<tr>
<td>Spinal cord swellingi</td>
<td>4 of 15 (27)</td>
<td>15 (56)</td>
<td>.11</td>
</tr>
<tr>
<td>Gadolinium-enhancing lesion (≥1)</td>
<td>14 (56)</td>
<td>20 (74)</td>
<td>.17</td>
</tr>
<tr>
<td>Central location on axial imagesg</td>
<td>16 of 29 (55)</td>
<td>12 of 53 (23)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>T1 hypointense foci</td>
<td>4 of 14 (29)</td>
<td>0 of 24 (0)</td>
<td>.01</td>
</tr>
<tr>
<td>Subsequent myelitis longitudinally extensiveh</td>
<td>12 of 13 (92)</td>
<td>0 of 8 (0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Brain lesions meeting M5 criteriah</td>
<td>4 (16)</td>
<td>13 of 26 (50)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: AQP4-IgG, aquaporin-4–IgG; Hx, history; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; SSA, Sjögren syndrome antigen A; Sx, symptom; TM, transverse myelitis.

a Of those with race/ethnicity details available. Nonwhite races/ethnicities: Asian, 4; Hispanic, 2; African American, 1; and Native American Indian, 1.

b Personal history of autoimmunity (some multiple): thyroid autoimmunity, 4; systemic lupus erythematosus, 2; psoriasis, 2; acetylcholine receptor binding-IgG-positive myasthenia gravis, 1; rheumatoid arthritis, 2; rheumatic fever, 1; Sjögren syndrome, 1; autoimmune thrombocytopenia, 1; and Addison disease, 1.

c Of those with lumbar puncture performed at the time of initial myelitis.

d Lymphocyte predominant in all 4 patients who were AQP4-IgG positive with details available and in all 10 patients who were AQP4-IgG negative.

* In 14 patients, the MRI were not available for a second review. The details were taken from the radiology report or neurologist’s report of the features of the lesion. Locations of lesions in AQP4-IgG positive: cervical, 6 (cervicomedullary junction, 1); thoracic, 17, and both, 2. Locations of lesions in AQP4-IgG negative: cervical spine, 13; thoracic spine, 9; and both, 5.

f Of those with details available.

g Of those with multiple lesions, axial appearance of each was counted separately.

h Longitudinally extensive refers to those with T2 signals extending 3 or more vertebral segments.

i Brain lesions by revised criteria.7
Comparison of Patients With NMOSD With an Initial STM or an Initial LETM

In individuals with details of the severity of their initial myelitis available, patients with STM were less likely to need a gait aid at nadir (4 of 25 [16%]) than those with LETM (71 of 126 [56%]; \( P < .001 \)). The median interval from symptom onset to spine MRI was similar for patients with STM and LETM (15.5 days [range, 2-90 days] vs 14 days [range, 1-90 days]; \( P = .20 \)).
The median delay to diagnosis was greater for patients with initial STM (5 months [range, 0-20 months]) than for patients with initial LETM (0 months [range, 0-21 months]; \(P = .02\)).

Discussion

It is not uncommon for the first myelitis episode of NMOSD to be less than 3 vertebral segments long. Neurologists customarily consider STM incompatible with a diagnosis of NMOSD. In the present study, this misconception delayed the diagnosis and initiation of appropriate treatment, both being critical to minimize recurrent episode-related disability.\(^5,6\) Another practical consideration is that therapies favored for MS may exacerbate NMO.\(^9\) Of 10 patients initially misdiagnosed as having MS, 6 were treated with interferon-β; 1 patient reported increased frequency and severity of episodes and no benefit was seen in the other 5 patients.

Independent from AQP4-IgG seropositivity, several clinical and radiological clues helped identify patients at risk for NMOSD among those with STM. Nonwhite race/ethnicity was a significant predictor of NMOSD risk. Although the Olmsted County population (from which the study control participants were ascertained) has a relatively low proportion of nonwhite individuals (11.1%) by comparison with other regions of the United States, overrepresentation of nonwhite individuals in NMOSD is well-recognized.\(^16\)

Indeed, in a previously described African American patient, an initial STM episode delayed both NMOSD diagnosis and NMO-appropriate treatment.\(^9\) Other clinical predictors of AQP4-IgG seropositivity in patients with STM included older age, personal history of autoimmunity (eg, myasthenia gravis), and tonic spasms (recognized to be more frequent in NMO than MS).\(^17\) Centrally located axial T2-hyperintensities (MS lesions are typically peripheral)\(^7\) and T1-hypointensity were also significant predictors of AQP4-IgG positivity. Patients without typical MS brain lesions and lacking cerebrospinal fluid oligoclonal bands were also significantly more likely to be AQP4-IgG positive. In a previously reported NMOSD study, 4 patients had STM, 3 with central spinal cord MRI lesions. Two had antinuclear antibodies, and head MRI findings in 3 of the 4 patients did not meet McDonald 2010 criteria for MS.\(^13\) Other findings raising the likelihood of NMOSD diagnosis rather than MS in a patient with STM were antecedent severe or bilateral optic neuritis with poor recovery (frequent in our study patients) or an earlier or concomitant episode of protracted nausea or vomiting. We excluded 1 patient with a short lesion extending from the dorsal medulla to the upper cervical cord (Figure 3) because this was predominantly a brainstem lesion. This type of lesion (which may be associated with a short or longitudinally...
extensive cord lesion) is suggestive of NMOSD, although, in our experience, it is not pathognomonic.

By excluding seronegative NMO cases where diagnostic certainty was less than for seropositive cases, we ensured that the 14% frequency of STM at the first myelitis episode of NMOSD was not an overestimate. By restricting the study to the initial myelitis episode, we avoided problems of distinguishing acute nonenhancing lesions from chronic lesions and differentiating acute episodes from pseudo-exacerbations. Also, we excluded patients whose STM occurred after 1 or more LETM episode and patients with initial concurrent long and short lesions or discontinuous but long-appearing lesions (categorized as longitudinally extensive) because they presented less diagnostic dilemma. In 76% of the patients, seropositivity was confirmed by AQP4-transfected cell-based assay (M1 isoform) to minimize the low likelihood of false-positive AQP4-IgG results (more frequent with enzyme-linked immunosorbent assays). Our conclusion that NMOSD was the correct diagnosis in patients with seropositive STM was supported by the fact that in 92% of patients, lesions were longitudinally extensive at subsequent myelitis episodes. Therefore, it was apparent that recurrent myelitis lesions in NMOSD were rarely exclusively short.

The imaged cord lesion in NMOSD may be shorter in patients receiving maintenance immunosuppressant therapy at the time of the episode. In this study, only 12% of patients were receiving immunosuppressant therapies when the STM episode occurred. The timing of MRI in the evolution of NMOSD also may influence the length of the imaged lesion; early imaging may miss a long lesion and late imaging may reveal a discontinuous or short lesion or no lesion. The interval from symptom onset to MRI did not differ significantly for patients with LETM or STM. Imaging was performed within 90 days of symptom onset in all patients and lesional activity was confirmed by gadolinium enhancement in 56% of seropositive STM episodes. In patients with AQP4-IgG–positive NMOSD who were evaluated at the time of STM episode, the severity of myelitis at nadir was milder than those with LETM. These observations further support our contention that short spinal cord lesions in NMOSD in this study did not simply reflect the timing of MRI. Furthermore, encountering a short lesion owing to imperfect MRI timing may have occurred in patients with NMOSD because varied timing is a fact of clinical practice and sequential imaging of a single episode is rarely performed. Therefore, physicians must be mindful that a short spinal cord lesion does not exclude the diagnosis of NMOSD.

Conclusions

Short transverse myelitis is not uncommon in NMOSD and, when it is present, delays diagnosis and treatment. Clinical and radiological characteristics identified in this study may help select patients with STM who are at the highest risk for an NMOSD. Short transverse myelitis does not exclude consideration of AQP4-IgG testing or NMOSD diagnosis.
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ORIGINAL INVESTIGATION


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