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ORIGINAL ARTICLE

Elevated Plasma Vitamin D Levels are Associated with Pain Characteristics and Duration in Patients with Postherpetic Neuralgia

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SUMMARY

Background: **Aim is to analyze the correlation between plasma vitamin D (VD) level and pain characteristics and duration in patients with postherpetic neuralgia (PHN).**
Methods: **116 patients with PHN were prospectively collected as the PHN group, and another 102 non-PHN patients were selected as the control group. The plasma VD levels were detected by enzyme-linked immunosorbent assay. The factors affecting the plasma VD levels of PHN patients were analyzed by one-way and logistic regression analysis. The correlation between the plasma VD levels of the PHN patients with pain characteristics and duration was analyzed by Pearson correlation.**
Results: **Plasma VD levels [(26.63 ± 2.95) ng/mL] in patients in the PHN group were significantly lower compared with those in the control group [(31.39 ± 2.98) ng/mL] ($p < 0.001$). Plasma VD level was associated with LANSS score (OR = 1.302), pain type (OR = 3.218) and pain duration (OR = 1.392) in patients with PHN (all $p < 0.01$). Plasma VD levels were negatively correlated with LANSS score ($r = -0.346$) and pain duration ($r = -0.381$) in patients with PHN.**
Conclusions: **Plasma VD levels are significantly lower in patients with PHN, and plasma VD levels determine pain characteristics and duration.**
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KEYWORDS

Postherpetic neuralgia, plasma vitamin D, pain characteristics, pain duration, correlation

INTRODUCTION

Herpes zoster (HZ) is an infectious disease involving the nerves and skin caused by varicella-zoster virus and is contagious [1]. HZ is often accompanied by acute pain and itching, and although the rash and associated pain are self-limiting, a significant proportion of patients with HZ develop chronic pain after the disease has healed, called postherpetic neuralgia (PHN) [2]. In PHN, the painful area is often more extensive than the herpes-affected region and typically occurs in the unilateral intercostal, trigeminal, or cervical nerves, with

the pain described as burning, electric shock-like, cutting, pinprick, or tearing [3]. The characteristics of pain are categorized into dull sensation, abnormal pain, sensory anomalies, and increased nociceptive sensitivity [4]. It is generally accepted that the mechanisms of PHN are mainly related to abnormalities of CNS conduction, central sensitization, peripheral neuroinflammatory responses, and deafferentation after nerve damage [5,6]. Clinically, antidepressants, nonsteroidal anti-inflammatory drugs, and sympathetic nerve blockers are commonly used to relieve PHN, but these treatments usually fail to prevent the development of PHN [7]. In addition, there is a high degree of heterogeneity in the intensity and duration of pain in PHN, with pain lasting for years or even a lifetime in some patients [8]. This clinical heterogeneity suggests that the pathophysiological process of PHN may be regulated by multiple biomarkers, and exploring the molecular mechanisms associated with pain characteristics is important for optimizing individualized treatment strategies.

Vitamin D (VD), as a steroid hormone with a wide range of physiologic functions, has received much attention for its relationship with chronic pain disorders [9-12]. VD exerts immunomodulatory, neuroprotective, and anti-inflammatory effects by binding to the VD receptor (VDR) [13]. As a central hub for mood, emotion, and pain perception, the amygdala is rich in VDR, which, upon increased VD levels, boost opioid signaling and subsequently alleviate pain [14, 15]. Low VD increases neuropathic pain in patients with diabetes and rheumatoid arthritis [16]. It has been proposed that VD may serve as a potential adjuvant in the treatment of HZ, and that insufficient VD reserves may impair the body's immunity to the virus, thereby promoting VZV replication in the dorsal root ganglion and inducing the development of PHN in patients through persistent neuroinflammation [17].

The ongoing investigation into VD has highlighted its connection with PHN as a key research area, but the relationship between VD levels and pain characteristics remains unanalyzed. This study analyzed the correlation between plasma VD levels and pain characteristics and duration in patients with PHN to make early prediction of PHN and active intervention and to provide a theoretical basis for clinical treatment.

MATERIALS AND METHODS

Study population

The study size was determined by the number of cases examined during the study period. The clinical data of 116 PHN patients admitted to Taihe Hospital from January 2021 to December 2023 were selected. Inclusion criteria: 1) those who met the diagnostic criteria for PHN [17]: persistent pain for ≥ 90 days after the diagnosis of HZ, 2) those aged ≥ 18 years, 3) those who were not treated with any VD supplements in the past year, and 4) those who had complete clinical data. Exclusion criteria: 1) combined with severe heart, brain, kidney and other organ dysfunction, 2) combined with acute and chronic infections, 3) combined with acute and chronic pain caused by other diseases, 4) combined with malignant tumors and autoimmune system diseases, etc., 5) combined with severe psycho-neurological lesions, patients who could not cooperate. This study was reviewed and approved by the Ethics Committee of Taihe Hospital (No. 20190617HB5241). All patients were informed about the study and signed an informed consent form. This study was a hospital-based prospective study consisting of a case-control study and a cross-sectional study. A case-control study was conducted to automatically select 102 gender- and age-matched non-PHN patients from the electronic medical database of Taihe Hospital. In the cross-sectional analysis, PHN patients were included. The grouping flowchart is shown in Figure 1.

Clinical data collection

Basic information such as age, gender, smoking, alcohol consumption, body mass index, duration of disease, hypertension and diabetes mellitus were collected from the patients. Pain duration refers to the time span from when HZ was diagnosed to when the pain ended without taking any painkillers. PHN pain types mainly included ① persistent pain without stimulation (usually burning sensation), ② intermittent pain without stimulation (usually stabbing, cutting, or electric shock-like), and ③ pain disproportionate to stimulation (nociceptive hypersensitivity) [18]. The enrolled patients filled in the Chinese version of the LANSS scale by themselves, and the questions in the scale were interpreted by a uniformly trained investigator when necessary. The examination items in the LANSS scale were completed by the investigator. The hyperalgesia test examined the pain response by gently rubbing the non-painful site and the painful site with absorbent cotton. To measure the change in needling threshold, a 23-gauge needle (blue needle) fitted with a 2-mL syringe was used and gently placed on the non-painful site and the painful site successively. To prevent errors, measurements were taken using just the needle's gravitational force, without applying any external force. With a total LANSS score of 24, a score under 12 signifies non-neuropathic pain, while a score of 12 or more signifies neuropathic pain [19].

Evaluation of the severity of HZ

The severity of HZ was categorized as “mild,” “moderate,” or “severe” based on the rash area, rash characteristics, pain severity, and the degree of sensory abnormality or dullness. In mild cases of HZ, the rash area is less than 25% of the ganglion, appeared as papules, and the pain is mild or not observed, not disrupting daily life. In moderate HZ cases, the rash occupies 25% to 75% of the ganglion, appearing as papules and vesicles, with pain that disrupts daily life and significantly dull sensation. In severe cases of HZ, lesions occupy more

Table 1. Baseline characteristics of patients with PHN.

Variables	PHN group (n = 102)	Non-PHN group (n = 102)	p-values
Age	56.39 ± 10.26	58.28 ± 10.82	0.202
Gender			
Male	64 (62.75%)	58 (56.86%)	0.475
Female	38 (37.25%)	44 (43.14%)	
BMI (kg/m2)	24.01 ± 2.11	23.64 ± 2.14	0.224
Smoking	54 (52.94%)	50 (49.02%)	0.675
Drinking	42 (41.18%)	52 (46.08%)	0.572
Comorbid diabetes mellitus	25 (24.51%)	21 (20.59%)	0.616
Comorbid hypertension	38 (37.25%)	33 (32.35%)	0.557
Site of onset			
Extremities	29 (28.43%)	34 (33.33%)	0.73
Trunk	36 (35.29%)	31 (30.39%)	
Face	22 (21.57%)	25 (24.51%)	
Mixed	15 (14.71%)	12 (11.77%)	
Herpes zoster typing			
Gangrenous or hemorrhagic	33 (32.35%)	21 (20.59%)	0.042
Bullous	40 (39.22%)	36 (35.29%)	
Generalized or tonic	29 (28.43%)	45 (44.12%)	
Glucocorticoid therapy	72 (70.59%)	88 (86.27%)	0.007
Herpes zoster severity			
Mild	20 (19.61%)	68 (66.67%)	< 0.001
Moderate	35 (34.31%)	20 (19.61%)	
Severe	47 (46.08%)	14 (13.72%)	
Pain type			
Pain disproportionate to stimulation	37 (36.27%)	17 (16.67%)	< 0.001
Persistent pain without stimulation	45 (44.12%)	29 (28.43%)	
Intermittent pain without stimulation	20 (19.61%)	56 (54.90%)	
Pain duration	6 (3, 8)	3 (2, 5)	< 0.001

than 75% of the area, comprising necrosis and ulcers, with pain that is severe enough to disturb sleep and results in noticeable sensory hypersensitivity or numbness.

Plasma VD assay

Blood samples were collected within 2 hours of admission and plasma was separated, frozen in liquid nitrogen, and stored at -80°C. Every sample was processed in the same manner within individual batches, and the laboratory team was not informed about the case, control, or quality control samples. The mean intra-assay variation was ≦ 9%. Plasma 25-OH-D was measured using human (25-OH-D) ELISA (Epitope Diagnostics Co., USA). Levels below 20 ng/mL were deemed low, between 20 and 30 ng/mL were seen as insufficient, and above 30 ng/mL were regarded as normal [20].

Follow-up

All patients were followed up for 1 year after discharge from the hospital and were instructed to record the time of pain disappearance. Patients were followed up in the hospital outpatient clinic every month for the first 3 months, and every 3 months for the next 9 months by phone, WeChat and outpatient visits.

Statistical analysis

Statistical analysis was performed using SPSS26.0 software. Normally distributed measurements were expressed as (x ± s), and comparisons were made using the independent samples *t*-test. Non-normally distributed measurements were expressed as median and interquartile spacing [M (P25, P75)], and comparisons were made using the Mann-Whitney U rank-sum test. Enumeration information was expressed as [n (%)], and comparisons were made using the χ^2 test. ANOVA was

Table 2. Univariate analysis of plasma vitamin D levels in the PHN group of patients.

Variables	Cases	Plasma vitamin D (ng/mL)	p-value
Age			
< 60	61	27.91 ± 3.50	0.002
≥ 60	41	25.82 ± 2.83	
Gender			
Male	64	26.89 ± 3.27	0.418
Female	38	27.43 ± 3.61	
BMI			
≤ 24 kg/m^2	45	26.40 ± 2.87	0.079
＞ 24 kg/m^2	57	27.59 ± 3.70	
Smoking			
Yes	54	27.55 ± 3.41	0.219
No	48	26.53 ± 3.33	
Drinking			
Yes	42	26.64 ± 3.12	0.295
No	60	27.37 ± 3.57	
Diabetes mellitus			
Yes	25	27.34 ± 3.61	0.648
No	77	26.98 ± 3.34	
Comorbid hypertension			
Yes	38	27.69 ± 3.55	0.159
No	64	26.70 ± 3.27	
Site of onset			
Extremities	29	25.89 ± 3.11	0.138
Trunk	36	27.81 ± 2.82	
Face	22	27.07 ± 3.84	
Mixed	15	27.56 ± 4.16	
Herpes zoster typing			
Gangrenous or hemorrhagic	33	28.36 (25.03, 30.54)	0.033
Bullous	26	26.13 (23.91, 28.16)	
Generalized or tonic	29	27.92 (24.07, 29.31)	
Glucocorticoid therapy			
Yes	72	27.89 ± 3.21	< 0.001
No	30	25.09 ± 3.02	
LANSS score			
< 12	33	28.63 ± 3.51	0.001
≥ 12	69	26.32 ± 3.09	
Herpes zoster severity			
Mild	20	28.60 ± 3.40	0.007
Moderate	35	27.63 ± 3.00	
Severe	47	26.00 ± 3.39	
Pain type			
Pain disproportionate to stimulation	37	28.92 (28.21, 32.14)	< 0.001
Persistent pain without stimulation	45	26.43 (23.95, 28.61)	
Intermittent pain without stimulation	20	26.15 (23.67, 28.36)	
Pain duration			
≤ 6 months	58	27.99 ± 3.69	0.001
> 6 months	44	25.86 ± 2.53	

Table 3. Multifactorial logistic regression analysis of plasma vitamin D levels in patients in the PHN group.

Factors	B value	SE value	Wald χ^2	OR (95% CI)	p-value
Age	0.067	0.037	3.205	1.069 (0.994 - 1.151)	0.073
Herpes zoster typing	0.029	0.461	0.004	1.029 (0.417 - 2.538)	0.951
Glucocorticoid therapy	-0.921	0.942	0.954	0.398 (0.063 - 2.526)	0.329
LANSS score	0.256	0.111	5.276	1.292 (1.038 - 1.607)	0.022
Herpes zoster severity	0.089	0.484	0.034	1.093 (0.423 - 2.823)	0.855
Pain type	1.113	0.542	4.22	3.044 (1.052 - 8.806)	0.04
Pain duration	0.338	0.154	4.801	1.402 (1.036 - 1.896)	0.028

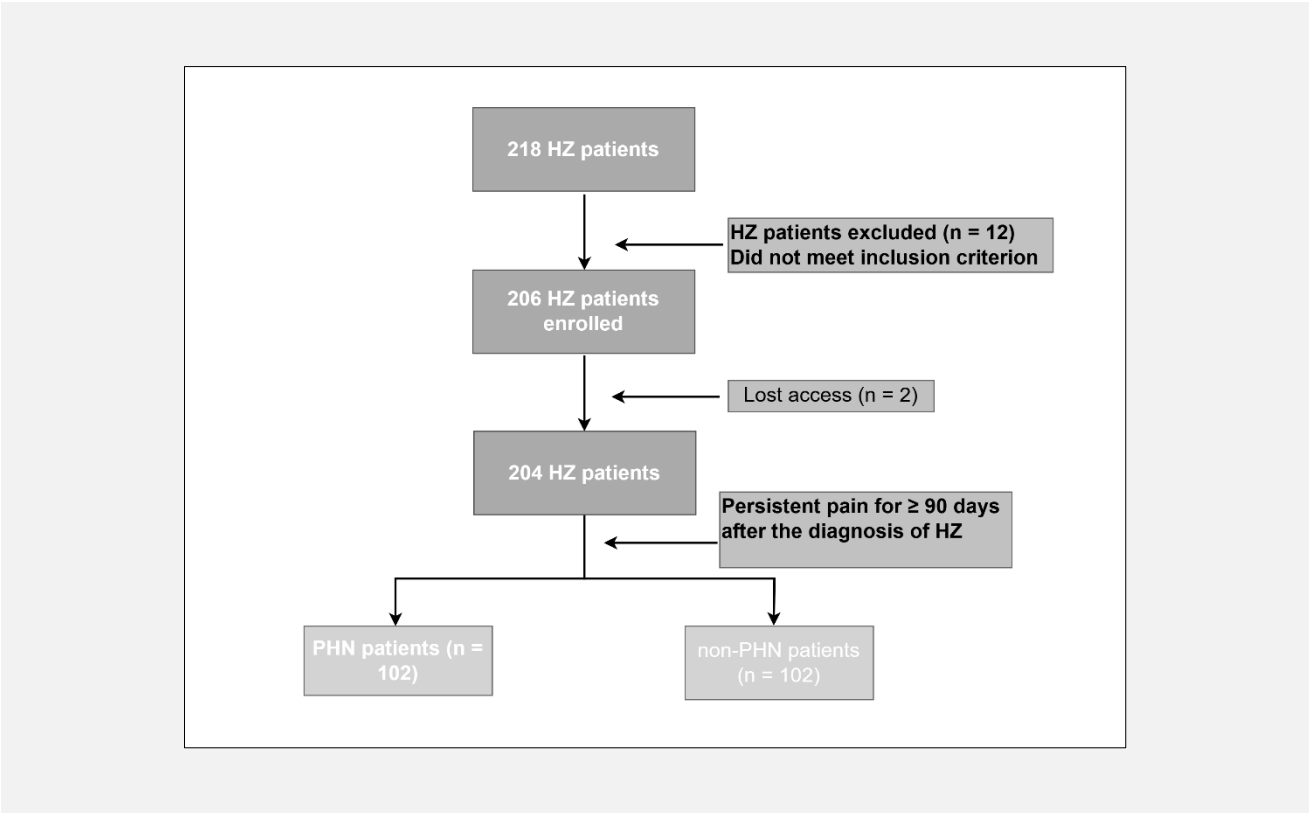

Figure 1. The flowchart graph of our study.

This study enrolled a total of 218 subjects, comprising 116 PHN patients and 102 non-PHN controls selected through a case-control design. Among the 116 PHN patients, 14 were excluded due to loss to follow-up or failure to meet inclusion criteria, resulting in 102 PHN patients ultimately included in the final analysis.

employed for comparisons between multiple groups. For correlation, the Pearson correlation test was applied, and multifactorial analyses were conducted using the logistic analysis method, $p < 0.05$ was taken as statistically significant difference.

RESULTS

Clinical data of patients with PHN

All patients were treated with antiviral drugs prior to the baseline assessment. Among all participants, 122 (61.88%) were males and 82 (38.12%) were females with a mean age of 57.77 ± 10.76 years. The HZ pa-

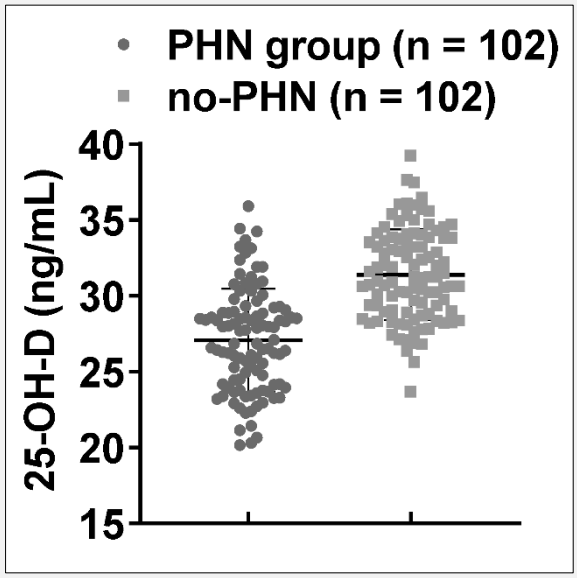

Figure 2. Plasma VD levels in patients with PHN.

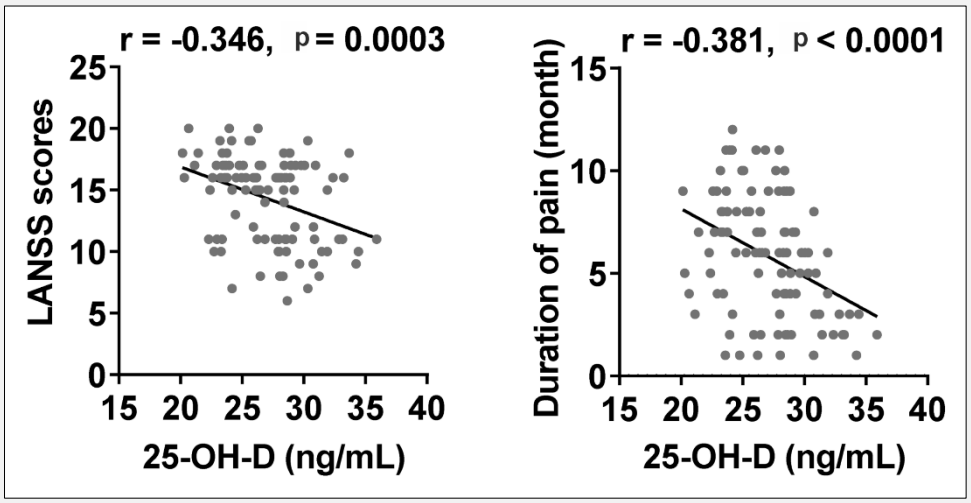

Figure 3. Correlation of plasma VD levels with LANSS scores and pain duration in PHN patients.

tients were categorized into PHN group (n = 102) and non-PHN group (n = 102). Statistically significant differences were found among these patients in terms of HZ typing, glucocorticoid treatment, HZ severity, pain type, and pain duration ($p < 0.05$). There were no significant differences between groups for age, gender, BMI, history of smoking, alcohol consumption, history of hypertension, history of diabetes mellitus, and site of on-

set. Table 1 shows the demographic and clinical characteristics of the two groups.

Plasma VD levels in patients with PHN

Plasma VD was [(26.63 ± 2.95) ng/mL] in the PHN group and [(31.39 ± 2.98) ng/mL] in the non-PHN group. Plasma VD levels were significantly higher in the PHN group, and the difference was statistically significant ($t = 10.94$, $p < 0.01$), as shown in Figure 2. Plasma VD deficiency (≦30 ng/mL) occurred in 85 patients in the PHN group, or 83.33% of the PHN patients, compared with only 35 patients in the non-PHN group, or 34.3% of that group.

Univariate analysis of plasma VD in PHN patients

Through assignment, categorical variables were generated, including age (< 60 = 0, ≥ 60 = 1), gender (female = 0, male = 1), BMI (≦ 24 kg/m^2 = 0, > 24 kg/m^2 = 1), smoking (yes = 1, no = 0), drinking (yes = 1, no = 0), diabetes mellitus (yes = 1, no = 0), and hypertension (yes = 1, no = 0), site of onset (extremities = 1, trunk = 2, face = 3, mixed = 4), HZ typing (gangrenous or hemorrhagic = 1, bullous = 2, generalized or tonic = 3), glucocorticoid therapy (yes = 1, no = 0), LANSS score (< 12 = 0, ≥ 12 = 1), HZ severity (mild = 1, moderate = 2, severe = 3), pain type (pain disproportionate to the stimulation, persistent pain without stimulation , intermittent pain without stimulation), and pain duration (≦ 6 months = 0, > 6 months = 1). Univariate analysis showed that the differences in plasma VD levels in PHN patients were statistically significant between age, HZ typing, glucocorticoid treatment, LANSS, HZ severity, pain type, and pain duration (all $p < 0.05$), as shown in Table 2.

Multifactorial analysis of plasma VD in patients with PHN

Statistically significant factors ($p < 0.05$) in the univariate analysis were included in the multifactorial logistic regression analysis, and the results showed that LANSS score (OR = 1.302), pain type (OR = 3.218), and pain duration (OR = 1.392) in patients with PHN were the influencing factors of plasma VD levels, as shown in Table 3.

Correlation of plasma VD with pain characteristics and duration in patients with PHN

Pearson's correlation analysis showed that plasma VD levels were negatively correlated with LANSS score ($r = -0.346$) and pain duration ($r = -0.381$) in patients with PHN (all $p < 0.05$), as shown in Figure 3.

DISCUSSION

PHN is an intractable disease that can last for more than 4 months and is characterized by persistent or intermittent burning, tingling, or severe pain, which seriously affects the quality of life of patients and can also lead to complications such as anxiety, depression, and sleep disorders, and shorten the life expectancy of elderly patients [21]. The incidence of PHN is increasing, but the etiology and pathogenesis of the disease are not yet fully understood, and the treatments still have limitations [22]. It is generally recognized that the treatment of PHN is a long and arduous process, and there are still many patients who are insensitive to all therapies. Less than 50% of PHN patients can achieve 50% pain relief through conservative drug treatment [23]. Patients experience large differences in drug effectiveness and safety, and some are required to discontinue their medications because of tolerance or severe adverse reactions [23]. Other treatments, including physical therapy, nerve block therapy, Chinese medicine therapy, and spinal cord electrical stimulation therapy, do not yield very satisfactory overall therapeutic results [24]. Clinically, patients with PHN suffer from pain for months or even years, and their health and quality of life are affected [25].

VD deficiency is not only involved in bone destruction, neuromuscular dysfunction, inflammation, and chronic diseases [26]. It has been found that patients with HZ have low serum levels of VD [27]. In this study, plasma VD levels were significantly lower in patients with PHN compared with controls. VD deficiency was found in 83.33% (85/102) of PHN patients. These findings suggest that VD deficiency is common in patients with PHN, but the role of VD has not been sufficiently emphasized in the current clinical management of PHN. Therefore, further studies on the role of VD in the pathogenesis of PHN are necessary.

The LANSS scale consists of 7 items (5 symptoms and 2 physical findings) and is a questionnaire-based assessment tool used to differentiate between neuropathic and injurious pain. The LANSS scale, initially utilized by BENNETT [19], is concise and simple to evaluate. A score of 12 or higher indicates that neuropathic mechanisms may contribute to the pain, and its validity has been verified by several studies [28,29]. A total of 102 patients with PHN were included in this study, and the prevalence of PHN as assessed by the LANSS scale was found to be 67.65% (69/102). In the study by Wang et al. 93 out of 120 PHN patients had LANSS questionnaire scores ≥ 12, with an overall accuracy rate of 77.5% [30]. However, pain in patients with PHN is often overlooked in clinical practice, and there is little literature on the risk factors for pain in patients with PHN and treatment options. A meta-analysis has shown that VD supplementation significantly relieves pain in patients with long-term chronic pain [31].

PHN can cause a chronic pain syndrome, which produces persistent or intermittent pain in the absence of stimulation and is characterized by neuropathic pain, especially pronounced mechanically abnormal pain and thermal hyperalgesia [32]. In patients with PHN, the severity of the type of pain decreased in the order of pain disproportionate to stimulation, persistent pain without stimulation, and intermittent pain without stimulation,

with the percentage of patients decreasing in that order. Most patients had the more severe type of pain. In addition, pain type was negatively correlated with VD levels. A recent study has found that PHN patients with VD deficiency have higher pain levels and longer pain duration, while the degree of VD deficiency in PHN patients is moderately correlated with increased severity and pain duration [33]. Our study found that PHN patients with longer pain duration possessed lower VD levels. The negative correlation between VD and pain duration reveals that chronic pain states affect VD metabolic homeostasis, while changes in VD levels may also sway pain duration.

In conclusion, plasma VD levels in patients with PHN have a relationship with LANSS scores, pain type, and pain duration, but the results still need to be validated by a large sample size of clinical data. VD is safe and low-cost, and can be further investigated as a potential drug against PHN. More prospective, multicenter, large-scale randomized controlled research is required to investigate supplementation in the HZ or PHN phase, define safe dosage ranges, consider its use alone or in combination, and prevent VD toxicity.

Availability of Data and Materials:

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics Approval:

The present study was approved by the Ethics Committee of Taihe Hospital, Affiliated Hospital of Hubei University of Medicine (No. 20190617HB5241) and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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