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# Clinical significance of methyl-CpG binding protein 2 in postherpetic neuralgia: an observational study.

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**Key words:** MECP2; postherpetic neuralgia; inflammatory factors; quality of life.

**Abstract.** The present study was aimed to investigate the clinical significance of methyl-CpG binding protein 2 (MECP2) in patients with postherpetic neuralgia (PHN). This prospective case control study enrolled 319 cases of PHN patients from April 2017~December 2019. The patients' sleep quality and quality of life were evaluated using the Pittsburgh sleep quality score and the SF-36 scale, respectively. The serum levels of MECP2, CRP, IL-6 and TNF-α were tested using enzyme linked immunosorbent assay (ELISA). The pain condition of the patients was evaluated using the visual analogue scale (VAS). The levels of MECP2 were significantly increased in PHN patients compared with the patients without PHN. Serum MECP2 levels were the highest in patients with severe pain, and were the lowest in patients with mild pain. Similarly, the frequency of severe pain in patients with low expression of MECP2 was significantly lower than the patients with higher MECP2 expression. Besides, serum levels of inflammatory factors CRP, IL-6 and TNF-α were markedly increased in PHN patients, which were also increased with the increase of the severity of pain. CRP, IL-6 and TNF-α were positively correlated with serum levels of MECP2 in PHN patients. Before the study, patients with lower MECP2 levels showed a significantly higher SF-36 score and lower Pittsburgh and VAS scores than patients with higher levels of MECP2. However, after one month, no significant difference was found between the patients. ROC curve showed MECP2 had the potential as a diagnostic biomarker for PHN. In conclusion, higher serum MECP2 levels are associated with a more severe pain condition and increased release of inflammatory factors.

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## Importancia clínica de la proteína 2 de unión a metil-CpG (MECP2) en la neuralgia posherpética: un estudio observacional.

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**Palabras clave:** MECP2; neuralgia posherpética; factores inflamatorios; calidad de vida.

**Resumen.** El objetivo de este estudio fue investigar la importancia clínica de la MECP2 en pacientes con neuralgia posherpética (NPH). Este estudio observacional prospectivo incluyó 319 pacientes con NPH entre abril de 2017 y diciembre de 2019. La calidad del sueño y la calidad de vida de los pacientes se evaluaron con la escala de calidad del sueño de Pittsburgh y la escala SF - 36, respectivamente. Los niveles séricos de MECP2, PCR, IL-6 y TNF-α fueron determinados por ELISA. Se utilizó la escala visual analógica (EVA) para evaluar la intensidad del dolor. Los niveles de MECP2 en pacientes con NPH aumentaron significativamente en comparación con los pacientes sin NPH. El nivel sérico de MECP2 fue más alto en pacientes con dolor grave y el más bajo en pacientes con dolor leve. Además, la incidencia de dolor grave en pacientes con baja expresión de MECP2 fue significativamente menor que en pacientes con alta expresión de MECP2. Además, los niveles séricos de PCR, IL-6 y TNF-α aumentaron significativamente en pacientes con NPH, y se incrementaron con el aumento del grado de dolor. Los niveles séricos de PCR, IL-6 y TNF-α en pacientes con NPH se correlacionaron positivamente con los niveles séricos de MECP2. Antes del estudio, los pacientes con niveles más bajos de MECP2 tenían puntuaciones significativamente más altas de SF - 36, y puntuaciones más bajas de Pittsburgh y EVA que los pacientes con niveles más altos de MECP2. Sin embargo, no se encontraron diferencias significativas entre los pacientes un mes después. Las curvas ROC mostraron que la MECP2 podría ser un biomarcador de diagnóstico para la NPH. En general, los niveles séricos más altos de la MECP2 se asociaron con condiciones de dolor más graves y un aumento de la liberación de factores inflamatorios.

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### INTRODUCTION

Postherpetic neuralgia (PHN) is a common complication after an acute episode of herpes zoster, with an estimated incidence of 5∼20% in herpes zoster patients, especially in elderly patients [1-3]. Studies report that PHN can last for months to years, seriously affecting people's quality of life [4]. There are many risk factors to influence the incidence of PHN [5]. Generally, the PHN is thought to be due to the immune/inflammatory response by the reactivation and migration of varicella zoster virus [6,7]. Since pain is the most common symptom of PHN, both inflammation and pain related factors are of great significance in PHN investigation.

Methyl-CpG binding protein 2 (MECP2), a kind of protein that can bind methylated DNA, is thought to play important roles in nervous system diseases like seizure [8], and is also associated with pain [9]. It is found that the deficiency of MECP2 in forebrain excitatory neurons could lead to cortical hyperexcitation and seizures [10]. However, overexpression of MECP2 resulted in higher susceptibility

toward seizures [11]. Furthermore, MECP2 is found to be elevated in several pain and inflammation conditions [12, 13]. Generally, an increased MECP2 level is accompanied with nerve injury, like dorsal root ganglia injury and increased pain sensitivity [14]. However, up to now, there is no study focusing on the role of MECP2 in PHN.

In the present study, we performed a prospective observational research to investigate the clinical significance of MECP2 in PHN patients. This study might provide a new research target and biomarker for PHN.

## MATERIAL AND METHODS

### Patients

This prospective observational study enrolled 319 patients with and without postherpetic neuropathy from April 2017～December 2019. The diagnosis of herpes zoster was established according to the Chinese Consensus of Herpes Zoster [15]. The diagnosis of PHN was determined according to the Chinese expert consensus on diagnosis and treatment of postherpetic neuralgia [16]. Briefly, the herpes zoster diagnostic criteria were defined as patients with irregular erythema occurred in a certain nerve distribution area, followed by a majority or cluster of millet to mung bean sized herpes, which quickly turned into blisters and was accompanied by neuralgia. The diagnostic criteria of PHN were defined as after the skin lesions of herpes zoster subsided, the patient developed local pain, pruritus and paresthesia for more than one month. The inclusion criteria were: 1) all patients were diagnosed as PHN according to the above criteria and didn't receive any treatment before; 2) the patients showed abnormal pain and touch feeling distributed by innervation area and sometimes showed skin pigmentation; 3) the pain types were as sharp pain or persistent burning pain, or tight bundle pain; and 4) patients showed other discomfort on lesion position after nerve injury, including itching, tight feeling and ant feeling. The following patients were excluded: 1) patients with severe inflammation diseases, such as pneumonia; 2) patients with fractures or other severe system diseases like myocardial infarction or stroke within three months before the study; 3) patients with other neuralgia like intercostal neuralgia, cephalalgia nervosa, post-stroke neuralgia, etc. All patients received routine strategy therapy including anti-pain treatment like treatment with pregabalin (150 mg×2/d for 14 d) or carbamazepine (100 mg/d for 14 d), and the grade of pain was recorded by the patients in awake state. Additionally, serum samples and medical records were collected from the 319 herpes zoster patients whose skin lesions of herpes zoster subsided without PHN. The inclusion of herpes zoster patients without PHN was according to the above diagnostic criteria of herpes zoster as well as the above inclusion criteria. All participants signed a written informed consent. The ethic approval was obtained from the Ethic Committee of the First Affiliated Hospital of Nanchang University and a written informed consent was obtained from all patients.

### Measurement of MECP2 and inflammatory factors

Blood samples of all PHN patients were collected at the day they came to the outpatient department. The samples were collected in tubes without anticoagulant and were centrifuged at 12000 g for 20 min. The serum levels of MECP2, CRP, IL-6 and TNF-α were tested using commercially available enzyme linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The kits used were MECP2 (MYBioSource, cat. No. MBS2515729), CRP (BOSTER Bio, cat. No. EK1316), IL-6 (BOSTER Bio, cat. No. EK0410) and TNF-α (BOSTER Bio, cat. No. EK0525).

### Data collection

The pain condition of patients was evaluated at the time of diagnosis using the visual analogue scale (VAS). The severity of the pain condition of PHN patients were defined as: mild

VAS 1~3, moderate VAS 4~6, or severe VAS 7~10. Patient's demographic data including age, sex, BMI, complications, and clinical characteristics including disease course, rash types and sites of skin involvement, were collected. The patients' sleep quality and quality of life were evaluated using the Pittsburgh sleep quality score and the SF-36 scale before the study and after one month of treatment, respectively.

**Statistical analysis**

All data distributed normally were expressed by means ± SD. The distribution of the data was analyzed by Kolmogorov-Smirnov method. Comparison between the two groups was conducted by t test and comparison among three or more groups was performed using one-way analysis of variance (ANOVA) followed by Tukey post hoc test. Rates were compared by Chi square test. ROC curve was used for diagnostic value of MECP2 in PHN patients. All calculation was performed using SPSS 18.0 (SPSS Inc., Chicago, USA) and GraphPad 6.0 (GraphPad Software, San Diego, CA, USA).

## RESULTS

**MECP2 was upregulated in PHN patients**

The basic clinical characteristics of all patients are listed in Table 1. There were no significant differences in age, sex, BMI and complications between the PHN patients and the controls. The mean VAS score of all PHN patients was 3.38±2.26. Serum levels of MECP2 were determined in PHN patients and the herpes zoster patients without PHN. It was found that the levels of MECP2 were significantly increased in PHN patients when compared with the non-PHN patients ($P<0.05$, Fig. 1).

**Table 1**
Basic characteristics of all participants.

| Variables | PHN, n=319 | non-PHN, n=319 | P value |
|---|---|---|---|
| Age, y | 58.32±8.71 | 58.71±8.88 | 0.571 |
| Sex, male (%) | 179 (56.11) | 170 (53.29) | 0.689 |
| BMI, kg/m$^2$ | 25.33±3.81 | 25.34±3.79 | 0.985 |
| Complications, n (%) | | | 0.848 |
| Diabetes | 33 (10.34) | 38 (11.91) | |
| Hypertension | 56 (17.55) | 47 (14.73) | |
| Current smoker | 112 (35.11) | 108 (33.86) | |
| Disease course (PHN), Mon | 4.40±1.12 | - | |
| Sites of skin involvement, n (%) | | | 0.908 |
| Lumbosacral nerve area | 154 (48.28) | 161 (50.47) | |
| Intercostal nerve area | 61 (19.12) | 52 (16.30) | |
| Trigeminal nerve area | 43 (13.48) | 37 (11.60) | |
| Brachial plexus area | 25 (7.84) | 30 (9.40) | |
| Perineal nerve area | | | |
| VAS score | 3.38±2.26 | - | |
| Distribution of VAS score, n (%) | | | |
| Mild | 152 (47.65) | - | |
| Moderate | 98 (30.72) | - | |
| Severe | 69 (21.63) | - | |

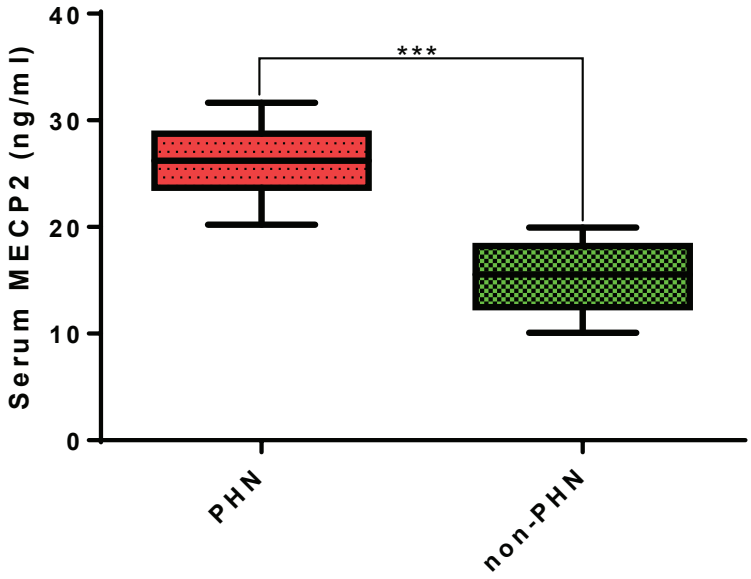


**Fig. 1.** Serum levels of MECP2 in PHN patients and the non-PHN.

**MECP2 was positively correlated with pain severity of PHN patients**

Then, levels of MECP2 were detected in PHN patients with different pain severities. As shown in Fig. 2, serum MECP2 levels were the highest in patients with severe pain, and were the lowest in patients with mild pain, and the difference was significant between the groups ($P<0.05$). The patients were then further divided into high MECP2 expression group and low MECP2 expression group according to the mean serum levels in PHN patients (45.83 ng/mL). It was found that the frequency of severe pain in patients with low expression of MECP2 was significantly lower than the patients with higher MECP2 expression ($P<0.05$, Table 2). Notably, patients with mild pain were found to be markedly decreased in patients with higher MECP2 than patients with higher MECP2 ($P<0.05$).

**Relationship between MECP2 and inflammatory factors in PHN patients**

To further investigate the role of MECP2 in PHN, the serum levels of inflammatory factors CRP, IL-6 and TNF-α were determined. It was found all these factors were markedly increased in PHN patients compared with the no-PHN patients ($P<0.05$, Fig. 3), and serum levels of CRP, IL-6 and TNF-α increased with the severity of pain in PHN patients ($P<0.05$), except for the difference of TNF-α between severe and moderate pain. The Pearson's correlation test showed that CRP, IL-6 and TNF-α were positively correlated with serum levels of MECP2 in PHN patients ($P<0.05$, Table 3).

**Association between MECP2 and quality of life of PHN patients**

The Pittsburgh sleep quality score and the SF-36 scale, as well as the VAS score were then evaluated before the study and after one month of treatment. It was found that before study, patients with lower MECP2 levels showed significantly higher SF-36 score and lower Pittsburgh and VAS scores than patients with higher MECP2 ($P<0.05$, Table 4). However, after one month, no significant differences were found between the patients.

**Diagnostic value of MECP2 in PHN**

Finally, we determined the diagnostic value of MECP2 for PHN in herpes zoster

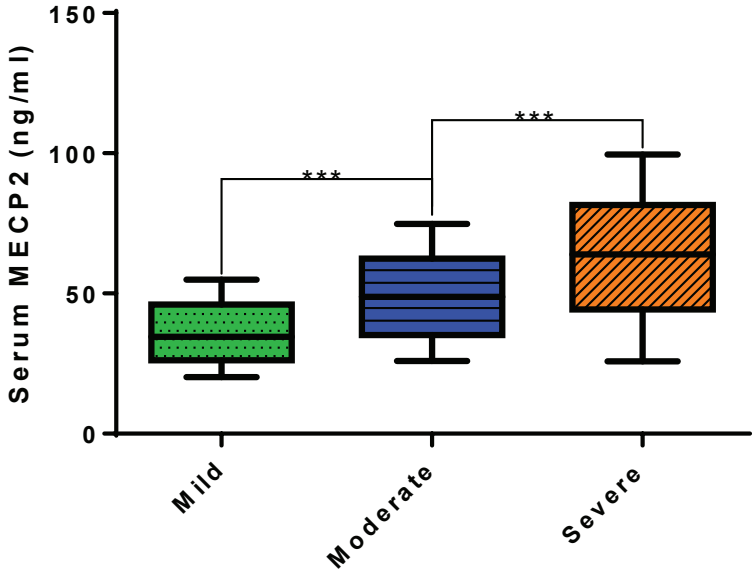


**Fig. 2.** Serum levels of MECP2 in patients with different pain severity.

**Table 2**
Pain severity in PHN patients with different expression of MECP2.

| Variables | Low MECP2, n=173 | High MECP2, n=146 | P value |
|---|---|---|---|
| VAS distribution, n (%) | | | <0.0001 |
| Mild | 113 (65.32) | 39 (26.71) | |
| Moderate | 43 (24.86) | 55 (37.67) | |
| Severe | 17 (9.83) | 52 (35.62) | |

patients. It was found that MECP2 has the potential as a biomarker for PHN diagnosis, with a ROC curve ACU, cutoff value 33.56 ng/mL, sensitivity 70.5%, specificity 65.5% (Fig. 4).

## DISCUSSION

Postherpetic neuralgia is a common complication after treatment of herpes zoster and may decrease the patients' quality of life. Since the prevention of PHN is an effective method to reduce the patients' pain after herpes zoster, biomarkers for diagnosis and prediction of PHN are also important. In the present study, we demonstrated that serum MECP2 was up-regulated in PHN patients and higher MECP2 was associated with a more severe pain condition, higher levels of inflammatory factors, and lower quality of life before treatment.

Rzeszotarska have reported that MECP2 is a factor associated with both inflammatory factors and pain [12]. Generally, most studies found that increased MECP2 is associated with increased pain sensitivity and increased pro-inflammatory factors. It was found in the mouse chronic pain model, that MECP2 was increased in S1 glutamate (GluS1) neurons and increased MECP2 was associated with increased neuronal activity and knockdown of MECP2 diminished the offspring pain sensitization, which was increased by overexpressing MECP2. In 2,4,6-trinitrobenzenesulfonic acid-induced- pelvic inflammation pain in a rat model, MECP2 was also

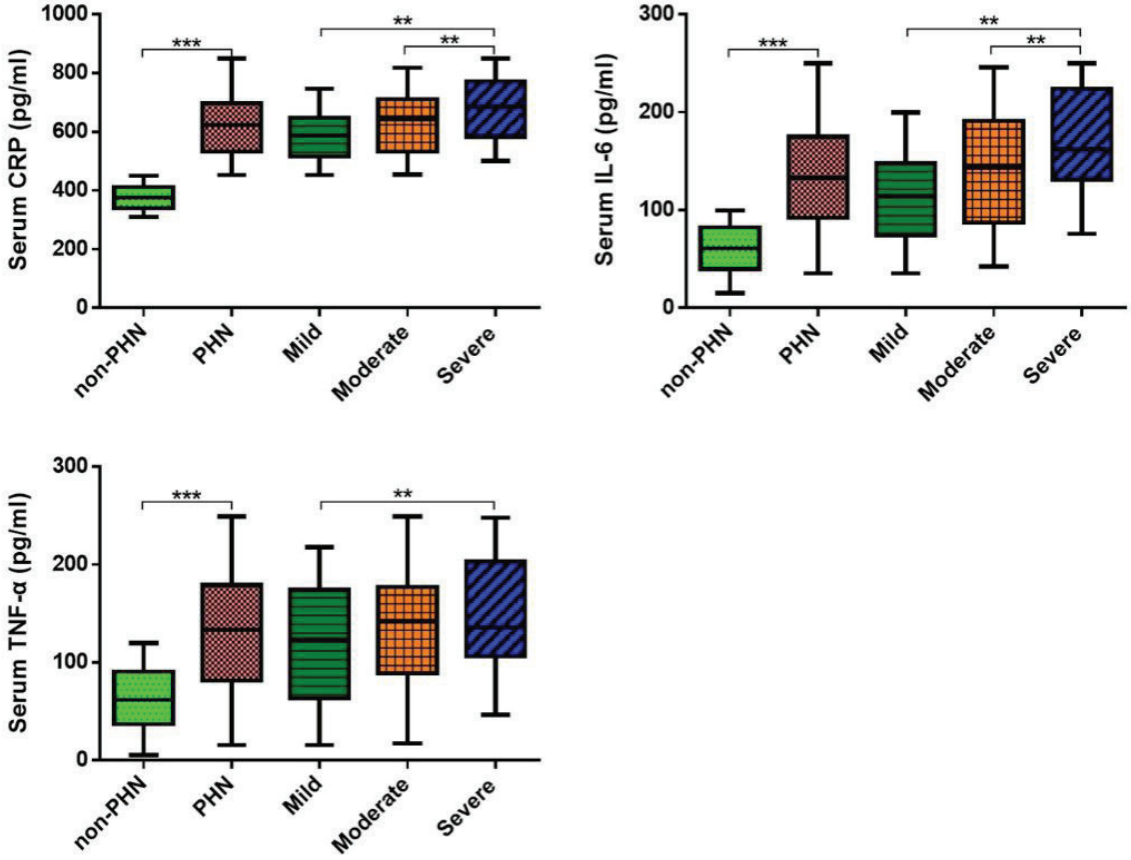


**Fig. 3.** Serum levels of CRP, IL-6 and TNF-α in non-PHN patients and PHN patients with different pain severity.

**Table 3**
Correlation between MECP2 and inflammatory factors in PHN patients.

| Factors | Pearson' correlation | P value |
|---|---|---|
| CRP | 0.495 | <0.001 |
| IL-6 | 0.471 | <0.001 |
| TNF-α | 0.354 | <0.001 |

found to be overexpressed in neurons and the increased MECP2 was accompanied with increased cAMP response element-binding protein [13]. In chronic constriction injury, global DNA methylation and MeCP2 expression were both increased in the rats' spinal cord, which could be decreased by intrathecal 5-azacytidine [17]. Besides, the deficiency of MECP2 resulted in an increase in neutrophil infiltration and anti-inflammatory factor IL-10, as well as decreased level of TNF-α [18]. The inhibition of MECP2 was also found to alleviate inflammation, while overexpression of MECP2 promoted inflammation response in different kinds of cells [19-21]. However, several studies also found positive results, demonstrating overexpression of MECP2 led to decreased acute mechanical pain, thermal pain in acute pain transduction and overexpression improved neuropathic pain [22]. In Rett syndrome, mutation and duplication of MECP2 both induce decreased pain sensitivity [9]. Besides, MECP2 deficiency might also exacerbate neuroinflammatory setting and autoreactive response during an autoimmune challenge [23]. In the present study, we observed that serum MECP2 was up-regulated in PHN patients and was associated with

**Table 4**
Association between MECP2 and quality of life of PHN patients.

| Variables | | Low MECP2, n=173 | High MECP2, n=146 | *P* value |
|---|---|---|---|---|
| VAS | Before | 3.38±2.26 | 5.40±2.54 | <0.0001 |
| | After 1 month | 1.99±0.63 | 2.11±0.65 | 0.0958 |
| SF-36 | Before | 63.87±7.87 | 62.01±8.39 | 0.0422 |
| | After 1 month | 73.13±7.45 | 73.12±7.00 | 0.9902 |
| Pittsburgh score | Before | 12.30±2.47 | 13.78±2.78 | <0.0001 |
| | After 1 month | 7.80±4.55 | 7.63±4.14 | 0.7293 |

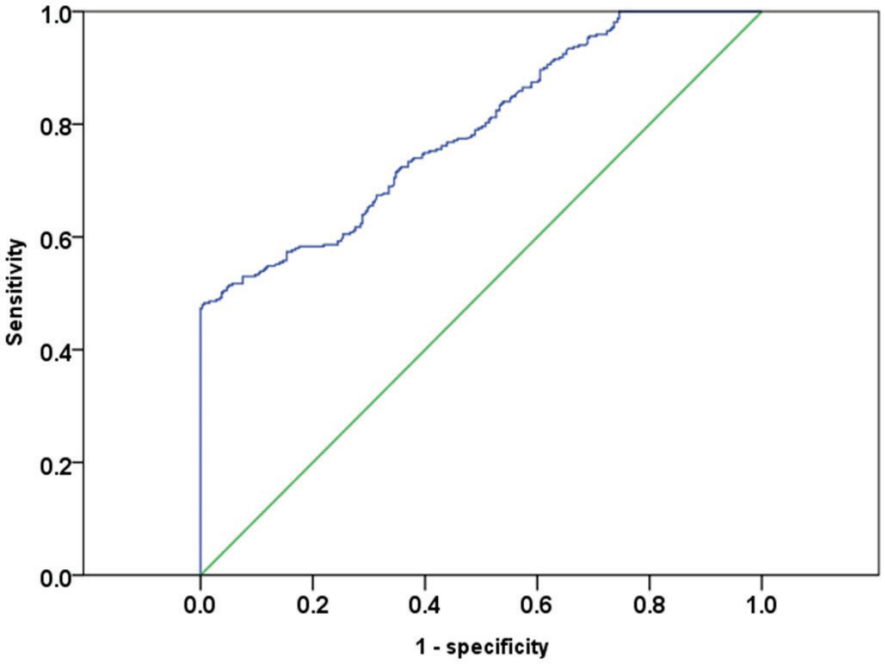


**Fig. 4.** ROC curve for diagnostic value of MECP2 in PHN.

patients' release of inflammatory factors and pain condition, which was consistent with most of the above researches. Since the relationship between MECP2 and pain remains controversial, the elevated MECP2 can be either as a pro-inflammatory factor or a compensatory mechanism to reduce inflammation and pain. In both of the two conditions, MECP2 can be increased in pain and inflammation. However, this speculation needs more studies to further confirm. Besides, we also found that serum MECP2 was associated with patients' quality of life before study. However, different levels of MECP2 didn't influence the quality of life after one-month treatment.

Inflammation is closely related to the pain, including correlated with PHN. It was reported that PHN patients showed higher levels of IL-1β and lower levels of BDNF in cerebrospinal fluid [24]. Another study found the expression of IL-1α, IL-16, intercellular adhesion molecule-1, and monocyte chemoattractant protein-1 was elevated in skin of PHN patients [25]. Besides, Üçeyler *et al.* demonstrated that in some PHN patients, the ex-

pression of IL-10 and IL-6 on skin might increase than unaffected skin [26]. In our study, we also found that inflammatory factors CRP, IL-6 and TNF-α were increased in PHN patients. Besides, we demonstrated that serum MECP2 levels were positively correlated with serum inflammatory factors. All these results indicated that increased MECP2 was correlated with increased inflammation and pain of PHN patients.

The present study includes some limitations, The VAS scale and Pittsburg sleep quality are subjective scales, these factors depended of the subjective appreciation of the individual, so there was no confirmation that the levels of MECP2 correspond to the exact grade of pain because each subject can express the pain sensation in different form and may be an inexact measure of pain´s classification. In addition, the sample size of the study is small and we didn't investigate the molecular mechanism for MECP2 in PHN, and how the phosphorylated-MECP2 changes is also unclear, which need further investigations to reveal.

In conclusion, this observational study demonstrated that higher serum MECP2 levels were associated with a more severe pain condition and increased release of inflammatory factors, as well as a poorer quality of life of PHN patients before treatment. This study provided a novel potential biomarker for diagnosis of PHN.

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### Declaration of conflict of interest

All authors declare no conflict of interest.

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### Authors' contributions

Each author has made an important scientific contribution to the study and has assisted with the drafting or revising of the manuscript.

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