The risk factors of neuropathic pain in neuromyelitis optica spectrum disorder: a retrospective case-cohort study

Xiaojun Li1†, Haoyou Xu2†, Zequan Zheng2, Huijing Ouyang1, Guixian Chen1, Zhenzhen Lou1, Haoxuan Chen1, Jiahui Zhang2, Yibo Zhan1, Hui Mao1, Changlin Zhang1, Min Zhao2*† and Yuanqi Zhao2*†

Abstract

Background: Neuropathic pain is a common complication in neuromyelitis optica spectrum disorder (NMOSD), which seriously affects the quality of life of NMOSD patients, with no satisfactory treatment. And risk factors of neuropathic pain are still uncertain.

Objective: To investigate the risk factors of neuropathic pain in a NMOSD cohort.

Materials and methods: Our study was a retrospective case-cohort study, the patients diagnosed with NMOSD in the Department of Neurology from the Second Affiliated Hospital of Guangzhou University of Chinese Medicine from January 2011 to October 2021 were screened. Inclusion criteria were: (1) patients diagnosed as NMOSD according to the International Panel for NMO Diagnosis (IPND) criteria, (2) the aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) test was performed. Patients without AQP4-IgG antibody were excluded. Clinical data, including sex, age of the first onset, symptoms of the first episode including neuropathic pain and attack types, localization of lesions of the first episode on Magnetic Resonance Imaging (MRI), Extended disability status Scale (EDSS) of the first onset, treatment of immunosuppression in the first acute phase, disease modifying therapy (DMT), treatment of neuropathic pain and AQP4-IgG status were collected from the hospital system database. Neuropathic pain was defined according to the International Association for the Study of Pain criteria and was described as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”.

Results: One hundred nineteen patients were screened and finally 86 patients fulfilling the inclusion and exclusion criteria were enrolled in our study. The prevalence of neuropathic pain in patients with NMOSD was 43.0%. Univariate analysis showed that the factors associated with neuropathic pain were the age at the onset, the attack type of optic neuritis, the attack type of myelitis, length of spinal cord involvement, localization of thoracic lesion, optic lesion, upper thoracic lesions, lower thoracic lesions, extended spinal cord lesions (≥ 3 spinal lesions), extended thoracic lesions (≥ 4 thoracic lesions), intravenous immunoglobulin and mycophenolate mofetil. Multivariate regression analysis showed that extended thoracic lesions (OR 20.21 [1.18–346.05], \(P = 0.038\)) and age (OR 1.35 (1–1.81))
Introduction
Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing inflammatory central nervous system disorder mainly involving the optic nerve and spinal cord. Except for the high recurrence rate and disability rate [1, 2], pain is highly prevalent in patients with NMOSD [3–5]. Pain has been an important factor affecting patients’ quality of life [6–10]. Neuropathic pain (NP) is one of types of pain being most characteristic [3, 4, 6]. However, there was no satisfactory treatment so far. At the same time, several studies have found that high doses of painkillers do not cure pain, but are associated with more severe cognitive impairment and fatigue [4, 11].

Several clinical observations suggested that some factors such as age, myelitis and mood were associated with NP in patients with NMOSD [3, 12, 13]. Our study was designed to investigate the risk factors of NP among NMOSD patients.

Methods
Patients
Our study was a retrospective case-cohort study, the patients diagnosed with NMOSD in the Department of Neurology from the Second Affiliated Hospital of Guangzhou University of Chinese Medicine from January 2011 to October 2021 were screened. Inclusion criteria were (1) patients diagnosed as NMOSD according to the International Panel for NMO Diagnosis (IPND) criteria [14], (2) the aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) test was performed (Fig. 1) [15]. Patients without AQP4-IgG antibody were excluded. Clinical data, including sex, age of the first onset, symptoms of the first onset including neuropathic pain and attack types, localization of lesions of the first onset on Magnetic Resonance Imaging (MRI), Extended disability status Scale (EDSS) of the first onset, treatment of immunosuppression in the first acute phase, disease modifying therapy (DMT), treatment of neuropathic pain and AQP4-IgG status were collected from the hospital system database. Neuropathic pain was defined according to the International Association for the Study of Pain criteria and was described as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [16]. The patients were divided into NP group and non-NP group. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (YE2021-308).

Conclusion:
Extended thoracic lesions (≥4 thoracic lesions), age and gender might be independent risk factors of neuropathic pain among patients with NMOSD. However, with a small sample size and predominantly female, caution must be applied and these results need validating in further cohorts.

Keywords: Neuromyelitis optica spectrum disorder, Neuropathic pain, AQP4-IgG antibody
Statistical analyses
The dichotomous data were reported as the number with percentage, and the continuous data were expressed as the mean and standard deviation. 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 non-parametric test. The variables that were statistically significant in the univariate analysis at P value less than 0.1 were included in a multivariate logistic regression model to assess the independent risk factors of neuropathic pain among NMOSD patients. The cut-off for statistical significance was P value less than 0.05.

Result
Demographic and clinical characteristics
Totally, 119 patients with NMOSD were screened. After the exclusion of 33 patients without AQP4-IgG antibody information, 86 patients were enrolled in this study (Fig. 1). Among the 86 patients, 75 (87.2%) patients were women, mean age of the first onset was 46.2 years. 74 (86.0%) patients with NMOSD were positive for the AQP4-IgG antibody. At the first attack, the mean EDSS is 4.3 ± 2.7 in NMOSD patients. The predominant clinical presentation was myelitis (73.3%) followed by optic neuritis (31.4%). 8 (11.9%) patients had optic lesions, 18 (26.9%) patients had brain stem lesions and 43 (50.0%) patients had spinal cord lesions. The predominant spinal lesion type was thoracic lesion (49.3%) followed by cervical lesion (44.8%). 27 (40.3%) patients had upper thoracic lesions (thoracic 1-thoracic 6). 18 (26.9%) patients had lower thoracic lesions (thoracic 7-thoracic 12). 18 (26.9%) patients had extended thoracic lesions (≥4 thoracic lesions). 40 (59.7%) patients had extended spinal cord lesions (≥3 spinal lesions). Intravenous methylprednisolone (87.8%) and intravenous immunoglobulin (21.6%) were used mainly in the acute phase, and oral glucocorticoid (96.5%), azathioprine (52.3%), and mycophenolate mofetil (15.1%) were used mainly in the remission phase (Table 1).

Univariate analysis
In our study, 37 (43.0%) patients had neuropathic pain. The mean age of the first onset in the NP group was higher than in the non-NP group (51.2 ± 13.3 years VS 42.5 ± 13.2 years) (OR 1.05 [1.02–1.09], P = 0.006). The mean EDSS of patients in NP and non-NP group was separately 4.5 ± 2.6 and 4.0 ± 2.8 (P = 0.435). The mean length of spinal cord involvement of patients with NP was longer than patients in non-NP group (5.8 ± 5.0 VS 3.0 ± 3.8) (OR 1.16 [1.03–1.32], P = 0.018). 32 (86.5%) patients with NP had myelitis while only 31 (63.3%) patients in non-NP group had myelitis during the first episode of the disease (OR 3.72 [1.23–11.24], P = 0.02). 7(18.9%) and 20(40.8%) patients in NP group and non-NP group had optic neuritis (OR 0.34 [0.12–0.92], P = 0.034). About the localization of the lesions, the percentage of patients with cervical lesions was similar between two groups. There were more patients with thoracic lesion in NP group (61.8%) than non-NP group (36.4%). 1 (2.9%) patient in NP group and 7 patients (21.2%) in non-NP group had optic lesions (P = 0.047). The proportion of patients with upper thoracic lesions in the NP group was higher than in the non-NP group (52.9% VS 27.3%) (OR 3 [1.08–8.32], P = 0.035).

Statistical analyses
The dichotomous data were reported as the number with percentage, and the continuous data were expressed as the mean and standard deviation. 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 non-parametric test. The variables that were statistically significant in the univariate analysis at P value less than 0.1 were included in a multivariate logistic regression model to assess the independent risk factors of neuropathic pain among NMOSD patients. The cut-off for statistical significance was P value less than 0.05.

Result
Demographic and clinical characteristics
Totally, 119 patients with NMOSD were screened. After the exclusion of 33 patients without AQP4-IgG antibody information, 86 patients were enrolled in this study (Fig. 1). Among the 86 patients, 75 (87.2%) patients were women, mean age of the first onset was 46.2 years. 74 (86.0%) patients with NMOSD were positive for the AQP4-IgG antibody. At the first attack, the mean EDSS is 4.3 ± 2.7 in NMOSD patients. The predominant clinical presentation was myelitis (73.3%) followed by optic neuritis (31.4%). 8 (11.9%) patients had optic lesions, 18 (26.9%) patients had brain stem lesions and 43 (50.0%) patients had spinal cord lesions. The predominant spinal lesion type was thoracic lesion (49.3%) followed by cervical lesion (44.8%). 27 (40.3%) patients had upper thoracic lesions (thoracic 1-thoracic 6). 18 (26.9%) patients had lower thoracic lesions (thoracic 7-thoracic 12). 18 (26.9%) patients had extended thoracic lesions (≥4 thoracic lesions). 40 (59.7%) patients had extended spinal cord lesions (≥3 spinal lesions). Intravenous methylprednisolone (87.8%) and intravenous immunoglobulin (21.6%) were used mainly in the acute phase, and oral glucocorticoid (96.5%), azathioprine (52.3%), and mycophenolate mofetil (15.1%) were used mainly in the remission phase (Table 1).

Univariate analysis
In our study, 37 (43.0%) patients had neuropathic pain. The mean age of the first onset in the NP group was higher than in the non-NP group (51.2 ± 13.3 years VS 42.5 ± 13.2 years) (OR 1.05 [1.02–1.09], P = 0.006). The mean EDSS of patients in NP and non-NP group was separately 4.5 ± 2.6 and 4.0 ± 2.8 (P = 0.435). The mean length of spinal cord involvement of patients with NP was longer than patients in non-NP group (5.8 ± 5.0 VS 3.0 ± 3.8) (OR 1.16 [1.03–1.32], P = 0.018). 32 (86.5%) patients with NP had myelitis while only 31 (63.3%) patients in non-NP group had myelitis during the first episode of the disease (OR 3.72 [1.23–11.24], P = 0.02). 7(18.9%) and 20(40.8%) patients in NP group and non-NP group had optic neuritis (OR 0.34 [0.12–0.92], P = 0.034). About the localization of the lesions, the percentage of patients with cervical lesions was similar between two groups. There were more patients with thoracic lesion in NP group (61.8%) than non-NP group (36.4%). 1 (2.9%) patient in NP group and 7 patients (21.2%) in non-NP group had optic lesions (P = 0.047). The proportion of patients with upper thoracic lesions in the NP group was higher than in the non-NP group (52.9% VS 27.3%) (OR 3 [1.08–8.32], P = 0.035). The percentage of patients with lower thoracic lesions in the NP group was higher than in the

| Characteristic | NMOSD(n=86) |
|---------------|-------------|
| Female: male (ratio) | 75:11(7:1) |
| Age, y, mean ± sd | 46.2 ± 13.8 |
| AQP4-IgG-positive, n (%) | 74(86.0) |
| History of myelitis during the disease, n (%) | 83(96.5) |
| EDSS, mean ± sd | 4.3 ± 2.7 |
| Length of spinal cord involvement, mean ± sd | 4.4 ± 4.7 |
| Attack type, n (%) | |
| Optic neuritis | 27(31.4) |
| Myelitis | 63(73.3) |
| Brain stem | 17(19.8) |
| MR lesion type, n (%) | |
| Cervical | 30(44.8) |
| Thoracic | 33(49.3) |
| Lumbar | 2(3.0) |
| Brain stem | 18(26.9) |
| Optic | 8(11.9) |
| Isolated thoracic, n (%) | 13(19.4) |
| Upper thoracic lesions, n (%) | 27(40.3) |
| Lower thoracic lesions, n (%) | 18(26.9) |
| ≥4 thoracic lesions, n (%) | 18(26.9) |
| ≥3 spinal lesions, n (%) | 40(59.7) |
| IVMP, n (%) | 65(87.8) |
| Intravenous immunoglobulin, n (%) | 16(21.6) |
| Plasma exchange, n (%) | 2(2.7) |
| Oral glucocorticoid, n (%) | 83(96.5) |
| AZA, n (%) | 45(52.3) |
| MMF, n (%) | 13(15.1) |

AQP4-IgG Aquaporin-4 immunoglobulin G, EDSS Extended disability status Scale, Th Thoracic, Th1-Th6 Upper thoracic lesions, Th7-Th12 lower thoracic lesions, IVMP Intravenous methylprednisolone, AZA Azathioprine, MMF Mycophenolate mofetil

* Missing 19 cases
non-NP group (38.2% VS 15.2%) (OR 3.47 [1.07–11.24], \( P = 0.038 \)). The proportion of patients with extended thoracic lesions (≥ 4 thoracic lesions) in the NP group was higher than in the non-NP group (44.1% VS 9.1%) (OR 7.9 [2.01–30.95], \( P = 0.003 \)). Among the patients with myelitis lesions, the proportion of patients with extended spinal cord lesions (≥ 3 spinal cord lesions) in the NP group was higher than in the non-NP group (76.5% VS 42.4%) (OR 4.41 [1.54–12.62], \( P = 0.006 \)). Among them, more patients with neuropathic pain use intravenous immunoglobulin in the acute phase (35.3% VS 10%, \( P = 0.013 \)), and more patients with neuropathic pain used mycophenolate mofetil during remission (24.3% VS 8.2%, \( P = 0.047 \)). In terms of pain treatment, 13.5% of patients with neuropathic pain did not use analgesics, 86.5% used antiepileptic drugs, and 24.3% used antidepressants (Table 2).

### Multivariate analysis
In multivariate regression analysis, extended thoracic lesions (≥ 4 thoracic lesions) were independent risk factors of neuropathic pain in NMOSD patients (OR 20.21 [1.18–346.05], \( P = 0.038 \)) after adjusting for age, gender, optic neuritis, upper thoracic lesions, intravenous immunoglobulin, MMF and EDSS. Meanwhile, age was an independent risk factor of neuropathic pain in NMOSD patients (OR 1.35 (1–1.81) \( P = 0.050 \)). Gender might be also an independent risk factor of neuropathic pain in NMOSD patients (OR 1.35 (1–1.81) \( P = 0.050 \)) (Table 3).

### Table 2 The univariate analysis of neuropathic pain among patients with NMOSD

| Characteristic | NP (\( n = 37 \)) | Non-NP (\( n = 49 \)) | OR (95% CI) | \( P \) value |
|---------------|------------------|----------------------|-------------|-------------|
| Female: male (ratio) | 33.3(11:1) | 42.8 (5:1) | 2.21 (0.54–8.99) | 0.267 |
| Age, y, mean ± sd | 51.2±13.3 | 42.5±13.2 | 1.05 (1.02–1.09) | 0.006 |
| AQP4-IgG-positive, n (%) | 34(91.1) | 40(81.6) | 2.55 (0.64–10.18) | 0.174 |
| Length of spinal cord involvement, mean±sd | 5.8±5.0 | 3.0±3.8 | 1.16 (1.03–1.32) | 0.018 |
| EDSS, mean±sd | 4.5±2.6 | 4.0±2.8 | 1.07 (0.9–1.28) | 0.435 |
| Attack type, n (%) | | | | |
| Optic neuritis | 7(18.9) | 20(40.8) | 0.34 (0.12–0.92) | 0.034 |
| Myelitis | 32(86.5) | 31(63.3) | 3.72 (1.23–11.24) | 0.02 |
| Brain stem | 9(24.3) | 8(16.3) | 1.65 (0.57–4.79) | 0.359 |
| MR lesion type, n (%) | | | | |
| Cervical | 19(55.9) | 11(33.3) | 2.53 (0.94–6.83) | 0.066 |
| Thoracic | 21(61.8) | 12(36.4) | 2.83 (1.05–7.61) | 0.04 |
| Lumber | 1(2.9) | 3(9.1) | 0.97 (0.06–16.17) | 0.983 |
| Brain stem | 10(29.4) | 8(24.2) | 1.30 (0.44–3.86) | 0.634 |
| Optic | 1(2.9) | 7(21.2) | 0.11 (0.01–0.97) | 0.107 |
| Isolated thoracic, n (%) | 8(23.5) | 5(15.2) | 1.72 (0.5–5.94) | 0.389 |
| Upper thoracic lesions, n (%) | 18(52.9) | 9(27.3) | 3.10 (1.08–8.32) | 0.035 |
| Lower thoracic lesions, n (%) | 13(38.2) | 5(15.2) | 3.47 (1.07–11.24) | 0.038 |
| ≥ 4 thoracic lesions, n (%) | 15(44.1) | 3(9.1) | 7.92 (2.0–30.95) | 0.003 |
| ≥ 3 spinal lesions, n (%) | 26(76.5) | 14(42.4) | 4.41 (1.54–12.62) | 0.006 |
| IVMP, n (%) | 32(94.1) | 33(82.5) | 3.39 (0.66–17.58) | 0.145 |
| Intravenous immunoglobulin, n (%) | 12(35.3) | 4(10) | 4.91 (1.41–17.13) | 0.013 |
| Plasma exchange, n (%) | 0(0) | 2(5) | 0(0–0) | 0.999 |
| Oral glucocorticoid, n (%) | 37(100) | 46(93.9) | Inf | 0.999 |
| AZA, n (%) | 19(51.4) | 26(53.1) | 0.93 (0.4–2.19) | 0.875 |
| MMF, n (%) | 9(24.3) | 4(8.2) | 3.62 (1.02–12.86) | 0.047 |
| Antidepressants, n (%) | 9(24.3) | - | - | - |
| Antiepileptic, n (%) | 32(86.5) | - | - | - |
| Antispasticity, n (%) | 12(32.4) | - | - | - |
| Opioids, n (%) | 2(5.4) | - | - | - |

AQP4-IgG Aquaporin-4 immunoglobulin G, EDSS Extended disability status scale, Th1-Th6 Upper thoracic lesions, Th7-Th12 Lower thoracic lesions, NP Neuropathic pain, IVMP Intravenous methylprednisolone, AZA Azathioprine, MMF Mycophenolate mofetil

\( a \) Missing 19 cases
Discussion

The key finding of the present study was that among NMOSD patients, extended thoracic lesions (≥4 thoracic lesions) were independent risk factors of neuropathic pain in NMOSD patients which were not reported in the previous studies. Patients with extended thoracic lesions had a 20.21-fold higher risk of neuropathic pain. Furthermore, age and gender might be also associated with neuropathic pain.

Correlation between spinal lesion level and neuropathic pain

The prevalence of neuropathic pain in patients with NMOSD was 31.5-85.5% [3, 6, 12, 17]. Consistent with the previous studies, the prevalence of neuropathic pain in our study was 43%.

About the mechanism of neuropathic pain, the possible hypothesis was that neurons with bilateral descending projections to the lumbosacral superficial dorsal horn were concentrated in the autonomic intermediomedial nucleus surrounding the central canal of the upper/mid-thoracic spinal cord, and lesions of the upper/mid-thoracic segment may accompany pain easily [18].

On the basis of this hypothesis, some studies began to investigate the relationship between neuropathic pain of NMOSD patients and the spinal cord. Several studies found that the number of involved spinal segments (OR 1.14 [1.03–1.28], \( P = 0.024 \)), especially the upper 6 thoracic segments (OR 1.31 [1.01–1.63], \( P = 0.018 \)) was associated with pain among NMOSD patients, and that pain score was higher in patients with than in those without extended spinal cord lesions (≥3 spinal cord lesions) (median, 17.5 vs. 10.0; IQR, 9.5 vs. 10.0; \( P = 0.036 \)) [3, 19]. In Oxford and Liverpool’s prospective study, they showed that the presence of thoracic lesions (std. \( \beta = -0.46, P = 0.03 \)) predicts greater myelitis-associated chronic pain than the presence of cervical lesions (std. \( \beta = 0.48, P = 0.04 \)) [12]. On the contrary, another cohort showed that there was no significant difference in the length of the lesion between NP and non-NP groups (8.8 VS 7.6 spinal cord segments, respectively, \( P = 0.422 \)) [6].

However, these studies suggested the number of involved spinal segments especially the upper 6 thoracic segment or the presence of thoracic lesions or extended spinal cord lesions (≥3 spinal lesions) might be associated with pain among NMOSD patients while our study pointed out the extended thoracic lesions (≥4 thoracic cord lesions) was an independent risk factor of neuropathic pain among patients with NMOSD which was the novelty of the present paper. Since the association between neuropathic pain and the features of spinal lesions is still controversial, prospective cohort studies were needed.

Correlation between gender and neuropathic pain

In this study, gender might be also an independent risk factor of neuropathic pain in NMOSD patients which was not found in the previous studies [17, 20]. Female patients had a 12.11-fold higher risk of neuropathic pain than male patients. Up to now, there is an unknown mechanism between gender and neuropathic pain in NMOSD patients. But several studies advanced the hypothesis that there is a difference between the sexes in the mechanism of the initiation and maintenance of neuropathic pain. Firstly, neuroinflammation which could cause pain is driven by different cells. Neuroinflammation seems to have more microglia involved in males, whereas in females it seems to be driven primarily by T lymphocytes. Secondly, sex hormones such as testosterone might alter the main immune cells that

| Table 3 | The multivariate analysis of neuropathic pain among patients with NMOSD. (neuropathic pain as dependent variable) |
|---|---|---|
| | Crude OR (95% CI) | \( P \) value | Adjusted model OR (95% CI) | \( P \) value |
| Age at the onset, each 5 years | 1.30(1.08–1.56) | 0.006 | 1.35(1.1–1.81) | 0.05 |
| Gender, female | 2.21(0.54–8.99) | 0.267 | 12.11(0.97–151.64) | 0.053 |
| Optic neuritis | 0.34(0.12–0.92) | 0.034 | 0.43(0.05–3.66) | 0.443 |
| Upper thoracic lesion \( ^a \) | 3.00(1.08–8.32) | 0.035 | 0.75(0.11–4.97) | 0.763 |
| ≥4 thoracic lesions \( ^a \) | 7.90(2.01–30.95) | 0.003 | 20.21(1.18–346.05) | 0.038 |
| EDSS | 1.07(0.90–1.28) | 0.435 | 1.19(0.91–1.56) | 0.216 |
| Intravenous immunoglobulin | 4.91(1.41–17.13) | 0.013 | 2.43(0.5–11.73) | 0.269 |
| MMF | 3.62(1.02–12.86) | 0.047 | 7.32(0.83–64.15) | 0.072 |

\( ^a \) Missing 19 cases

Adjusted for age at the onset, gender, optic neuritis, upper thoracic lesions, ≥4 thoracic lesions, EDSS, Intravenous immunoglobulin, MMF

AQP4-IgG Aquaporin-4 immunoglobulin G, Th Thoracic, Th1-Th6 Upper thoracic lesions, EDSS Extended disability status Scale, MMF Mycophenolate mofetil
Correlation between age and neuropathic pain
The correlation of neuropathic pain and age might be related to decreased small fibers and a declined neural plasticity [27, 28]. Previous study showed controversial results [12, 20]. In our study, the age of NMOSD patients with neuropathic pain was higher than those without in this study (51.2 ± 13.3 VS 42.5 ± 13.2, \(P = 0.006\)). The multivariate analysis showed that age might increase the incidence of NP among NMOSD patients (OR 1.35 (1–1.81) \(P = 0.050\)).

Correlation between AQP4-IgG antibody status and neuropathic pain
Until now, there were several hypotheses about the mechanism of neuropathic pain related with AQP4-IgG antibody status among NMOSD patients.

Firstly, under physiological conditions, AQP4 is co-expressed with the excitatory amino acid transporter 2, which enables glutamate uptake by astrocytes [29]. Glutamine is the material basis of γ-aminobutyric acid (GABA) [30]. Loss of AQP4 may lead to an excessive accumulation of glutamate in the extracellular space and reduce the production of GABA.

Secondly, extensive loss of AQP4 could induce reactive astrocytes. A2 astrocytes secrete neuroprotective factors that promote neuronal survival, and then may inhibit the progression of chronic pain. A1 astrocytes not only secrete toxic factors that rapidly kill mature oligodendrocytes and neurons but also produce small molecules such as cytokines, chemokines and growth factors that influence the glutamine-glutamate-GABA axis [31–33].

Therefore, the reactive astrocyte played an important role in the development of neuropathic pain among NMOSD patients.

Some clinical studies found that patients had neuropathic pain were tended to be AQP4-IgG-positive than those without pain (89.55% VS 79.07%, \(P = 0.082\)) [34]. In our study, the proportion of AQP4-IgG-positive patients in the NP group was higher than in the non-NP group (91.1% VS 81.6%, \(P = 0.174\)). Whether the neuropathic pain was associated with AQP4-IgG antibody status needed more studies to verify.

Limitation
As a retrospective study, the pain score of patients at the onset was not assessed. Therefore, we could not find out whether extended thoracic lesions were associated with the severity of neuropathic pain. Further prospective studies with a more detailed evaluation of neuropathic pain were needed to verify our conclusion.

Conclusions
Extended thoracic lesions (≥ 4 thoracic lesions), age and gender might be independent risk factors of neuropathic pain among patients with NMOSD. However, with a small sample size and predominantly female, caution must be applied and these results need validating in further cohorts.

Abbreviations
NMOSD: Neuromyelitis optica spectrum disorder; AQP4-IgG: Aquaporin-4 immunoglobulin G; NP: Neuropathic pain; GABA: γ-Aminobutyric acid; Th: Thoracic; MRI: Magnetic Resonance Imaging; IPND: International Panel for NMO Diagnosis; OR: Odds ratio; CI: Confidence interval; IVMP: Intravenous methylprednisolone; AZA: Azathioprine; MMF: Mycophenolate mofetil; EDSS: Extended disability status Scale.

Acknowledgements
Not applicable.

Authors’ contributions
Study concept and design, drafting of manuscript: Xiaojun Li, Haoyou Xu. Acquisition of data, or analysis of data: Zequan Zheng, Huiying Ouyang, Guixian Chen, Zhenzhen Lou, Haoyuan Chen, Jiashui Zhang, Yibo Zhan, Hui Mao, Changlin Zhang. Revision of manuscript for important intellectual content: Min Zhao, Yuanqi Zhao. All authors have read and approve of the final version of the manuscript.

Funding
This study was supported by a grant from of Guangdong Natural Science Foundation project (2020A1515010595), Special fund for Traditional Chinese Medicine Science and technology research of Guangdong Hospital of Traditional Chinese Medicine (20221166), Guangdong Bureau of Traditional Chinese Medicine (20225030).

Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This study has been approved by the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine (No.YE2021-308) and conducted on the basis of the Declaration of Helsinki. According to ethic guidelines, the requirement of informed consent was waived since this study had no potential to harm the rights or welfare of subjects. And the Ethics Committee of the Second Affiliated Hospital of Guangzhou University of Chinese Medicine approved the waiver of informed consent.
Consent for publication
Not applicable.

Competing interests
The authors declare that there is no conflict of interest.

Author details
1 The Second Clinical College of Guangzhou, University of Chinese Medicine, Guangzhou 510006, China. 2 Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, 111 Dade Road, Guangzhou 510120, China.

Received: 23 April 2022 Accepted: 10 August 2022

Published online: 19 August 2022

References
1. Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Wegner B, Hellwig HP, Ringelstein M, Geis C, Kleinschitz C, Berthele A, Hemmer B, Angstwurm K, Stellmann JP, Schuster S, Stangel M, Lua da, Tumani H, Mayer C, Zeltner L, Ziemann U, Linker R, Schwab M, Marzinaki M, Then Bergh F, Hofstadt-von Ou Y, Neuhaus O, Winkelmann A, Marouf W, Fais J, Wildermann B, Paul F, Jarius S, Trebst C, Neuroumyelitis Optica Study. Neuroumyelitis optica: Evaluation of 871 attacks and 1,153 treatment courses. Ann Neurol. 2016;79:206–21. https://doi.org/10.1002/ana.24554.

2. Weinshenker BG, Wingerchuk DM. Neuroumyelitis Optica Spectrum Disorders. Mayo Clin Proc. 2017;92:663–79. https://doi.org/10.1016/j.mayocp.2016.12.014.

3. Ayzenberg I, Richter D, Henke E, Asseyer S, Paul F, Trebst C, Hümmer MW, Hlava J, Kumpfel T, Ringelstein M, Akuts O, Wildermann B, Jarius S, Häubler V, Stellmann J-P, Senel M, Klotz L, Pelkkofer HL, Weber MS, Pavlički M, Rommer PS, Berthele A, Wennecke K-D, Hellwig K, Gold R, Kleiter I. On behalf of the NEMOS (Neuroumyelitis Optica Study Group), Pain, Depression, and Quality of Life in Neuromyelitis Optica Spectrum Disorder: A Cross-Sectional Study of 166 AQP4 Antibody-Positive Patients. Neurol - Neuroimmunol Neuroinflammation. 2021;8:e985. https://doi.org/10.1212/NXI.0000000000124958.

4. Qian P, Lancia S, Alvarez E, Klawiter EC, Cross AH, Naismith RT. Association of neuromyelitis optica with severe and intractable pain. Arch Neurol. 2012;69:1482. https://doi.org/10.1001/archneur.2012.678.

5. Kanamori Y, Nakashima I, Takai Y, Nishiyama S, Kuroda H, Takahashi T, Kanaoka-Suzuki C, Misu T, Fujihara K, Itaiyama Y. Pain in neuromyelitis optica and its effect on quality of life: a cross-sectional study. Neurology. 2011;77:652–8. https://doi.org/10.1212/01.wnl.0000381229.26969.9a.

6. Zhao S, Mutch K, Eison L, Nurmikko T, Jakob A. Neuropathic pain in neuromyelitis optica affects activities of daily living and quality of life. Mult Scler J. 2014;20:1658–61. https://doi.org/10.1177/1352458514522103.

7. Barzegar M, Sadeghi-Bahmani D, Mirmovassayeb D, Azarbayegni R, Afshari-Safavi A, Vahebe S, Nezhatur N, Dana A, Shahgannejad V, Most RW, Brand S. Higher disease and pain severity and fatigue and lower balance skills are associated with higher prevalence of falling among individuals with the inflammatory disease of Neuromyelitis Optica Spectrum Disorder (NMO/SD). J Clin Med. 2020;9:5604. https://doi.org/10.3390/jcm9111604.

8. Beecks JW, Keesler A, Pedrada O, Granier L, Kim NV, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Vincent A, Leite MI, Tracey I, Jacob A, Palace J. Chronic neuropathic pain severity is determined by lesion level in aquaporin 4-antibody-positive patients. J Neurol Neurosurg Psychiatry. 2017;88:165–9. https://doi.org/10.1136/jnnp-2016-314991.

9. Kong Y, Okouwa H, Revis J, Tackley G, Leite ML, Lee M, Tracey J, Palace J. Pain in patients with transverse myelitis and its relationship to aquaporin 4 antibody status. J Neurol Sci. 2016;368:84–8. https://doi.org/10.1016/j.jns.2016.06.041.

10. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, de Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lempicke M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Weiskell KE, Weinshenker BG. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85:177–89. https://doi.org/10.1212/WNL.0000000000001279.

11. Asseyer S, Kuchling J, Gaetano L, Komnenić D, Siebert N, Chien C, Nurmikko T, Sjerra J. Neuropathic pain: Redefinition and a grading system for clinical and research purposes. Neurology. 2008;70:1630–5. https://doi.org/10.1212/01.wnl.0000282763.29778.59.

12. Wang T, Lian Z, Wu X, Kong Y, Zhou H, Wei M. Subcortical structural abnormalities in neuromyelitis optica patients with neuropathic pain. Mult Scler Relat Disord. 2020;37:101432. https://doi.org/10.1016/j.msard.2019.101432.

13. Okuda DT, Melmed M, Katsuwaki T, Blomqvist A, Craig ADB. Central neuropathic pain in MS is due to distinct thoracic spinal cord lesions. Ann Clin Transl Neurol. 2014;1:554–61. https://doi.org/10.1002/actn.385.

14. Masuda H, Mori M, Uzawa A, Uchida T, Ohrtani S, Kuwabara S. Difference in fatigue and pain between neuromyelitis optica spectrum disorder and multiple sclerosis. PLoS One. 2020;15:e0224419. https://doi.org/10.1371/journal.pone.0224419.

15. Asseyer S, Kuchling J, Gaetano L, Komnenic D, Siebert N, Chien C, Scheel M, Oertel FC, Ruprecht K, Bellmann-Strobl J, Finke C, Chakravarty MM, Magon S, Wuerfel J, Paul F, Papadopoulos A, Brandt AU. Ventral posterior nuclear volume is associated with neuropathic pain intensity in neuromyelitis optica spectrum disorders. Mult Scler Relat Disord. 2020;46:102579. https://doi.org/10.1016/j.msard.2020.102579.

16. Coraggio V, Guida F, Boccella S, Scalfaro M, Paino S, Romano D, Maione S, Luongo L. Neuroimmune-driven neuropathic pain establishment: a focus on gender differences. Int J Mol Sci. 2018;19:281. https://doi.org/10.3390/ijms19010281.

17. Hallevski K, Ghaziaieedi S, Salter MW. Sex-dependent mechanisms of chronic pain: a focus on microglia and P2X4R. J Pharmacol Exp Ther. 2020;375:202–7. https://doi.org/10.1124/jpet.120.265017.

18. Machellika H, Gelik MO. Recent advances in understanding neuropathic pain: glia, sex differences, and epigenetics. J Pain. 2018;19:1005–15. https://doi.org/10.1016/j.jpain.2018.10.066.

19. Li et al. BMC Neurology (2022) 22:304 Page 7 of 8
26. Machelska H, Celik MO. Recent advances in understanding neuropathic pain: glia, sex differences, and epigenetics. F1000Res. 2016;5:2743. https://doi.org/10.12688/f1000research.9621.1.

27. Fitzgerald M, Mckelvey R. Nerve injury and neuropathic pain — A question of age. Exp Neurol. 2016;275:296–302. https://doi.org/10.1016/j.expneurol.2015.07.013.

28. da Silva L, Lin S, Teixeira M, de Siqueira J, Jacob Filho W, de Siqueira S. Sensory differences according to sex and ages. Oral Dis. 2014;20:e103–10. https://doi.org/10.1111/odi.12145.

29. Hinson SR, Roemer SF, Lucchinetti CF, Fryer JP, Kryzer TJ, Chamberlain JL, Howe CL, Prutko SJ, Lennon VA. Aquaporin-4–binding autoantibodies in patients with neuromyelitis optica impair glutamate transport by down-regulating EAAT2. J Exp Med. 2008;205:2473–81. https://doi.org/10.1084/jem.20081241.

30. Albrecht J, Sidoryk-Węgrzynowicz M, Zielińska M, Aschner M. Roles of glutamine in neurotransmission. Neuron Glia Biol. 2010;6:263–76. https://doi.org/10.1017/S1740925X11000093.

31. Bradl M, Kanamori Y, Nakashima I, Misu T, Fujihara K, Lassmann H, Sandkühler J. Pain in neuromyelitis optica—prevalence, pathogenesis and therapy. Nat Rev Neurol. 2014;10:529–36. https://doi.org/10.1038/nrneurol.2014.129.

32. Li T, Chen X, Zhang C, Zhang Y, Yao W. An update on reactive astrocytes in chronic pain. J Neuroinflammation. 2019;16:140. https://doi.org/10.1186/s12974-019-1524-2.

33. Ji RR, Donnelly CR, Nedergaard M. Astrocytes in chronic pain and itch. Nat Rev Neurosci. 2019;20:667–85. https://doi.org/10.1038/s41583-019-0218-1.

34. Li Q, Wang B, Yang J, Zhou L, Bao JZ, Wang L, Zhang A, Liu C, Quan C, Li F. Painful tonic spasm in Chinese patients with neuromyelitis optica spectrum disorder: Prevalence, subtype, and features. Mult Scler Relat Disord. 2020;45:102408. https://doi.org/10.1016/j.msard.2020.102408.

**Publisher’s Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

---

**Ready to submit your research? Choose BMC and benefit from:**

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions