Painful Tonic Spasm in Neuromyelitis Optica

Incidence, Diagnostic Utility, and Clinical Characteristics

Sung-Min Kim, MD; Min Jin Go, MS; Jung-Joon Sung, MD, PhD; Kyung Seok Park, MD, PhD; Kwang-Woo Lee, MD, PhD

Objectives: To evaluate the diagnostic utility and clinical characteristics of painful tonic spasm (PTS) in neuromyelitis optica (NMO).

Design: Retrospective study.

Setting: Two referral hospitals.

Patients: Forty patients who had NMO spectrum disorder with anti–aquaporin 4 autoantibody or met the revised diagnostic criteria for definite NMO; 35 patients with multiple sclerosis; and 41 patients with idiopathic acute transverse myelitis without anti–aquaporin 4 antibody.

Main Outcome Measures: The incidence and clinical characteristics of PTS in the different groups, diagnostic value of PTS in identifying patients with NMO, and predictors of PTS in NMO.

Results: The incidence of PTS was significantly higher in the patients with NMO (10 patients [25.0%]) than in those with multiple sclerosis (1 patient [2.9%]) or idiopathic acute transverse myelitis without anti–aquaporin 4 antibody (1 patient [2.4%]). Most PTS episodes (in 8 of 10 patients [80.0%]) in the NMO group occurred after a mean interval of 48.13 days from the onset of the first myelitis episode and were not accompanied by another demyelinating episode with its onset. Painful tonic spasm associated with myelitis had a specificity of 98.7% for identifying the NMO group. Myelitis at disease onset was a predictor of PTS in the NMO group (odds ratio=6.545, presence vs absence).

Conclusions: Painful tonic spasm is a common symptom in NMO. When associated with myelitis, it is relatively specific to patients with NMO and is most commonly observed during recovery from the first myelitis episode. Patients with NMO presenting with myelitis at disease onset appear to be at higher risk for developing PTS compared with other patients with NMO.

comprising patients who met the proposed diagnostic criteria for iATM, the control patients had a negative anti-AQP4 antibody test result. Patients who met the revised diagnostic criteria for definite NMO, had a positive anti-AQP4 autoantibody test result, had bilateral diencephalic lesions, extensive brain lesions, lesion extension from the cervical cord to the brainstem, or cloudlike enhancement on brain magnetic resonance imaging (MRI) or were followed up for less than 6 months were excluded from the control groups.

Painful tonic spasm was defined as a paroxysmal episode of intense pain that accompanied tonic postures of the limbs with or without being precipitated by abrupt movement or sensory stimulation, according to the original description. It was classified as either associated with myelitis or associated with brain lesions depending on the MRI findings, neurological examination findings, and symptoms that preceded or accompanied the PTS episode. We assessed the demographic characteristics, MRI findings, accompanying lesions, duration of the PTS, score on the Kurtzke Expanded Disability Status Scale measured at the disease nadir of the first NMO episode, and the organs involved (spinal cord, optic nerve, or brain). An acute response of PTS was assessed 2 weeks after treatment. Patients were tested for the presence of anti-AQP4 antibodies at the Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, England, using cell-based assays as previously described.

The study was approved by the institutional review boards of Seoul National University Hospital and Seoul National University Bundang Hospital.

Fisher exact test was used to compare the incidence of PTS between groups, and logistic regression analysis was used to identify predictors of developing PTS in NMO. The significance level was set at P < .05. Analyses were performed using SPSS software version 17 (SPSS Inc).

### RESULTS

## PATIENTS

There were 40 patients in the NMO group. Among the control groups, 35 patients were in the MS group and 41 were in the iATM group (Table 1).

### INCIDENCE OF PTS IN THE NMO, MS, AND iATM GROUPS

Ten patients in the NMO group (25.0%) experienced PTS, compared with 1 patient in the MS group (2.9%) and 1 patient in the iATM group (2.4%). The incidence of PTS was significantly higher in the NMO group than in the MS and iATM groups (P = .001) (Figure).

### CLINICAL CHARACTERISTICS OF PTS IN NMO

As shown in Table 2, 9 of the PTS cases in the NMO group were associated with spinal cord lesions; in 1 case (NMO case 2), the exact structure associated with PTS was not identified. In contrast, the case of PTS in the MS group was classified as being associated with a brain lesion based on the observation of a contralateral thalamocapsular lesion on brain MRI, as in previous reports.

Although all of the PTS episodes in NMO showed a paroxysmal episode of intense pain that accompanied tonic postures of the limbs, the detailed manifestations of PTS varied among the patients. One patient (NMO case 4) had PTS that involved only her right hand, repeated every 3 minutes, and lasted for 1 minute. Her thumb was adducted and all fingers were flexed during the episodes. These episodes were preceded by brief paresthesia of the right arm, but no precipitating factors of tactile stimulus or voluntary movements were observed (video, http://www.archneurol.com). In contrast, another patient (NMO case 7) had PTS that involved all of

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Table 1. Demographic Characteristics of Patients in the NMO, MS, and iATM Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NMO (n = 40)</th>
<th>MS (n = 35)</th>
<th>iATM (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, No.</td>
<td>5/35</td>
<td>17/18</td>
<td>35/6</td>
</tr>
<tr>
<td>Age at disease onset, mean (SD), y</td>
<td>44.54 (14.05)</td>
<td>30.96 (9.01)</td>
<td>44.32 (13.18)</td>
</tr>
<tr>
<td>Follow-up duration, mean (SD), mo</td>
<td>71.30 (62.32)</td>
<td>81.26 (61.84)</td>
<td>34.17 (55.17)</td>
</tr>
<tr>
<td>Patients with optic neuritis, No. (%)</td>
<td>25 (62.5)</td>
<td>16 (45.7)</td>
<td>0</td>
</tr>
<tr>
<td>Anti-AQP4 antibody–positive patients, No./patients tested, No. (%)</td>
<td>34/35 (97.1)</td>
<td>0/11</td>
<td>0/41</td>
</tr>
<tr>
<td>Length of spinal cord involvement, mean (SD), No. of segments</td>
<td>6.47 (4.55)</td>
<td>1.70 (2.05)</td>
<td>3.49 (1.93)</td>
</tr>
</tbody>
</table>

Abbreviations: AQP4, aquaporin 4; iATM, idiopathic acute transverse myelitis; MS, multiple sclerosis; NMO, neuromyelitis optica.

The NMO group showed female predominance, high positivity to anti-AQP4 antibody, and long spinal segment involvement.

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Figure. Incidence of painful tonic spasm (PTS) in patients with neuromyelitis optica (NMO), patients with multiple sclerosis (MS), and patients with idiopathic acute transverse myelitis without anti–AQP4 antibody (iATM). The incidence of PTS was significantly higher in the NMO group than in the MS group or in the iATM group (P = .001).
his extremities simultaneously. His PTS was precipitated by an abrupt movement of the arms or legs, lasted several minutes, and occurred up to 6 times a day. During individual PTS episodes, his elbows and knees were involuntarily semiflexed and he could rarely move his extremities voluntarily owing to the increased tonicities of his muscles.

The majority of PTS episodes in the NMO group (8 of 10 cases [80.0%]) occurred during recovery from the first myelitis episode, with a mean interval of 48.13 days between the onset of myelitis and PTS. They were not accompanied by new neurological deficits or new lesions on MRI (Table 2).

In the NMO group, PTS responded well to treatment with phenytoin sodium, carbamazepine, or gabapentin. However, 1 patient (NMO case 2) still had PTS that impaired his daily activity. Another patient (NMO case 8) reported the recurrence of mild PTS after her phenytoin treatment had been changed to gabapentin.

Most patients with NMO and PTS reported the disappearance of symptoms after long-term follow-up. However, 1 patient (NMO case 3) experienced recurrence of PTS with discontinuation of carbamazepine after 7 years of PTS onset, which persisted with decreased frequency for 11.17 years (Table 3).

### DIAGNOSTIC VALUE OF PTS IN IDENTIFYING PATIENTS WITH NMO

Because the incidence of PTS in NMO was high (10 of 40 patients [25.0%]) and most cases were associated with myelitis (Table 2), we evaluated the diagnostic value of PTS associated with myelitis in identifying patients with NMO. Among our 116 study and control patients (with NMO, MS, and iATM), the specificity and sensitivity of PTS associated with myelitis for identifying the NMO group were 98.7% and 22.5%, respectively.

### PREDICTORS OF PTS IN THE NMO GROUP

Myelitis at disease onset was a significant predictor of PTS in the NMO group (odds ratio = 6.545, presence vs absence), with a sensitivity of 80.0% and specificity of 63.3%. Age at disease onset, sex, mean annual relapse rate, optic neuritis at disease onset, Expanded Disability Status Scale at nadir, and spinal segments involved were not significant predictors.

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**Table 2. Summary of the Clinical and Radiological Characteristics of Patients With PTS in the NMO, MS, and iATM Groups**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis</th>
<th>Age at Onset, y</th>
<th>Distribution of PTS</th>
<th>Simultaneous Symptoms or Signs With Onset of PTS</th>
<th>Myelitis Episodes Before PTS, No.</th>
<th>Interval to PTS Onset, d</th>
<th>First Myelitis Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMO 1</td>
<td>NMO, definite</td>
<td>34.2</td>
<td>Both legs</td>
<td>No</td>
<td>1</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>NMO 2</td>
<td>NMO, definite</td>
<td>42.8</td>
<td>Both legs</td>
<td>No</td>
<td>4</td>
<td>4490</td>
<td>NA</td>
</tr>
<tr>
<td>NMO 3</td>
<td>NMO, definite</td>
<td>59.6</td>
<td>Right arm</td>
<td>Arm paresthesia</td>
<td>1</td>
<td>1963</td>
<td>5.5</td>
</tr>
<tr>
<td>NMO 4</td>
<td>NMO, definite</td>
<td>50.0</td>
<td>Right arm</td>
<td>No</td>
<td>1</td>
<td>42</td>
<td>7.5</td>
</tr>
<tr>
<td>NMO 5</td>
<td>NMO, definite</td>
<td>32.2</td>
<td>All extremities</td>
<td>No</td>
<td>1</td>
<td>128</td>
<td>6.5</td>
</tr>
<tr>
<td>NMO 6</td>
<td>NMO, definite</td>
<td>66.5</td>
<td>Both arms</td>
<td>No</td>
<td>1</td>
<td>48</td>
<td>7.0</td>
</tr>
<tr>
<td>NMO 7</td>
<td>NMO, definite</td>
<td>72.8</td>
<td>All extremities</td>
<td>No</td>
<td>1</td>
<td>48</td>
<td>7.0</td>
</tr>
<tr>
<td>NMO 8</td>
<td>NMO, definite</td>
<td>51.0</td>
<td>Left hand</td>
<td>No</td>
<td>1</td>
<td>162</td>
<td>9.5</td>
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<tr>
<td>NMO 9</td>
<td>NMO, definite</td>
<td>53.4</td>
<td>Both legs</td>
<td>No</td>
<td>1</td>
<td>16</td>
<td>2.5</td>
</tr>
<tr>
<td>NMO 10</td>
<td>NMO, definite</td>
<td>50.5</td>
<td>Left leg</td>
<td>No</td>
<td>1</td>
<td>299</td>
<td>3.0</td>
</tr>
<tr>
<td>MS 11</td>
<td>MS</td>
<td>43.4</td>
<td>Right arm and leg</td>
<td>Paroxysmal dystarhia</td>
<td>0</td>
<td>197</td>
<td>1.5</td>
</tr>
<tr>
<td>iATM 12</td>
<td>iATM</td>
<td>54.4</td>
<td>Both hands</td>
<td>No</td>
<td>0</td>
<td>Simultaneous</td>
<td>1.5</td>
</tr>
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**Abbreviations:** Ab, antibody; AQP4, aquaporin 4; C, cervical; EDSS, Expanded Disability Status Scale; iATM, idiopathic acute transverse myelitis; IC, internal capsule; Jxn, cervicomedullary junction; MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not assessed; NMO, neuromyelitis optica; NMOSD, NMO spectrum disorder; PTS, painful tonic spasm; T, thoracic; +, positive.

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<td>Right arm</td>
<td>No</td>
<td>1</td>
<td>1963</td>
<td>C3, C4</td>
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<tr>
<td>NMO 5</td>
<td>NMO, definite</td>
<td>32.2</td>
<td>All extremities</td>
<td>No</td>
<td>1</td>
<td>42</td>
<td>C2-T11</td>
</tr>
<tr>
<td>NMO 6</td>
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<td>66.5</td>
<td>Both arms</td>
<td>No</td>
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<td>C1-C6</td>
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<tr>
<td>NMO 7</td>
<td>NMO, definite</td>
<td>72.8</td>
<td>All extremities</td>
<td>No</td>
<td>1</td>
<td>48</td>
<td>C2-C7, T2, T4</td>
</tr>
<tr>
<td>NMO 8</td>
<td>NMO, definite</td>
<td>51.0</td>
<td>Left hand</td>
<td>No</td>
<td>1</td>
<td>162</td>
<td>Jxn-C7</td>
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<td>197</td>
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<td>iATM 12</td>
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Scale score at disease onset, length of the spinal cord lesion, and presence of lesions on brain MRI were not significantly associated with PTS (Table 4).

In this study, PTS occurred in 10 of 40 patients in the NMO group (25.0%), in contrast to fewer than 5% of the patients in the MS group (1 of 35 patients [2.9%]) or iATM group (1 of 41 patients [2.4%]). Most PTS symptoms in the NMO group (in 8 of 10 patients [80.0%]) followed the first myelitis episode, with a mean interval of 48.13 days, and were not accompanied by another demyelinating attack with onset of PTS. Painful tonic spasm associated with myelitis was another specific symptom for patients with NMO. Myelitis at disease onset was a significant predictor (odds ratio = 6.545, presence vs absence) of PTS in the NMO group.

The incidence of PTS was significantly higher in the NMO group than in the MS or iATM groups in this study. In general, typical features of NMO, compared with MS or iATM, include a severe acute attack, a high mean annual relapse rate, and longitudinally extensive myelitis. However, because these phenotypical characteristics were not associated with the presence of PTS in the NMO group (Table 4), we speculate that the distinct pathophysiology of the spinal cord lesions of NMO, ie, severe demyelination, the early loss of AQP4 expression, and astrocyte damage, is responsible for PTS. Further studies are needed to determine the exact cause.

Despite earlier studies of MS in the Western population reporting a low incidence of PTS (<2.1%), studies performed in the Japanese population reported an incidence as high as 17.2%. However, most Japanese patients with MS and PTS had severe opticospinal involvement, which may reflect a manifestation of...
NMO,9,10,26 These results also support our findings in that PTS is common in NMO but not in MS.

Painful tonic spasm–associated myelitis was another specific symptom in the NMO group in this study (specificity, 98.7%). Therefore, patients with these symptoms can benefit from anti-AQP4 antibody tests for their exact diagnosis.10

In our NMO group, most PTS occurred during recovery from a first myelitis episode. This finding suggests that the partial remyelination of the spinal cord may play a more important role in the development of PTS in patients with NMO than the demyelination itself.

The presence of myelitis at disease onset was significantly associated with the development of PTS in the NMO group (odds ratio = 6.545). A previous study proposed that the ephaptic transmission of centripetal signals to corticospinal fibers could be the cause of PTS.20 We hypothesized that the early disruption of the centripetal fibers in the spinal cord when the corticospinal fibers were relatively intact or showed less damage may contribute to the risk of PTS development in patients with NMO, as previously reported in patients with MS.4

In contrast to other PTS cases that displayed a favorable treatment response with carbamazepine or phenytoin, a patient treated with gabapentin (NMO case 2) showed an insufficient response to treatment, while another patient (NMO case 8) experienced the recurrence of PTS after switching her medication from phenytoin to gabapentin (Table 3). These findings imply that phenytoin or carbamazepine may possess a higher efficiency than gabapentin in PTS treatment; however, additional studies investigating a larger number of cases will be necessary for exact evaluation.

Despite the majority of patients with PTS reporting a disappearance of symptoms with long-term follow-up, PTS reappeared in 1 patient (NMO case 3) following medication withdrawal and persisted after 11.17 years of follow-up (Table 3). This implies that some patients with NMO who have PTS require long-term treatment.

One patient in the MS group (MS case 11) showed PTS (Table 2). Although this patient had PTS, which is a common symptom of NMO,3 she had no spinal cord lesion and had negative results on anti-AQP4 autoantibody testing with a cell-based assay. Therefore, it seems unlikely that this patient had NMO.

Our study has several limitations. First, it was a retrospective study, although the incidences of PTS in our NMO and MS groups were similar to those reported previously.20,22 Second, the follow-up period of the iATM group was shorter than that of the NMO group. However, given that 90.0% of the PTS episodes occurred within 80 days from the first myelitis episode and that the mean and minimum follow-up periods of the iATM group were 34.24 and 6 months, respectively, we believe that this limitation did not significantly affect our finding that the incidence of PTS was higher in the NMO group than in the iATM group. Third, although we showed the clinical characteristics and importance of PTS in patients with NMO, we could not clearly define the underlying pathophysiological mechanism. Additionally, we could not explain the cause of the high incidence of PTS in NMO or the cause of myelitis at disease onset as a risk factor because the study was designed as a retrospective observational study. Finally, only 1 patient in the NMO group (NMO case 2) developed PTS 4490 days after both disease onset and the initial myelitis episode. This differed from other NMO cases. Diverse medical conditions such as metabolic abnormalities and ischemic lesions of the putamen or pons,27,28 which may be related to PTS, should have been excluded in this patient.

In summary, PTS was common in patients with NMO but not in patients with MS or iATM. The PTS associated with myelitis was specific and relatively common to NMO. Our finding may have importance for identifying patients with NMO with limited manifestations who do not meet the diagnostic criteria of definite NMO.8,9 In addition, the majority of PTS in NMO is not associated with a new demyelinating NMO episode but appears during recovery from the initial myelitis episode. Patients with NMO who present with myelitis at disease onset appear to be at higher risk for developing PTS compared with other patients with NMO who present with optic neuritis or brain lesions.

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Author Contributions: Drs Sung and Park contributed equally to this article. Study concept and design: Kim and Park. Acquisition of data: Kim, Sung, Park, and Lee. Analysis and interpretation of data: Kim and Go. Drafting of the manuscript: Kim and Lee. Critical revision of the manuscript for important intellectual content: Kim, Go, Sung, and Park. Statistical analysis: Kim and Go. Obtained funding: Kim and Park. Administrative, technical, and material support: Kim, Sung, and Park. Study supervision: Park.

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REFERENCES


