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Logistic Analysis of Risk Factors for Postherpetic Neuralgia

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Abstract

Background: Currently, old age is the only recognized risk factor for postherpetic neuralgia (PHN), and the effects of degree of acute pain, severity of skin lesions, comorbidities, emotional state, treatment methods and laboratory indices on PHN remain unclear.

Methods: Four hundred patients with herpes zoster treated from January 2014 to December 2017 were enrolled. A self-made questionnaire was used for clinical data investigation. They were followed up to observe the incidence of PHN. The clinical data of patients with and without PHN were compared.

Results: Of the 400 patients, 348 (87.0%) were successfully followed up, including 52 PHN patients (observation group) and 296 cases without PHN (control group). The incidence rate of PHN was 14.9%. The risk factors of PHN were age of ≥50 years old, severe skin lesions, lesion area proportion of >5%, severe acute pain, initial treatment time of ≥3 days, complication with diabetes mellitus as well as abnormalities of fasting blood glucose level, albumin/globulin ratio and CD4+/CD8+ cell ratio. Among the 348 patients, 24, 272 and 52 had subacute neuralgia, acute neuralgia and PHN, respectively. PHN group had significantly more cases with age of ≥50 years, severe acute pain and severe skin lesions than subacute and acute neuralgia groups ($P<0.05$). Acute neuralgia group had significantly more cases with severe skin lesions than subacute neuralgia group ($P<0.05$).

Conclusions: Patients who are old with severe skin lesions, large lesion area, severe acute pain, long duration of initial treatment and complication with diabetes mellitus are prone to PHN. Immune status may be related to the occurrence of PHN. Subacute neuralgia is more than a temporal transition state between acute neuralgia and PHN.

Keywords: herpes zoster, postherpetic neuralgia, risk factor, logistic

Introduction

Postherpetic neuralgia (PHN) is the most common complication of herpes zoster and a chronic refractory neuropathic pain syndrome (1). The clinical symptoms of PHN are as follows. Three months after cure, there is still significant pigmentation in the affected area with persistent or paroxysmal severe pain. Patients suffer from obvious sensation and tactile abnormality in the affected area, with hyperalgesia as the most common clinical manifestation. Even a gentle touch can produce severe and unbearable pain. Besides, some patients are typified by shallow sensation and apparent tactile sensation. The pain is mostly spontaneous, knifing-like or lightning-like, and most patients have extremely untolerable pain. Due to the fear of severe pain, patients suffer from heavy psychological burden and emotional depression. Therefore, particular attention should be paid (2). Approximately 10%-27% of patients with herpes zoster are subjected to PHN. Although PHN can be almost relieved within one year, 10%-20% of the cases undergo chronic persistent pain that cannot be alleviated (3). Meanwhile, 40%-50% of PHN patients are insensitive to various treatments (4). The long-term pain not only hinders the daytime social activities, but also causes appetite loss, insomnia and depression, exerting a serious impact on the quality of life of patients (5).

The prevention and treatment of PHN have attracted attention owing to population aging, PHN seriousness and complexity. Researchers have endeavored to find out the risk factors and preventive measures for PHN (6). Until now, old age is the only recognized risk factor (7). PHN has been correlated with gender, affected area, presence or

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absence of pre-existing pain, initial treatment time, degree of pain and fever in the acute phase, severity of skin lesions, comorbidities and treatment methods (8), which still needs further verification. Thereby motivated, we herein aimed to explore the risk factors of PHN by univariate and multivariate logistic regression analyses, and to provide clinical evidence for the prevention and alleviation of PHN.

Methods

Subjects: A total of 400 patients with herpes zoster treated in our hospital from January 2014 to December 2017 were enrolled. This study has been approved by the ethics committee of our hospital and written informed consent has been obtained from all patients. The skin lesions of herpes zoster were classified into three types according to the property, size, blister content and nerve involvement upon diagnosis (9): common: with erythema and small blisters; abortive: only with erythema and papulae, and without obvious blisters; severe: with blood blisters, local skin necrosis and nerve involvement. According to the study of Dworkin and Portenoy (10), herpes zoster pain can be staged into subacute neuralgia, acute neuralgia and PHN. Acute pain was scored with the visual analog scale (VAS), and a higher score meant more severe pain (11). The lesion area was estimated based on patient's palm. The palm area was defined as 1% of the body surface area. Small area: <3%; medium area: 3%-5%; large area: >5% (12).

Methods: A self-made questionnaire was used to analyze the possible risk factors of PHN, including gender, age, cause for disease, comorbidities, pre-existing pain, rash distribution, lesion area, treatment method and laboratory indices (blood glucose level, blood lipid level, albumin/globulin (A/G) ratio and T cell subsets). Follow-up was performed by outpatient recheck visit, telephone call and questionnaire to observe the incidence of PHN. The clinical data of patients with and without PHN were compared to analyze the related risk factors.

Statistical analysis: All data were statistically analyzed by SPSS 16.0 software. The numerical data were expressed as percentage. The differences between two groups were compared by the χ^2 test. Multivariate logistic regression analysis was conducted to determine the risk factors for PHN. P<0.05 was considered statistically significant.

Results

Follow-up results: Of the 400 patients with herpes zoster, 348 (87.0%) were successfully followed up, including 52 patients with PHN (observation group) and 296 cases without PHN (control group). The incidence rate of PHN was 14.9%.

Univariate analysis of risk factors for PHN: Univariate analysis showed that PHN was significantly related to age, pre-existing pain, type and area of lesion, degree of acute pain, initial treatment time, complication with diabetes mellitus, fasting blood glucose level, A/G ratio and CD4+/CD8+ cell ratio (P<0.05) (Table 1).

Multivariate logistic regression analysis of risk factors for PHN: Multivariate logistic regression analysis showed that the risk factors of PHN were age of ≥50 years old, severe skin lesions, lesion area proportion of >5%, severe acute pain, initial treatment time of ≥3 days, complication with diabetes mellitus as well as abnormalities of fasting blood glucose level, albumin/globulin ratio and CD4+/CD8+ cell ratio (Table 2).

Clinical characteristics of patients in different pain phases: The PHN group had significantly more cases with age of ≥50 years, severe acute pain and severe skin lesions than subacute and acute neuralgia groups (P<0.05). The acute neuralgia group had significantly more cases with severe skin lesions than the subacute neuralgia group (P<0.05) (Table 3).

Discussion

Herpes zoster is a skin disease mainly caused by varicella-zoster virus (VZV). After VZV infects the body, it lurks in sensory neurons. After exposure to external stimuli such as malignant tumors and trauma, the immunity is significantly reduced, and VZV is activated to invade sensory nerves and peripheral nerve fibers, eventually resulting in skin lesions (13). The incidence rate of PHN after VZV infection ranges from 10% to 27% (14), being consistent with rate (14.94%) in this study.

Gilden et al. reported that the occurrence of PHN was related to the affected parts and pre-existing pain (15). Herein, the risk factors for PHN were age of ≥50 years old, severe skin lesions, lesion area proportion of >5%, severe acute pain, initial treatment time of ≥3 days, complication with diabetes mellitus as well as abnormalities of fasting blood glucose level, albumin/globulin ratio and CD4+/CD8+ cell ratio.

At presents, old age is the only recognized risk factor for PHN. Ultsch et al. found that the

incidence rate of PHN in patients aged >50 years was 10%-20%, and that of patients >80 years old reached as high as 30% (16). Consistently, this study showed that the proportion of patients aged ≥50 years in the PHN group was higher than that of the control group.

Pre-existing pain refers to the pain, itching and burning sensation before herpes zoster, which occurs mostly on the first day of herpes appearance (17). This study showed that pre-existing pain was a risk factor for PHN. Acute pain is caused by peripheral inflammatory reaction and skin damage. After being activated, a large amount of VZVs replicate, causing necrosis of nerve fibers, herpes on the skin and inflammatory reaction (18). Kothur et al. found that in the lesions of PHN patients, the number of ganglia decreased, accompanied by collagen deposition and formation of scars (19). When herpes zoster is cured, the skin scars heal, and the peripheral nerves also undergo remodeling changes, which in turn causes changes in nerve function and ultimately PHN (20). In this study, severe acute pain was a risk factor for PHN. Therefore, patients with herpes zoster plus severe acute pain should be given sufficient attention, and active treatment measures should be taken to prevent PHN.

Severe skin lesions reflect the degree of infection in the acute phase that may inuduce PHN (21). We herein found that severe skin lesion was a risk factor for PHN. Johnston et al. reported that PHN in patients with severe skin lesions was not associated with age or acute pain, and some young people with mild pain but severe skin lesions were prone to PHN (22). Thus, particular attention should be paid to patients with severe herpes zoster to inhibit viral replication, shorten healing time and reduce the incidence rate of PHN.

This study also found that the proportion of patients receiving treatment within 3 days in the PHN group was lower than that of the control group, suggesting that the occurrence of PHN was associated with initial treatment time. Singh et al. reported that inhibition of VZV replication shortened the acute phase of herpes zoster and relieved acute pain, but this method only worked within 72 h after disease onset (23). Therefore, the appearance of herpes indicates viral replication, and an earlier drug administration gives better effects. At present, the commonly used antiviral drugs in clinical practice are acyclovir, famciclovir, valacyclovir, etc. This study showed that there was no statistically significant difference between PHN and control groups, which may be attributed to the small number of included cases.

Currently, glucocorticoids are often used to treat herpes zoster. O'Connell et al. found that glucocorticoids played an immunosuppressive role and promoted viral spread (24). Nevertheless, Bagdonaite et al. showed that glucocorticoids can be used as an adjuvant treatment for antiviral therapy to prevent PHN (25). In this study, there was no significant difference in the proportion of patients taking glucocorticoids between PHN and control groups.

Furthermore, diabetes mellitus was a risk factor for PHN, probably because elevated blood glucose levels enhanced the activity of the polyol metabolic pathway, decreased the protein kinase C activity, and ultimately led to swelling of the neuron myelin sheath, neuropathy and necrosis (26). Hence, for patients with diabetes mellitus, especially the elderly, active treatment is needed to avoid PHN once herpes zoster occurs.

Woestenberg et al. detected the T cell subsets in the peripheral blood of patients with herpes zoster (27). The results showed that the CD4+/CD8+ cell ratio and number of CD4+ cells decreased significantly, and the number of CD8+ cells increased significantly. We herein also found that A/G ratio and CD4+/CD8+ ratio abnormalities were risk factors for PHN, indicating that patients with low immunity were prone to PHN and their immune function should be enhanced during clinical treatment.

Conclusion

In summary, patients who are old with severe skin lesions, large lesion area, severe acute pain, long duration of initial treatment and complication with diabetes mellitus are prone to PHN. Immune status may be related to the occurrence of PHN. Subacute neuralgia is more than a temporal transition state between acute neuralgia and PHN. Instead, there may be complicated relationships between them.

Competing interests:

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All unpublished data related to this research project are available from the author.

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Table 1. **Univariate analysis of risk factors for PHN [case (%)]**

Group		Control group	Observation group	χ^2 value	P value
Case No.		296	52		
Age (year)	<50	94 (31.8)	4 (7.7)	12.661	<0.001
	≥50	202 (68.2)	48 (92.3)		
Gender	Male	140 (47.3)	23 (5.8)	0.167	0.683
	Female	156 (52.7)	29 (94.2)		
Fever		62 (20.9)	12 (23.1)	0.12	0.729
Involved nerve	Trigeminal nerve	78 (26.4)	18 (34.6)	1.701	0.637
	Intercostal nerve	124 (41.9)	18 (34.6)		
	Lumbar plexus nerve	72 (24.3)	12 (23.1)		
	Brachial plexus nerve	22 (7.4)	4 (7.7)		
Lesion type	Common	208 (70.3)	16 (30.8)	59.527	<0.001
	Abortive	40 (13.5)	2 (3.8)		
	Severe	48 (16.2)	34 (65.4)		
Lesion area	<3%	94 (31.8)	10 (17.9)	11.203	0.004
	3%~5%	122 (41.2)	16 (30.8)		
	>5%	80 (27.0)	26 (50.0)		
Acute pain	Mild	56 (18.9)	2 (3.8)	20.692	<0.001
	Moderate	122 (41.2)	12 (23.1)		
	Severe	118 (39.9)	38 (73.1)		
Complication	Cardiovascular and cerebrovascular diseases	50 (16.9)	14 (26.9)	2.965	0.085
	Diabetes mellitus	16 (5.4)	18 (34.6)	42.808	<0.001
	Digestive system disease	34 (11.5)	8 (15.4)	0.633	0.426
	Respiratory system disease	26 (8.8)	6 (11.5)	0.402	0.526
	Malignant tumor	8 (8.3)	2 (3.8)	0.207	0.649
	Connective tissue disease	8 (8.3)	4 (7.6)	3.307	0.069
Initial treatment time	<3 d	166 (56.1)	16 (30.8)	11.359	0.001
	≥3 d	130 (43.9)	36 (69.2)		
Pre-existing pain		162 (54.7)	44 (84.6)	16.355	<0.001
Use of glucocorticoids		144 (48.6)	18 (34.6)	0.286	0.593
Use of antiviral drugs	Acyclovir	48 (16.2)	8 (15.4)	0.185	0.98
	Famciclovir	132 (44.6)	22 (42.3)		
	Valacyclovir	106 (35.8)	20 (38.5)		
	Others	10 (3.4)	2 (3.8)		
Abnormality of laboratory indices	Fasting blood glucose	34 (11.5)	47 (90.4)	154.174	<0.001
	A/G	40 (13.5)	42 (80.8)	111.083	<0.001
	Blood lipid	80 (27.0)	12 (23.1)	0.355	0.551
	CD4+/CD8+	42 (14.2)	44 (84.6)	117.908	<0.001

Table 2. **Multivariate logistic regression analysis of risk factors for PHN**

Factor	Regression coefficient	Standard error	Wald value	P value	Odds ratio	95%CI
Age ≥50	-3.145	0.827	7.654	0.023	1.345	1.067~1.435
Severe lesion	-2.182	0.456	4.417	0.012	1.398	1.081~2.472
Lesion area >5%	-0.748	0.629	5.137	0.001	2.987	1.282~3.438
Severe acute pain	-2.498	0.786	6.446	0.001	1.897	1.243~3.215
Initial treatment time ≥3 d	-1.028	0.762	10.192	0.000	3.415	2.432~5.762
Complication with diabetes mellitus	-1.987	0.329	10.981	0.000	7.143	3.452~15.762
Abnormality of fasting blood glucose	-2.043	0.902	5.004	0.024	3.246	2.447~6.892
A/G abnormality	-0.672	0.431	6.928	0.004	4.113	2.489~11.246
$CD4^+/CD8^+$ abnormality	-2.187	0.403	5.019	0.027	3.248	2.039~5.782

Table 3: **Clinical characteristics of patients in different pain phases [case (%)]**

Group	Case No.	Age ≥50	Severe acute pain	Severe lesion
Subacute neuralgia group	24	16 (66.7)	8 (33.3)	14 (58.3)
Acute neuralgia group	272	186 (68.4)	110 (40.4)	34 (12.5) [a]
PHN group	52	48 (92.3) [ab]	38 (73.1) [ab]	34 (65.4) [ab]
χ^2 value		12.693	20.177	77.252
P value		0.002	<0.001	<0.001

Compared with subacute neuralgia group, [a]P<0.05; compared with acute neuralgia group, [b]P<0.05.