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Validity of Plasma Neuropeptide Y in Combination with Clinical Factors in Predicting Neuralgia Following Herpes Zoster

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Background: Numerous lines of evidence suggest that neuropeptide Y (NPY) is critically involved in the modulation of neuropathic pain. Postherpetic neuralgia (PHN) is characterized by prolonged duration, severe pain, and significant treatment resistance, substantially impairing patients' quality of life. This study aims to evaluate the potential of plasma NPY levels in patients with PHN as a predictive biomarker for the development of this condition.

Methods: Between February 2022 and December 2023, 182 patients with herpes zoster (HZ) were recruited. Thirty-eight volunteers with no history of HZ were also recruited as controls. Clinical factors, NPY, brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) were assessed within 3 days of healing. Logistic regression analysis was used to predict the development of PHN.

Results: NPY levels were lower and BDNF and NGF were higher in HZ patients than those in controls. Only NPY levels were lower in patients with PHN (n = 59) compared with those without PHN (n = 123). Age, acute pain severity, and rash area were independent predictors of PHN, as were NPY levels. The area under the curve (AUC) to predict the development of PHN based on the combination of NPY levels and clinical factors was 0.873 (95% CI: 0.805 to 0.940), and the AUC was 0.804 based on only clinical factors (AUC: 0.804, 95% CI: 0.728 to 0.881).

Conclusion: Low plasma NPY levels are a predictor of developing PHN in patients with HZ. Combining clinical predictors with NPY levels may improve predictive accuracy.

Keywords: neuropeptide Y, herpes zoster, postherpetic neuralgia, sensory neurons

Introduction

Herpes zoster (HZ) is caused by reactivated varicella-zoster virus infection of sensory ganglia and peripheral nerves and is characterized by pain and rash.[1] HZ is classified as acute in the first 30 days after the onset of the rash, sub-acute in the subsequent 30 to 90 days, and post-acute within 90 days.[2] Postherpetic neuralgia (PHN) is the most common chronic complication of HZ, with a prevalence rate of 9–34%, and it increases as age increases (68% of patients are ≥ 50 years of age).[3] PHN manifests different patterns of sensory dysfunction and both spontaneous and stimulus-induced pain, with these altered sensations potentially persisting long after the HZ rash has healed.[4] There is no monotherapy that improves all pain or abnormality. Thus, PHN prevention involves antiviral drugs and aggressive interventional pain management during acute stages of HZ.[5] There are three contributing factors to the development of PHN: inflammation, viral damage, and atrophy of the spinal dorsal horn.[6] With regard to PHN, Devor proposed the ectopic pacemaker hypothesis, which suggests that spontaneous pain and tactile anomalous pain in the peripheral nervous system are caused by ectopic impulses in damaged nerve fibres. Neuropeptide Y (NPY) is a 36-amino-acid peptide in the pancreatic peptide family and

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is considered to be one of the major neural signaling pathways.[7] It has been controversial whether NPY acts to promote or inhibit injury perception. In light of this, it appears that the different roles of this peptide depend on how it is delivered.[8] It has been reported that NPY binds to receptors in the periphery and plays a role in promoting injury perception. As a result of sciatic nerve injury, peptides or Y2R agonists exacerbate mechanical and thermal sensory sensitization, while Y1R agonists affect mechanical sensory sensitization but reverse thermal sensory sensitization.[9] In addition, another study has shown that mTOR-NPY signaling promotes injury receptor sensitization, which drives neuropathic pain. mTOR promotes transcriptional induction of NPY through activation of signaling pathway and phosphorylation of transcription-activating factor 3, which acts on the Y2 receptor and enhances neuronal excitability.[10] On the other hand, intrathecal administration of NPY has been shown to inhibit nociceptive responses. For instance, in an inflammatory pain model induced by Complete Freund's Adjuvant (CFA), intrathecal injection of NPY impedes the progression from acute to chronic pain. This suggests that central administration of NPY can mediate anti-injury effects.[11] Neurotrophic factors are peptides that enhance cell growth, survival, and differentiation mainly through the receptor tyrosine kinase (TrkB).[12,13] Growth factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) enhance the survival and diversification of sensory neurons and play a role in harmful neurotransmission.[14,15] An increase in endogenous peripheral nerve growth factor induced by an inflammatory response may result in the release of large amounts of substance P from injured sensory neurons, leading to CNS hypersensitivity and nociceptive sensitization.[16,17] In a basic study, upregulation of peripheral BDNF mediates TrkB survival in neurons, leading to chronic osteoarthritic joint pain.[18] As well, NGF inhibitors provide pain relief, such as for patients experiencing musculoskeletal pain[19] and oral-facial pain.[20]

Given that PHN is regulated both peripherally and centrally, the roles of NPY and neurotrophic factors in PHN remain unexplored. This study aimed to examine plasma levels of NPY and neurotrophic factors in PHN patients and assess their predictive potency for PHN.

Materials and Methods

Subjects

This study was conducted from February 2022 to December 2023 at Peking University First Hospital Ningxia Women and Children's Hospital. Inclusion criteria: HZ patients were diagnosed based on clinical manifestations, with the onset of the disease not exceeding one week before admission. Exclusion criteria: patients with innate immune diseases; patients with chronic renal, hepatic and rheumatic diseases; patients with acute infection within the previous month; patients with trauma and/or fracture within the previous 6 months; patients with previous HZ vaccination and current use of steroids, including inhalers or non-steroidal anti-inflammatory drugs. Volunteers with no history of HZ were recruited as controls. All procedures were approved by the Peking University First Hospital Ningxia Women and Children's Hospital Ethics Committee. All participants provided informed consent.

Experimental Design

This was a non-matched, prospective, and single-centre case-control study. Patients with HZ were asked to complete a questionnaire about their baseline and clinical characteristics, including age, gender, body mass index (BMI), Numerical Rating Scale (NRS) score in the acute phase of HZ (within 30 days of rash onset), serum C-reactive protein (CRP) level, initial rash range (days of onset $\leq$ 7 d as the initial phase; the area of skin lesions was estimated using the palmar method[21]), rash duration, rash classification, affected nerves, main comorbidities (including diabetes mellitus and hypertension) and response to treatment. Peripheral blood samples were collected from HZ patients and controls within 7 days of rash healing. Telephone follow-up was performed every month from the onset of the rash. HZ-induced PHN is defined as pain that persists for more than 3 months after onset.

All patients were treated with non-steroidal anti-inflammatory and analgesic drugs (ibuprofen sustained-release capsules, 0.3 g/times, 2 times/d), tramadol (100 mg/times, 1 time/12 h), antiviral drugs (Valganciclovir tablets, 0.3 g/times, 2 times/d) for 1 week according to the disease condition after admission. As needed, oxycodone was given orally to control pain and aid sleep. Gastric mucosal protective agent was routinely administered.

Sample Collection and Preservation

Blood samples were collected in vacuum tubes with or without EDTA K2 anticoagulant. The anticoagulant-containing samples were centrifuged twice (15 min, 800 g, 4°C; 10 min, 1600 g, 4°C). The plasma was then dispensed into several cryovials and stored frozen at −80°C. The anticoagulant-free samples were left at room temperature for 2 h and then centrifuged for 20 min (1000 g, 4°C) and for 10 min (1600 g, 4°C).

Circulating Biomarker Measurements

NPY (Wuhan EIAab Science Co. Ltd., China), NGF (Liankebio Biotechnology Co. Ltd., Hangzhou, China), and BDNF (Liankebio Biotechnology Co. Ltd., Hangzhou, China) were measured in plasma samples obtained at the time of diagnosis of HZ (prior to treatment) using commercial ELISA kits. Serum human CRP levels were determined by ELISA kit (R&D System, MN, USA). All samples were duplicated in a single assay to avoid interassay variation. The intra-assay variation of ELISA assays was less than 5%.

Sample Size Estimation

The sample size was calculated using PASS software (version 11.0) with a significance level of 0.05 ($\alpha = 0.05$), a power of 80% ($\beta = 0.20$), and a two-sided test. The results determined that the sample size required for univariate analyses in each group was approximately 36. The total sample size should be 10 times the number of variables in logistic regression analysis. In this study, the number of variables was estimated to be 5 to 8, and the required sample size was 50 to 80.

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 software. The Shapiro–Wilk test was used to determine the normality of the data. For continuous variables in normal distribution, data were shown as mean ± standard deviation, and Student's *t*-test was used for between-group comparisons. For continuous variables in skewed distribution, data were shown as median (interquartile range, IQR), and Mann–Whitney *U*-test was used for between-group comparisons. Count data were expressed as frequency and ratio and compared using Chi square test. To screen candidate predictors, univariate analysis was performed first, followed by binary logistic regression analysis. Logistic regression analysis was used to construct predictive models using clinical factors and circulating biomarkers. The dependent variable was the presence or absence of PHN. Meanwhile, the independent variable was the parameters that significantly differed in one-way comparisons. The predictive value of each model was assessed using receiver operating characteristic curves (ROC). $p < 0.05$ was considered statistically significant.

Results

Elevated Plasma Biomarkers in HZ Patients

Figure 1 shows the flowchart of this study. This study included 38 volunteers as controls and 182 hZ patients. The incidence of PHN was 32.41%. There was no significant difference in age (64.56 ± 8.86, 63.71 ± 10.10) ($P = 0.519$), BMI (22.26 ± 2.81 kg/m^2, 22.03 ± 3.45 kg/m^2) ($P = 0.656$), and gender ($P = 0.721$) between controls and HZ patients. As shown in Table 1, after healing in HZ patients, NPY levels were decreased ($P = 0.001$), NGF levels were increased ($P = 0.001$), and BDNF levels were increased ($P = 0.009$).

Plasma NPY Levels in Patients with PHN

In addition, 90 days after the diagnosis of HZ, patients were categorized into two groups based on the degree of persistent pain, ie patients with PHN and patients without PHN. As shown in Figure 2, circulating levels of NPY were reduced in patients with PHN compared with patients without PHN ($P < 0.0001$). No significant differences in circulating NGF and BDNF levels were found between the two groups ($P > 0.05$).

Prediction of PHN Based on Clinical Factors

Table 2 shows the results of the one-way quantitative analysis of potential clinical predictors of PHN in 182 hZ patients. Age, acute pain severity, rash area, and rash classification showed significant differences between patients with PHN and

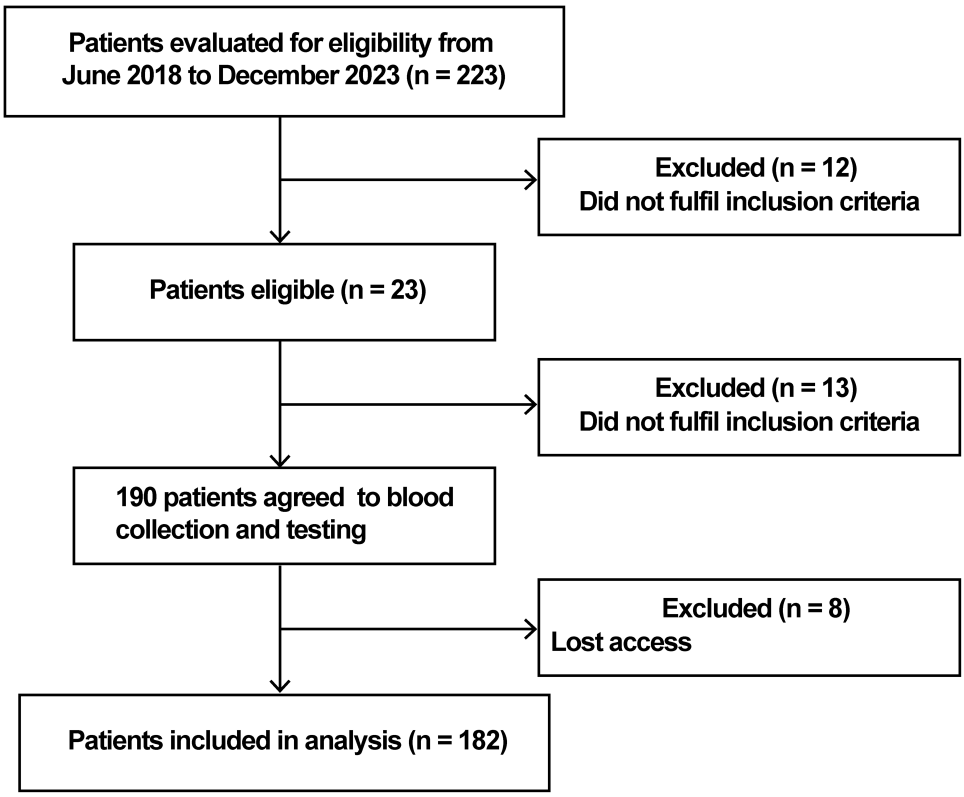

Figure 1 Flowchart of the clinical study.

patients without PHN. The remaining clinical factors, including gender, BMI, CRP level, rash area, rash duration, rash classification, affected nerves, main comorbidities, and response to treatment, were excluded from the analysis.

Clinical factors with significant differences based on univariate analyses were included according to the inclusion criteria of logistic regression analyses. Four factors, including age, acute pain severity, rash classification, and rash area were included in the regression analyses. In addition, gender was included as a confounder for correction. As shown in Table 3, age, acute pain severity, and rash area were identified as independent clinical factors for predicting PHN. Hosmer-Lemeshow test indicated a good model fit at $P = 0.600$ ($P > 0.05$). Based on the clinical prediction model as the reference model (Logit Mc), the AUC was shown to be 0.804 (95% CI: 0.728 to 0.881, $P < 0.001$) (Figure 3, green). The cut-off value was obtained by the Youden index, and the sensitivity and specificity were 91.87% and 62.71%, respectively.

Subsequently, plasma NPY was included as a potential predictor in logistic regression analyses along with identified predictive clinical factors (age, acute pain severity, and rash area) to obtain a new predictive model (Logit Mc + NPY). Gender was corrected as a confounder. As shown in Table 4, plasma NPY, age, acute pain severity, and rash area were independent predictors of PHN. The Hosmer-Lemeshow test resulted in a good model fit at $P = 0.340$ ($P > 0.05$). By

Table 1 Comparison of Plasma NPY, NGF and BDNF Levels in Controls and Patients with HZ

Indicators	Controls (n = 38)	Patients with HZ (n = 182)	*P* value
NPY	95.37 [67.36, 123.36]	80.54 [53.95, 98.04]	0.001
NGF	96.36 [79.36, 116.36]	104.93 [87.54, 139.27]	0.001
BDNF	18.36 [16.36, 25.75]	21.50 [18.06, 28.10]	0.009

Notes: Continuous data are expressed as median (interquartile range, IQR). Comparison of plasma factor levels between the two groups was performed using the nonparametric Mann–Whitney *U*-test. $p < 0.05$ was statistically significant.

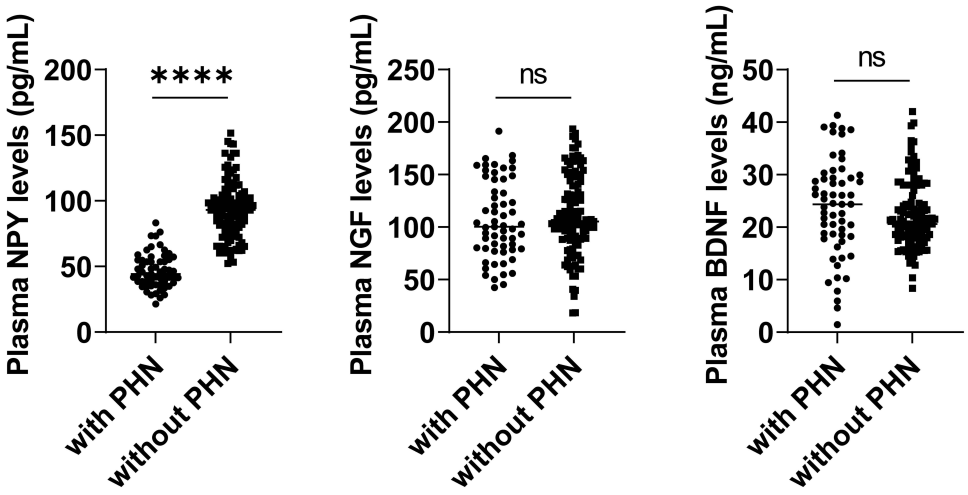

Figure 2 Comparison of plasma NPY, NGF, and BDNF levels in patients with PHN and patients without PHN. ****$P < 0.0001$, $^{ns}P > 0.05$.

plotting the ROC curve (Figure 3, red), an AUC of 0.873 (95% CI. 0.805 to 0.940, $P < 0.001$) was shown. The cut-off value was obtained by the Youden index, at which the sensitivity and specificity were 90.85% and 83.05%, respectively. These results indicate that plasma NPY is a predictor of PHN and that the model of plasma NPY combined with clinical

Table 2 Comparison of Clinical Data of Patients with PHN and Without PHN

Characteristic	With PHN (n = 59)	Without PHN (n = 123)	*P* value
Gender			
Male	28 (47.76%)	70 (56.91%)	0.231
Female	31 (52.54%)	53 (43.09%)	
Age, years	68.3 ± 7.7	61.0 ± 8.9	< 0.0001
BMI, kg/m^2	21.36 ± 4.02	22.15 ± 3.36	0.536
NRS score	6.05 ± 1.89	4.07 ± 1.80	< 0.0001
CRP	6.71 (4.65, 10.23)	5.86 (4.58–7.93)	0.274
Rash area (%)	2.5 [2.0, 3.0]	2 [1.0, 2.5]	0.008
Rash duration, days	16.33 ± 8.66	14.56 ± 9.06	0.366
Rash classification			0.038
Regular	25 (42.37%)	75 (60.98%)	
Bullous	20 (33.90%)	33 (26.83%)	
Hemorrhagic	14 (23.73%)	15 (12.20%)	
Affected nerves			0.186
Trigeminal nerve	20 (33.90%)	26 (21.14%)	
Intercostal nerve	17 (28.81%)	47 (38.21%)	
Lumbosacral nerve	14 (23.73%)	38 (30.89%)	
Cervical	8 (13.56%)	12 (9.76%)	
Main comorbidities			
Diabetes	12 (20.34%)	21 (17.07%)	0.592
Hypertension	18 (30.51%)	30 (24.39%)	0.381
Response to treatment			0.076
Pain relief < 50%	38 (64.41%)	62 (50.41%)	
Pain relief ≥ 50%	21 (35.59%)	61 (49.59%)	

Notes: Continuous data are shown as median (interquartile range, IQR) or mean ± SD, and categorical data are expressed as N (%). Categorical values were compared using the chi-square test. Student's *t*-test or Mann–Whitney test was used to assess the differences between the two groups. $p < 0.05$ was statistically significant.

Table 3 Independent Correlates of the Occurrence of PHN Based on Multivariate Analysis of Clinical Characteristics

Variables	*B*	*S.E,*	*Wals*	OR	95% CI.	*P* value
Age, years	0.096	0.024	14.993	1.101	1.050~1.154	0
NRS score	0.49	0.099	24.322	1.632	1.343~1.983	0
Rash area (%)	0.321	0.154	4.328	1.378	1.019~1.865	0.027

Notes: The model incorporates corrections for gender confounders. *B*, biased regression coefficient; S.E, standard error of the biased regression coefficient; OR, odd ratio; 95% CI., 95% confidence interval. $P < 0.05$ is statistically significant.

predictors (Logit Mc + NPY) showed higher predictive efficacy than the clinical predictive model (Logit Mc). Notably, among these independent predictors, plasma NPY level showed the largest odd ratio 0.840 with a negative partial regression coefficient.

Discussion

Patients with HZ had higher levels of NGF and BDNF and lower levels of plasma NPY than controls, indicating neurological abnormalities. NPY levels were lower in patients with PHN than in patients without PHN after healing of HZ, suggesting that NPY has anti-injury effects. NPY was an independent predictor of PHN. Compared with models based on clinical factors, the combination of NPY levels and clinical factors enhanced the predictive ability of PHN.

Increased levels of plasma nerve injury-related markers indicate neuronal cell damage in patients with acute HZ. It is evident that damaged neurons remain active with high levels of mediators even after the patient's rash has healed.

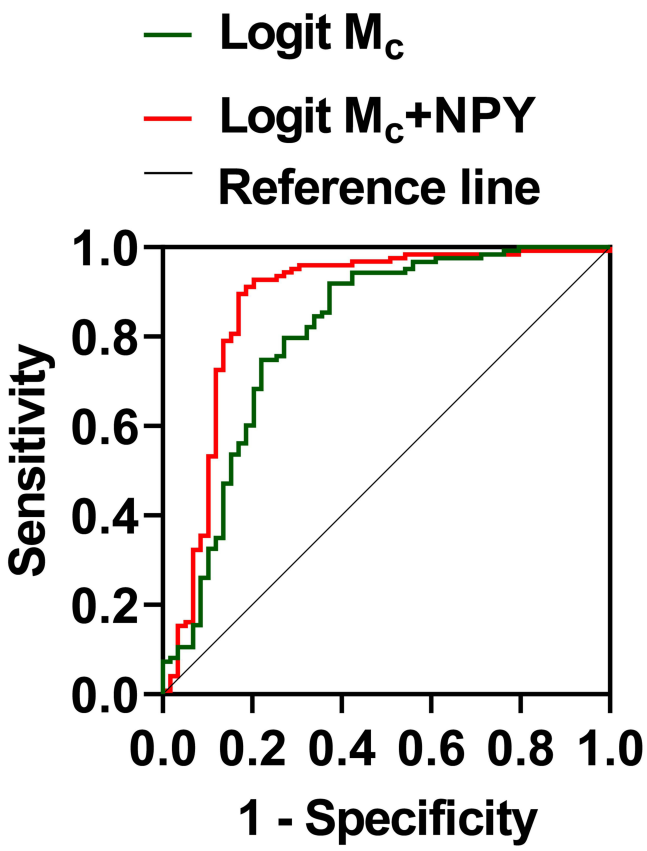

Figure 3 Receiver operating characteristic curves using multiple models containing plasma NPY (red) compared to the reference model (green).

Table 4 Independent Correlates of the Occurrence of PHN Based on Multivariate Analyses of Clinical Characteristics and Plasma NPY

Variables	*B*	*S.E,*	*Wals*	OR	95% CI.	*P* value
Plasma NPY	−0.175	0.035	24.686	0.84	0.784~0.900	0
Age, years	0.111	0.049	5.187	1.117	1.016~1.229	0.023
NRS score	0.48	0.186	6.619	1.487	1.120~1.953	0.01
Rash area (%)	0.469	0.276	2.888	1.467	1.041~2.093	0.039

Notes: The model incorporates corrections for gender confounders. *B*, biased regression coefficient; S.E, standard error of the biased regression coefficient; OR, odd ratio; 95% CI., 95% confidence interval. $P < 0.05$ is statistically significant.

However, we found that after the rash healed, NPY levels decreased in patients with PHN; HZ patients healed may be at risk for developing PHN, as PHN has anti-injury properties in acute and chronic pain.

NPY is a neuromodulator secreted mainly by neurons in the central and peripheral nervous system and is involved in regulating a range of physiological processes.[22] It is difficult to attack PHN because of its dual pathogenesis.[23] It is believed that the anti-injury sensory function of NPY is mainly exerted by a group of excitatory interneurons in the superficial dorsal horn expressing Y1 receptor (Y1R).[24,25] The dorsal horn of the spinal cord serves as the initial relay station for the transmission of nociceptive information to the central nervous system.[26] Primary afferent nociceptors predominantly terminate in laminae I, II, and V of the spinal dorsal horn, with C fibers terminating in laminae I, II, and III, while Aδ fibers terminate outside laminae I, II, and III, as well as in lamina V. The binding of NPY to its receptor Y1R results in the inhibition of excitatory interneurons, thereby terminating nociceptive transmission. Empirical studies have demonstrated that the selective ablation of Y1R-positive neurons in the dorsal horn leads to a reduction in nociceptive responses.[27] In addition, the release of substance P is negatively correlated with NPY expression.[28] Substance P is a neuropeptide containing 11 amino acids, which transmits injurious signals through primary afferent fibres to secondary neurons in the spinal cord and brainstem.[29] PHN is typically linked to abnormalities in nerve damage, inflammatory responses, and processes of nerve regeneration and repair. The varicella-zoster virus can infiltrate nerves, inducing neuroinflammation or necrosis, which subsequently results in neuropathic pain.[30] NPY exhibits neuroprotective properties that can mitigate nerve damage and facilitate nerve repair. In a study, it was shown that increasing the expression of NPY in the hippocampus after brain injury can promote neurogenesis and repair.[31] A reduction in NPY levels may attenuate this protective effect, thereby impeding the effective repair of damaged nerves and elevating the risk of PHN. NPY is implicated in the regulation of neurotransmitter release and neuronal activity.[32] The equilibrium of neurotransmitters is essential for sustaining normal nervous system function during herpes zoster infection. A reduction in NPY levels may disrupt this balance, potentially aggravating neurological disorders and intensifying pain perception. Furthermore, the development of PHN is associated with aberrant immune responses.[33] NPY, as an immune regulatory factor, plays a role in regulating immune cell activity and inflammatory response.[34] A reduction in NPY levels may impair the normal functioning of the immune system, potentially resulting in persistent or exacerbated inflammatory reactions and thereby intensifying neuropathic pain symptoms. Consequently, there appears to be a significant correlation between diminished NPY levels and the incidence of postherpetic neuralgia. Specifically, decreased levels of NPY may elevate the risk of postherpetic neuralgia by undermining neuroprotective mechanisms, disrupting neurotransmitter regulation, and adversely affecting immune responses. Therefore, this study suggests that the observed reduction in plasma NPY levels in PHZ patients may serve as a biomarker indicative of neuronal damage in PHN patients.

Both BDNF and NGF regulate neuronal growth, development, maintenance, and repair by mediating TrkB-related pathways.[35,36] However, the NGF-BDNF cascade promotes pain transmission in bone cancer.[37] It has also been shown that neurotrophic factor levels are elevated in the cerebrospinal fluid and decreased in the blood during chronic pain.[38] In our study, we did not observe differences in plasma BDNF and NGF between patients with PHN and patients without PHN. Of note was the elevation of plasma NGF and BDNF levels in HZ patients compared to controls. This suggests that plasma NGF and BDNF continue to regulate neuronal repair even after the rash has healed. However, more relevant studies are needed to confirm this.

Consistent with most studies, our study also showed that age, acute-phase pain, and rash area were independent risk factors for PHN.[39,40] Several clinical factors were excluded as they showed no correlation with PHN in univariate analyses, including gender, BMI, CRP level, rash area, rash duration, rash classification, affected nerves, main comorbidities, and response to treatment. Gender has been shown to be associated with PHN.[41] PHN risk was not observed to differ between men and women in our study, and we need to conduct further research in order to determine if women are at a higher risk than men. In the follow-up study, we corrected for gender as a confounding factor and constructed a multifactorial regression model. The results showed that elevated NPY was an independent predictor of PHN. Clinical factors combined with NPY had a better predictive value than clinical factors applied alone in a regression model.

Limitations

A limitation of this study is that because the duration of HZ after onset typically varies from patient to patient, we did not examine patients' biomarker levels at the time of diagnosis and are unsure how these markers may have changed over time. Although our study did not show differences in response to medication in different groups of patients, it cannot be excluded that biomarker levels are influenced by medication. Finally, we did not further analyze the correlation analysis between NPY and pain scores after PHN diagnosis. In future studies, plasma NPY levels will be followed in patients from the diagnosis of HZ to the on onset of PHN to analyze the role of NPY in disease progression.

Conclusion

In conclusion, plasma NPY is lower in HZ patients than in healthy individuals in the short-term period after rash healing. Low NPY is an independent predictor of PHN. Predicting PHN with clinical factors and NPY levels is more accurate than using only clinical factors. These results contribute to the early prediction of PHN and provide valuable implications for clinical treatment strategies.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The present study was approved by the Ethics Committee of Peking University First Hospital Ningxia Women and Children's Hospital (No. KJ-LLA-2023010) 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.

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Disclosure

The authors have no conflicts of interest to declare.

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