Original Article

The Prevalence and Predictive Factors of Painful Tonic Spasm in Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)

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Background: Painful tonic spasm (PTS) is a complication frequently observed in patients with neuromyelitis optica spectrum disorder (NMOSD).

Objective: To identify the prevalence of PTS, compare the factors associated with the occurrence of PTS, define the characteristics of PTS, and correlate the medication and prognostic factors with good recovery from PTS in patients with NMOSD.

Materials and Methods: A retrospective study was performed in patients with definite NMOSD in the Prasat Neurological Institute between January 1, 2014 and December 31, 2018. The prevalence and characteristics of PTS were explored. The characteristics and factors associated with the occurrence of PTS were investigated. Moreover, the factors associated with PTS recovery and pain medications were further analyzed in the present study.

Results: The prevalence of PTS in patients with NMOSD was 37.81%. The factors associated with the occurrence of PTS were the presence of acute myelitis (p=0.002, OR 39.00, 95% CI 3.89 to 391.23), and tobacco use (p=0.048, OR 13.38, 95% CI 1.02 to 175.52). In the subgroup analyses of the factors associated with PTS recovery, plasma exchange (p=0.007, OR 24.70, 95% CI 2.43 to 251.57), and Expanded Disability Status Scale range 1.0 to 4.5 (p=0.008, OR 6.92, 95% CI 1.67 to 28.65) were related to the recovery from PTS. While non-recovery was correlated with older age at last visit (p=0.013, OR 1.09, 95% CI 1.02 to 1.17) and longer segments of cord lesions (p=0.016, OR 1.21, 95% CI 1.04 to 1.42).

Conclusion: The present study supports that PTS is one of the common complications in patients with NMOSD in Thailand. The presence of acute myelitis and the tobacco use are associated with the presence of PTS. Plasma exchange treatment in the acute phase of NMOSD may be associated with good recovery from PTS, and longer segments of spinal cord lesions is correlated with poor recovery outcomes. The control of these factors may prevent the occurrence of PTS or at least facilitate the recovery from PTS in these patients.

Keywords: Neuromyelitis optica spectrum disorder (NMOSD), Painful tonic spasm (PTS)

Received 22 June 2020 | Revised 31 August 2020 | Accepted 2 September 2020

J Med Assoc Thai 2020;103(12):1354-61
Website: http://www.jmatonline.com

Neuromyelitis optica spectrum disorder (NMOSD) is a devastating central nervous system demyelinating disease. The pathological process is caused by a serum antibody that targets the water channel aquaporin-4 (AQP4), which is highly specific and relevant for clinical diagnosis[1,2]. In addition to the clinical attack, pain is one of the highly encountered disabilities in NMOSD patients. The two most common types of pain characteristics are painful tonic spasm (PTS) and ongoing neuropathic pain[3]. There have been many case reports and case series about PTS in NMOSD patients[4-8]. The incidence of PTS varies between 14% and 26%, and the mean onset occurs 30 to 48 days after the last myelitis. The predictive factors associated with PTS in NMOSD include myelitis at onset[6], higher age at onset, annualized relapse rate (ARR) of the disease, ARR of myelitis, and pruritus symptom[7]. PTS is one of the difficult-to-treat complications of NMOSD

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How to cite this article:

Khieukhajee J, Apiwattanakul M, Aungsumart S. The Prevalence and Predictive Factors of Painful Tonic Spasm in Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD). J Med Assoc Thai 2020; 103:1354-61.

doi.org/10.35755/jmedassocthai.2020.12.11578

because it is under-recognized. There have been only a few reports of responsive medication, such as carbamazepine and oxcarbazepine.

There is still a lack of data for the long-term treatment of PTS in NMOSD patients. The objective of the present study was to obtain information about the prevalence and factors associated with PTS occurrence in NMOSD patients. Moreover, the long-term treatment responsiveness of PTS was investigated in the present study.

Materials and Methods

Patients and study design

The present study was a cross-sectional study that retrospectively reviewed the medical records between January 1, 2014 and December 31, 2018, in the Prasat Neurological Institute, a tertiary referral neurological center in Bangkok, Thailand. The outpatients and inpatients who fulfilled the diagnostic criteria of NMOSD according to the International Panel for NMO Diagnosis (IPND) 2015 and had follow-up visits for at least six months were enrolled in the study. The exclusion criteria were patients with incomplete medical records and patients who had difficulties with the assessment. PTS was defined as a paroxysmal episode of increased muscle tone, abnormal posture, and intense pain in one or more limbs that is or is not triggered by movement or sensory stimulation[7]. The present study was approved by the Institutional Review Board of the Prasat Neurological Institute (approval number 62045). Written informed consents were obtained from all the enrolled patients.

The following patient information were recorded, demographic data including gender, age at the last visit, underlying diseases, any personal history of tobacco and alcohol use (whether in the past or the present), age at onset, disease duration, ARR, ARR of myelitis, presence of AQP4-immunoglobulin G antibody (IgG) biomarkers in the serum by cell-based assay, six core clinical presentations of the disease, cerebrospinal fluids (CSFs), magnetic resonance imaging (MRI) spinal cord lesion data at 3.0 T field strength, the presence of longitudinally extensive transverse myelitis (LETM) lesions defined by the involvement of at least three vertebral segments of the spinal cord lesion, pruritus, acute treatment by intravenous methylprednisolone (IVMP) and plasma exchange (PLEX) before the occurrence of PTS, maintenance treatment, and assessment of the functional ability of NMOSD patients defined by the ordinals of Kurtzke's Expanded Disability Status Scale (EDSS) after six months of treatment. There was no data regarding the myelin oligodendrocyte glycoprotein (MOG)-IgG due to the test was not available during the study period.

The estimated prevalence and clinical characteristics of PTS in NMOSD were determined. Moreover, the prognostic factors associated with PTS were evaluated. The clinical outcome in terms of 'recovery' was defined as at least 50% estimated reduction in pain evaluated at six months to ensure adequate time of medical adjustment. The treatment outcomes were categorized into recovery without medication, recovery with ongoing medication, or non-recovery (defined as persistent pain despite ongoing medication). The factors associated with recovery were evaluated in the present study.

Statistical analysis

The frequency data were reported as number with percentage, and the continuous data were expressed as the mean ± standard deviation. In continuous data with extreme outliers, the median and interquartile range (IQR) would be used instead of mean. The patients were dichotomized into two groups based on the presence or absence of PTS, and the presence of PTS group was further categorized into recovery or non-recovery groups. The associated factors were compared between these groups in the univariate analysis. The categorical variables were analyzed with a chi-square test. The continuous variables with normal distribution were analyzed using an independent two-sample Student's t-test and data that were not normally distributed were analyzed with a Mann-Whitney U test. The variables that were significant in the univariate comparisons at p-value less than 0.1 were included in a logistic regression model to assess the adjusted association of the variables that seemed predictive in multivariate analysis. The cut-off for statistical significance was p-value less than 0.05.

Results

Patient data, clinical course, investigation, and treatment

Four hundred sixty patients were recorded in the outpatient and inpatient NMOSD ICD-10 database of Prasat Neurological Institute between January 1, 2014 and December 31, 2018. Fifty-eight patients had a follow-up period less than six months, and 42 patients did not fulfill the diagnostic criteria of NMOSD. Moreover, 55 patients had other diagnoses in addition to NMOSD at the final visit. One hundred four patients with incomplete medical records were

excluded from the study. Therefore, 201 patients were included in the final analysis. The baseline clinical characteristics are presented in Table 1. Females were predominant (91%) with an average age of 47.15±13.20 years. The predominant clinical presentation was myelitis (82.1%) followed by optic neuritis (53.2%). Most of the patients had the characteristic of LETM on the spinal MRI (88.1%). AQP4-IgG was detected in 88.1% of patients, and the disease duration was 95.72±80.39 months. The ARR was 0.56±0.56, and the ARR of myelitis alone was 0.35±0.42. The symptoms of pruritus, which have previously been associated with PTS, were present in only 6% of the patients. Acute treatment included intravenous pulse methylprednisolone (79.1%) and plasmapheresis (24.4%). Most of the patients received preventive medication with concurrent steroid.

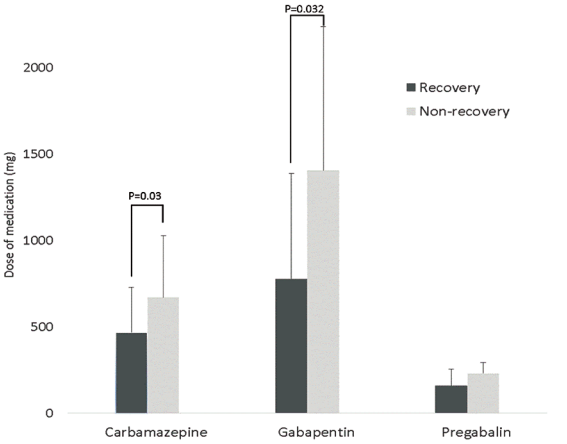

Figure 1. Comparison of 3 major drugs and doses used in PTS treatment between the recovery and non-recovery groups.

Prevalence and factors associated with occurrence of PTS

Of the 201 patients with NMOSD, PTS developed in 76 patients (37.81%). Of the patients with myelitis alone, 75 patients (45.45%) developed PTS from 165 myelitis attack NMOSD. Among these patients, there was only one patient with cerebral and brainstem lesions without myelitis lesion that also suffered from PTS. In 177 AQP4-IgG positive patients, there were 69 patients with PTS (38.98%). In 24 patients with AQP4-IgG negative or unknown status, seven patients had PTS (29.17%).

The univariate analyses results, in terms of the factors associated with the occurrence of PTS, are shown in Table 1. The following parameters were associated with the occurrence of PTS: older age at last visit (p=0.013), diabetes mellitus type 2 (p=0.023), dyslipidemia (p=0.04), coexisting autoimmune diseases (p=0.049), acute myelitis (p<0.001), ARR of myelitis (p=0.002), and cervical cord lesions in spinal cord MRI (p=0.034). The patients with mild disability, indicated by EDSS levels of 1.0 to 4.5, were associated with low occurrence of PTS compared to patients with moderate to severe disability (EDSS ≥5.0, p=0.002). Other potential factors associated with the occurrence of PTS, including tobacco use (p=0.052) and age at onset (p=0.052), were considered in the multivariate analyses. Other factors, such as gender, disease duration, CSF profile, acute treatment, and maintenance therapy, were not associated with the occurrence of PTS.

In the multivariate analyses, the presence of acute myelitis (OR 39.00, 95% CI 3.89 to 391.23, p=0.002) and the tobacco use (OR 13.38, 95% CI 1.02 to 175.52, p=0.048) exhibited a correlation with PTS. However, diabetes mellitus, dyslipidemia, autoimmune disease, ARR of myelitis, cervical cord lesion in spinal cord MRI, and age at onset were not correlated with PTS.

Characteristics of PTS in patients with NMOSD

The characteristics of PTS in 76 NMOSD patients are presented in Table 2. The most common involvements were both legs follow by ipsilateral arm and leg. PTS occurred after a median interval of four months (IQR 37 months) from the onset of the disease (all clinical presentations) and 61 days (IQR 69 days) from the onset of the associated myelitis episode. The authors also found that six patients had PTS that occurred simultaneously with the onset of myelitis. An abrupt movement was the most common precipitating event for PTS. Gabapentin, carbamazepine, and baclofen were the most frequently used medications for PTS. The treatment response, defined by the reduction of the estimated pain score by more than 50%, was considered as recovery and non-recovery. Eighteen patients (23.68%) were in the recovery group without pain medication, and 35 patients (46.05%) were in the recovery group with ongoing medication. However, twenty-three patients (30.26%) were considered to be in the non-recovery group due to persistent pain despite using multiple drugs. Regarding to pain medication in PTS, patients with non-recovered PTS used higher doses of carbamazepine (671.43±356.11 mg/day, p=0.032) and gabapentin (1,405.26±832.32 mg/day, p=0.002) compared to recovered patients (Figure 1). Moreover,

Table 1. Comparison of associated factors and occurrence of PTS

Associated factors	Total (n=201) n (%)	NMOSD; n (%)		p-value
		with PTS (n=76)	Without PTS (n=125)	
Sex				
Male	18 (9.0)	9 (11.8)	9 (7.2)	0.264
Female	183 (91.0)	67 (88.2)	116 (92.8)	
Age (years); mean±SD$	47.15±13.20	50.09±12.61	45.36±13.28	0.013*
Underlying disease				
Hypertension	43 (21.4)	19 (25.0)	24 (19.2)	0.331
Diabetes mellitus type 2	28 (13.9)	16 (21.1)	12 (9.6)	0.023*
Dyslipidemia	50 (24.9)	25 (32.9)	25 (20.0)	0.040*
Autoimmune disease	5 (2.5)	4 (5.3)	1 (0.8)	0.049*
Personal history				
Tobacco use	7 (4.0)	5 (7.7)	2 (1.8)	0.052
Alcohol use	1 (0.6)	1 (1.5)	0 (0.0)	0.190
NMO-IgG/AQP4-IgG positive	177 (88.1)	69 (90.8)	108 (86.4)	0.352
Clinical presentation				
Optic neuritis	107 (53.2)	38 (50.0)	69 (55.2)	0.474
Acute myelitis	165 (82.1)	75 (98.7)	90 (72.0)	<0.001*
Area postrema syndrome	60 (29.9)	19 (25.0)	41 (32.8)	0.241
Acute brainstem syndrome	49 (24.4)	16 (21.1)	33 (26.4)	0.392
Acute diencephalic syndrome	7 (3.5)	2 (2.6)	5 (4.0)	0.608
Symptomatic cerebral syndrome	7 (3.5)	3 (3.9)	4 (3.2)	0.779
Clinical course and progression				
Age at onset (years); mean±SD$	39.30±13.93	41.77±13.84	37.82±13.84	0.052
Disease duration (months); mean±SD$	95.72±80.39	101.86±80.35	91.98±80.51	0.400
Annualized relapse rate; median (IQR)#	0.40 (0.40)	0.42 (0.41)	0.40 (0.40)	0.988
Annualized relapse rate of myelitis; median (IQR)#	0.25 (0.37)	0.29 (0.30)	0.20 (0.43)	0.002*
CSF profile; median (IQR)#				
WBC (cells/cumm)	4 (15)	8 (17)	3 (14)	0.234
Protein (mg/dL)	42 (27.5)	44 (32)	41 (25)	0.293
Glucose (mg/dL)	61 (14.5)	61 (14)	61 (17)	0.444
Lesion site of myelitis				
Cervico-medullary	36 (22.0)	20 (27.4)	16 (17.6)	0.131
Cervical cord	119 (72.6)	59 (80.8)	60 (65.9)	0.034*
Thoracic cord	107 (65.2)	47 (64.4)	60 (65.9)	0.836
Lumbar cord	7 (4.3)	2 (2.7)	5 (5.5)	0.386
Presence of LETM	140 (88.1)	65 (89.0)	75 (87.2)	0.723
Segments of cord lesion (segments); mean±SD$	7.39±4.24	7.17±4.50	7.59±4.02	0.546
Pruritus	12 (6.0)	6 (7.9)	6 (4.8)	0.377
IVMP	159 (79.1)	57 (75.0)	102 (81.6)	0.264
Time from onset (days); median (IQR)#	14 (22)	12 (19)	14 (24)	0.562
PLEX	49 (24.4)	16 (21.1)	33 (26.4)	0.392
Time from onset (days); median (IQR)#	20 (20.75)	24 (20)	19 (21)	0.210
Maintenance treatment				
Prednisolone	198 (98.5)	76 (100)	122 (97.6)	0.174
Azathioprine	159 (79.1)	59 (77.6)	100 (80.0)	0.689
Mycophenolate mofetil	33 (16.4)	14 (18.4)	19 (15.2)	0.550
Other	3 (1.5)	1 (1.3)	2 (1.6)	
EDSS after 6 months treatment				
1.0 to 4.5	125 (62.5)	37 (48.7)	88 (71.0)	0.002*
5.0 to 5.5	23 (11.5)	13 (17.1)	10 (8.1)	0.067
6.0 to 6.5	30 (15.0)	14 (18.4)	16 (12.9)	0.354
7.0 to 9.5	22 (11.0)	12 (15.8)	10 (8.1)	0.113

NMOSD=neuromyelitis optica spectrum disorder; NMO=neuromyelitis optica; AQP4=aquaporin-4; IgG=immunoglobulin G; CSF=cerebrospinal fluid; WBC=white blood cell; LETM=longitudinally extensive transverse myelitis; IVMP=intravenous methylprednisolone; PLEX=plasma exchange; EDSS=expanded disability status scale; SD=standard deviation; IQR=interquartile range

* Indicates significant difference at p<0.05, $ Continuous data with normal distribution, # Continuous data with non-normal distribution

Table 2. Characteristics of PTS in patients with NMOSD

Characteristics	Total (n=76) n (%)
Distribution of PTS	
Single arm	8 (10.53)
Single leg	7 (9.21)
Both arms	3 (3.94)
Both legs	34 (44.74)
Ipsilateral arm and leg	13 (17.11)
Three extremities	5 (6.58)
All extremities	5 (6.58)
Head and neck*	4 (5.26)
Duration after disease onset (months); median (IQR)#	4 (37)
Duration after myelitis onset (days); median (IQR)#	61 (69)
Precipitating factor	
Abrupt movement	26 (34.21)
Stress	0 (0.00)
Sensory stimulus	17 (22.37)
No precipitating factor	39 (51.32)
Medical treatment for PTS	
Carbamazepine	51 (67.10)
Phenytoin	2 (2.60)
Gabapentin	59 (77.60)
Pregabalin	8 (10.50)
Benzodiazepine	13 (17.10)
Baclofen	44 (57.90)
Amitriptyline/nortriptyline	23 (30.30)
Tramadol	2 (2.60)
Others$	9 (11.80)
Treatment response (≥6 months)	
Recovery without medication	18 (23.68)
Recovery with ongoing medication	35 (46.05)
Nonrecovery with persistent pain	23 (30.26)

PTS=painful tonic spasm; IQR=interquartile range

* 1 patient had only neck involvement, and 3 other patients had neck and limb involvement; # Used median (IQR) instead of mean due to extreme outlier; $ Other medication included 4 tizanidine, 1 valproate, 1 topiramate, 1 paracetamol-orphenadrine, 1 pizotifen, and 1 oxcarbazepine

the rates of the use of amitriptyline or nortriptyline (p=0.028) and tramadol (p=0.030) were higher in the non-recovery group (Table 3).

Factors associated with PTS recovery

To explore the factors associated with PTS recovery, the authors divided the PTS patients into two groups, recovery (53/76) and non-recovery (23/76), as shown in Table 3. In the univariate analyses, the potential clinical factors associated with recovery included acute treatment with PLEX (p=0.082) and minimal disability as indicated by EDSS levels of 1.0 to 4.5 after six months of attacks (p=0.002). Older age (p=0.064), relapse rate of myelitis (p=0.015), presence of LETM (p=0.042) and longer segments of spinal cord lesions (p=0.014) were associated with non-recovery. In the multivariate analysis, good recovery from PTS was correlated with acute treatment with PLEX (OR 24.70, 95% CI 2.43 to 251.57, p=0.007) and EDSS range 1.0 to 4.5 after six months of attacks (OR 6.92, 95% CI 1.67 to 28.65, p=0.008). Moreover, non-recovery was correlated with older age at the last visit (OR 1.09, 95% CI 1.02 to 1.17, p=0.013) and longer segments of cord lesions (OR 1.21, 95% CI 1.04 to 1.42, p=0.016).

Discussion

In the present study, the prevalence of PTS in patients with NMOSD was 37.81%. The factors associated with the occurrence of PTS were the presence of acute myelitis and tobacco use. The factors associated with recovery from PTS were acute treatment with PLEX and minimal disability as indicated by EDSS levels of 1.0 to 4.5 after six months of attacks. Older age at the last visit and longer segments of spinal cord lesions were correlated with non-recovery from PTS.

The prevalence of PTS in the present study was 37.81%, which was higher than the results in previous reports that varied from 14% to 26%[4-8]. This finding can be explained by the referral bias of more severe cases to the authors' tertiary neurological center. Moreover, PTS may be more common than already known but not well recognized by many physicians. Some patients visited the authors' center one or two months after treatment with high dose steroids for acute myelitis attack. Although these patients started to recover from the acute attack, PTS still develops without appropriate management. This phenomenon reflects the knowledge gap of NMOSD management in Thailand.

There have been only a few studies that compare the clinical factors associated with PTS and the occurrence of PTS in patients with NMOSD. The multivariate analysis after adjustment for the covariate indicated that the presence of acute myelitis and the tobacco use were correlated with the occurrence of PTS. It has been previously reported that the presence of myelitis is associated with PTS. The association of myelitis with PTS may be due to early disruption of

Table 3. Factors associated with recovery from PTS in NMOSD

Associated factors	Recovery (n=53) n (%)	Non-recovery (n=23) n (%)	p-value
Sex: male/female	5 (9.4)/48 (90.6)	4 (17.4)/19 (82.6)	0.324
Age (years); mean±SD$	48.55±13.56	53.65±9.40	0.064
Personal history			
Tobacco use	3/49 (6.1)	2/16 (12.5)	0.406
Alcohol use	1/49 (2.0)	0/16 (0.0)	0.565
NMO-IgG/AQP4-IgG positive	49 (92.5)	20 (87.0)	0.447
Clinical course and progression			
Age at onset (years); mean±SD$	40.83±14.62	44.05±11.72	0.363
Disease duration (months); mean±SD$	94.64±60.40	118.48±113.89	0.352
Annualized relapse rate; median (IQR)#	0.42 (0.35)	0.40 (0.75)	0.559
Annualized relapse rate of myelitis; median (IQR)#	0.25 (0.23)	0.33 (0.80)	0.105
Presence of LETM	42/50 (84.0)	23/23 (100.0)	0.042*
Segments of cord lesion (segments); mean±SD$	6.27±4.06	9.04±4.88	0.014*
IVMP	39 (73.6)	18 (78.3)	0.665
Time from onset (days); median (IQR)#	14 (23)	10.5 (14)	0.174
PLEX	14 (26.4)	2 (8.7)	0.082
Time from onset (days) median (IQR)#	23 (28)	25.5	0.865
Maintenance treatment			
Prednisolone	53 (100)	23 (100)	-
Azathioprine	42 (79.2)	17 (73.9)	0.608
Mycophenolate mofetil	11 (20.8)	3 (13.0)	0.426
EDSS after 6 months of treatment			
1.0 to 4.5	32 (60.4)	5 (21.7)	0.002*
5.0 to 9.5	21 (39.6)	18 (78.3)	
Medical treatment for PTS			
Carbamazepine	37 (69.8)	14 (60.9)	0.446
Phenytoin	1 (1.9)	1 (4.3)	0.538
Gabapentin	40 (75.5)	19 (82.6)	0.493
Pregabalin	4 (7.5)	4 (17.4)	0.199
Benzodiazepine	8 (15.1)	5 (21.7)	0.480
Baclofen	28 (52.8)	16 (69.6)	0.175
Amitriptyline/nortriptyline	12 (22.6)	11 (47.8)	0.028*
Tramadol	0 (0.0)	2 (8.7)	0.030*

NMO=neuromyelitis optica; AQP4=aquaporin-4; IgG=immunoglobulin G; LETM=longitudinally extensive transverse myelitis; IVMP=intravenous methylprednisolone; PLEX=plasma exchange; EDSS=expanded disability status scale; PTS=painful tonic spasm; SD=standard deviation; IQR=interquartile range

* Indicates significant difference at p<0.05, $ Continuous data with normal distribution, # Continuous data with non-normal distribution

the afferent fibers in the spinal cord with relatively intact corticospinal fibers, which may contribute to the ephaptic transmission and lead to PTS development in patients with NMOSD[6]. The present study also found one PTS patient who had brainstem lesions without spinal cord lesions. The authors proposed that PTS may correlate with demyelinating lesions in the regions that have proximity between noxious sensory fibers and corticospinal tracts which explains the highest risk of PTS from lower brainstem and spinal cord lesions. Moreover, the present study was the first report to describe the relationship between

tobacco use and PTS. Previous reports have suggested that more severe inflammation in NMOSD results in higher prevalence of PTS compared to MS and cerebral infarction. Smoking is considered one of the aggravating factors in many autoimmune diseases, including MS, due to the increased systemic inflammation[9]. Therefore, the authors hypothesized that tobacco use may worsen the inflammatory lesions in NMOSD, cause more disruption of nerve fibers, and create more painful spasms. However, due to the small number of smokers in the present study data, further studies with higher smoker population should be considered to confirm this finding in the future.

The characteristics of PTS in the present study were the same as those in previous studies[4-8]. The most common presentation was tonic spasm in both legs, which is related to the transverse involvement of myelitis. The median onset of PTS after the myelitis episode in the present study was slightly longer than the previous report, while six patients already experienced PTS as the first presentation of relapse. This finding suggested that many patients may have only subtle symptoms at onset and that later spasms are the most disabling presentation of the disease. Moreover, this finding also suggested that the pathogenesis of PTS could be faster or slower than expected. Gabapentin and carbamazepine were still the most frequently used pain medications in this situation, but the prevalence of patients with persistent pain was high, with 30.26% patients in the non-recovery group. Although an increase dosage of medication was considered in unresponsive patients, the mean doses of gabapentin and carbamazepine were significantly higher in non-recovered patients who still experienced disabling pain. In addition, amitriptyline, nortriptyline, and tramadol were more often used without benefit. Thus, the authors hypothesize that titration of medication would be futile in some patients and that there should be a cut-off point in drug responsiveness.

In the multivariate subgroup analysis comparing associated factors and recovery of PTS, PLEX was related to good recovery outcome. PLEX is one of the most effective methods in the acute treatment of numerous autoimmune diseases. Early PLEX has been shown to be related to better clinical outcome due to rapid antibody clearance[10,11]. The present study showed, for the first time, the benefit of early PLEX in pain reduction. In addition, longer segments of spinal cord lesions were correlated with the PTS non-recovery group. The authors hypothesized that longer segment of spinal cord lesion associates with higher chance of ephaptic transmission, leading to poor response to medication. Older age at the last visit also slightly associated with non-recovery of PTS, which may reflect the effect of age at last presentation in the context of disease duration and follow-up time. EDSS range 1.0 to 4.5 after six months of treatment may represent good prognosis of PTS recovery. However, the authors cannot clearly assume whether low EDSS was a protective factor or the absence of PTS caused more favorable functional outcome in patients with NMOSD. Careful interpretation of age and EDSS factors should be considered and need further research.

The present study also had some limitations. First, this was a retrospective study, resulting in potential recall biases in several factors and outcome measurement. The nature of the cross-sectional study limited the exploration of the temporal relationship between the associated factors and PTS, which were unable to define the cause-effect data. Second, there was no universal clear-cut definition of PTS, resulting in potential interrater variability of PTS reports in medical records. Third, the severity of pain and spasms was not quantified by a numeric rating scale. The authors only defined 'recovery' by estimated reduction in pain score of approximately 50%, which may not be precise. Consequently, the treatment responsiveness, which depended on pain recovery, was also affected by this problem. Fourth, the information about the pathophysiology of PTS was lacking, requiring the dependence on previous hypotheses to describe this phenomenon. Fifth, the three associated factors in multivariate analysis had significant odd ratios but wide 95% confidence intervals, which can be explained by many reasons. Myelitis had a very strong association with the occurrence of PTS, which was the most likely cause for a broad confidence interval and can be confirmed with the sensitivity analysis. Sample size of patients with tobacco use and PLEX may be too small in the present study and would decrease the precision of odd ratios of these two factors.

However, the strength of the present research was that this was the first report about the prevalence of PTS in patients with NMOSD in Thailand, and it was the first multivariate analysis comparing the clinical features and PTS occurrence. Moreover, the present study was the first to report the relationship of the clinical factors and recovery from PTS in NMOSD. Thus, the outcomes of the present study could be beneficial and prompt additional PTS studies in the future.

Conclusion

PTS is one of the common complications in patients with NMOSD in Thailand. The presence of acute myelitis and tobacco use are associated with the presence of PTS. PLEX treatment in the acute phase of NMOSD may be associated with good recovery from PTS, and longer segments of spinal cord lesions are correlated with poor recovery outcomes. The control of these factors may prevent the occurrence of PTS or at least facilitate the recovery from PTS in these patients. However, better pain control medications are lacking, and the pathophysiology of this condition remains unknown. Further clinical and pathological studies are needed to solve these long-standing problems in NMOSD.

What is already known on this topic?

PTS is one of the common complications in patients with NMOSD. The incidence of PTS in the previously published article is about 14% to 26%. The predictive factors associated with PTS in NMOSD include myelitis at the onset, higher age at onset, the annualized relapse rate of the disease, annualized relapse rate of myelitis, and pruritus symptom.

What this study adds?

This study suggests the prevalence of PTS in patients with NMOSD might be as high as 40%. The possible associated factors with the occurrence of PTS is not only the presence of acute myelitis but also the use of tobacco. This study was the first to describe factors associated with PTS recovery, which is plasma exchange in acute phase associated with good recovery, while longer segments of spinal cord lesions associated with poor recovery.

Acknowledgement

This work was financially supported through Grant No. 62045 from the Prasat Neurological Institute, Department of Medical Services, Ministry of Public Health, Thailand.

Conflicts of interest

The authors declare no financial or other conflicts of interest.

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