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Original Article

Immune changes and their relationship with prognosis in patients with varicella-zoster virus encephalitis/meningitis

Yanrong Yuan[1*], Yan Zhang[1*], Jun Wang[1], Huili Liu[1], Hua Zhang[2], Yongxing Yan[1]

[1]Department of Neurology, The Third People's Hospital of Hangzhou, Hangzhou, Zhejiang, China; [2]Department of Anesthesiology and Pain Management, The Third People's Hospital of Hangzhou, Hangzhou, Zhejiang, China. [*]Equal contributors and co-first authors.

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Abstract: Objectives: This study aimed to investigate the immune changes in patients with varicella-zoster virus (VZV) encephalitis/meningitis and explored their relationships with prognosis. Methods: A total of 129 patients with herpes zoster (HZ), 32 patients with VZV encephalitis/meningitis and 31 non-HZ and non-VZV people as healthy controls were included into the present study. The numbers of peripheral T lymphocytes and the serum levels of complements 3 (C3), complements 4 (C4) and immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM) were detected and compared among groups. In 32 patients with VZV encephalitis/meningitis, the immune related variables were compared between the favorable and the unfavorable prognosis group and their relationships with prognosis were further evaluated. Results: There were marked differences in the peripheral CD3+, CD4+ and CD8+ cells and CD4+/CD8+ ratio in the three groups (P<0.05). As compared with HZ and control groups, the peripheral CD3+ and CD4+ cells were reduced dramatically in patients with VZV encephalitis/meningitis (P<0.05). In 32 patients with VZV encephalitis/meningitis, the absolute CD3+ and CD4+ cells in patients with favorable prognosis were significantly higher than in patients with unfavorable prognosis (P<0.05), and they were positively related to the prognosis of these patients (r=0.3852, P=0.0295; r=0.3719, P=0.0361). Conclusion: These immune changes were compromised in VZV encephalitis/meningitis. The peripheral CD3+ and CD4+ levels may be employed to predict prognosis.

Keywords: Varicella-zoster virus, encephalitis, meningitis, immune function, T lymphocyte subsets, prognosis

Introduction

Herpes zoster (HZ) is a skin disease caused by the infection of reactivated varicella zoster virus (VZV) in the human body [1]. Currently, the incidence of herpes zoster is increasing over the year, and herpes zoster tends to be diagnosed in younger patients. Epidemiological studies have shown that people who suffer from herpes zoster once or more times in their lives account for about one-third of the total adult population [2]. Not only does herpes zoster increase the burden on the individual, family and society, but it may also cause complications within the peripheral and central nervous system, which seriously affects the quality of life of these patients. Among them, postherpetic neuralgia is the most common complication, and central VZV infection (such as encephalitis and meningitis) is a serious complication of herpes zoster, which can even cause death in severe cases [3-5]. In recent years, clinical studies have indicated that the incidence of VZV related central nervous system (CNS) complications is increasing and the clinical manifestations of these complications have become more complex [6-8].

Herpes zoster is a T-cell immunity related disease. Advanced age, use of immunosuppressive agents, concomitant tumors, being female and organ transplantation are risk factors for herpes zoster. Clinical studies have found that patients with acute herpes zoster present with immune dysregulation and abnormal distribution of peripheral T lymphocyte subsets that

reflect cellular immunity [9-11]. VZV encephalitis/meningitis is a common serious complication of herpes zoster and is associated with immunosuppression. However, few studies have been conducted to investigate the peripheral T cells, B cells and natural killer (NK) cells in patients with VZV encephalitis/meningitis and there is no consensus on the role of immunosuppression in the prognosis of patients with VZV encephalitis/meningitis [6, 12-14]. The early assessment of progression, risk factors of concurrent encephalitis/meningitis and prognosis is crucial for the early intervention and improvement of prognosis and quality of life of these patients. Currently, the distribution of peripheral T lymphocyte subsets and the relationship between immune function and prognosis are still poorly understood in patients with VZV encephalitis/meningitis. This study aimed to investigate the distribution of peripheral T lymphocyte subsets and the concentrations of immunoglobulins reflecting humoral immunity in patients with VZV encephalitis/meningitis in our center, and explore their relationships with prognosis. Our findings may provide evidence on the immune function of patients with VZV encephalitis/meningitis, which will be helpful for early prediction of prognosis in these patients.

Materials and methods

General information

A total of 161 patients who were admitted due to acute herpes zoster between April 2019 and April 2022 were included into the present study. They were divided into VZV encephalitis/meningitis group (n=32) and herpes zoster group (n=129) according to the clinical findings and results from routine examination, biochemical examination and VZV DNA detection in cerebrospinal fluid (CSF). We also selected 31 people as the control group. They were randomly selected people who came to our hospital for physical examination at the same time, had no infectious diseases within 1 month, and had normal blood biochemical examination results.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) The clinical symptoms, signs and auxiliary examinations of all patients met the diagnostic criteria of herpes zoster [15], and the diagnosis of herpes zoster was determined by a dermatologists; (2) Within 7 days of onset, and no relevant treatment was given after onset; (3) Aged over 18; (4) All patients were diagnosed with herpes zoster for the first time; (5) Had complete clinical data. Exclusion criteria were as follows: (1) Patients with zoster sine herpete; (2) Women during lactation or pregnancy; (3) Human immunodeficiency virus (HIV)-infected people; (4) Patients with severe infection in other sites of the body; (5) People with mental illness, severe dementia, etc. who could not accurately express pain and psychology.

Methods

Data collection: General demographic information, gender, age, clinical characteristics (mainly including duration of disease, the site of zoster, treatment, etc.), comorbidity and history of past illness of enrolled patients were collected.

Main testing reagents and instruments: BD FACSCalibur flow cytometry (US BD Company); Detection of lymphocyte subsets: monoclonal antibodies CD3FITC, CD4 PE-Cy7, CD8 APC-Cy7, CD16+/CD56 PE, CD19 APC and hemolysin (products of BD Company in the United States); Low temperature high-speed centrifuge (Heraeus, Germany); 7600-020 Automatic Biochemical Analyzer (Hitachi, Japan).

Detection of humoral immune related variables in peripheral blood: On the second day, fasting venous blood was collected (5 ml). Under sterile conditions, centrifugation was carried out at a speed of 3000 r/min for 15 minutes to extract the supernatant. Complements 3 (C3), complements 4 (C4), immunoglobulin A (IgA), immunoglobulin G (IgG) and immunoglobulin M (IgM) reagents were added to the serum samples and processed for the detection of complements (C3 and C4) and immunoglobulins (IgA, IgG and IgM) by Immunoturbidimetry in an automatic biochemical analyzer (Hitachi 7600-020 Biochemical Analyzer, Japan).

Detection of peripheral lymphocyte subsets: Flow cytometry was performed to detect the peripheral lymphocyte subsets (CD3+, CD4+, CD8+, CD4+/CD8+, CD19+ and CD56+). In brief, fluorescence conjugated monoclonal antibodies against CD3+/CD4+/CD8+/CD19+/CD56+ (20 μL) were added to a tube, followed

by addition of peripheral blood (50 μL). After vortexing, the mixture was incubated in the dark for 15 min at room temperature. Then, hemolysin (1000 μL) was added, followed by vortexing and incubation in dark for 10 min at room temperature. After centrifugation at 1500 r/min for 5 min, the supernatant was removed, and sediment was rinsed once with 1 ml of PBS. After centrifugation at 1500 r/min for 5 min, the supernatant was removed, and the sediment was re-suspended with 500 μL of PBS. The solution was subjected to flow cytometry with BD FACSCalibur flow cytometer (BD, USA). Data were stored and analyzed with CELLQuest software.

Pain assessment: The degree of pain was evaluated by numerical rating scale (NRS). Self-rating was conducted on the scale of 10 points according to the degree, which was divided into levels 1-10. Zero points represented no pain, 10 points represented the most pain, and increased from 1 to 10 according to the severity of the pain. A score of 1-3 points: slight pain, patient can endure; that of 4-6 points: patient can endure pain and it affects sleep; that of 7-10 points: the patient has intense pain, which is unbearable.

Prognosis judgment of patients with VZV encephalitis/meningitis on discharge: According to the clinical manifestations upon discharge, 32 VZV encephalitis/meningitis patients were divided into a favorable prognosis group and an unfavorable prognosis group. In the favorable prognosis group, they had no clinical symptoms, mild neuralgia (NRS score <3) or nerve palsy involving a single cranial nerve which did not affect the daily activities. In the unfavorable prognosis group, they had cerebral function impairment (such as neuralgia [NRS score ≥4], cognitive impairment, nerve palsy involving two or more cranial nerves, or death) which affected the daily activities. The clinicians determined the prognosis on the day of discharge.

Ethical consideration

This study was approved by the Ethics Committee of The Third People's Hospital of Hangzhou (NO.2021KA013). All procedures involving human subjects were conducted in accordance with the Helsinki Declaration revised in 1983.

Statistical analysis

SPSS 25.0 software was used for data processing and statistical analysis. The categorical data are expressed as frequency and percentage and compared with Chi-square test or Fisher's exact test between groups. Quantitative data are expressed as mean ± standard deviation (X ± SD) and compared with one-way analysis of variance (ANOVA) among groups and S-N-K test between the two groups. The factors with statistically significant difference in ANOVA were included in the multivariate logistic regression analysis. Pearson correlation analysis was used to evaluate the relationships of different variables. A value of $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of patients in different groups

Among the 129 patients in the herpes zoster group, 61 were males and 68 were females with the mean age of 59.9±14.7 years (range: 24-86 years). Among the 32 patients in the VZV encephalitis/meningitis group, 22 were males and 10 were females with the mean age of 54.1±17.6 years (range: 21-81 years). In the control group, there were 20 males and 11 females with the mean age of 58.6±19.4 years (range: 24-89 years). There were no marked differences in the gender, age, and concomitant diseases (hypertension, diabetes, coronary heart disease, stroke, chronic obstructive pulmonary disease, tumor, immune disease, and the use of immunosuppressive agents) among three groups (P>0.05) (**Table 1**).

In the VZV encephalitis/meningitis group, there were 22 cases with herpes zoster in the head and face, followed by 7 cases in the chest and back, 3 cases in the neck, 1 case in the waist, and 1 case in the limbs. While in the herpes zoster group, zoster was also mainly distributed in the head and face in 91 cases, followed by chest and back in 20 cases, waist in 16 cases, limbs in 6 cases, and neck in 3 cases. There were also no differences in the sites of zoster between two groups (P>0.05) (**Table 1**).

Serum levels of humoral immune variables in three groups

As shown in **Table 2**, there were no significant differences in the serum levels of C3, C4, IgG,

Table 1. Baseline characteristics of patients in different groups on admission

	VZV encephalitis/meningitis group (n=32)	Herpes zoster group (n=129)	Control group (n=31)	F/X^2	P
Age (mean ± SD) (years)	54.1±17.6	59.9±14.7	58.6±19.4	1.67	0.19
Gender					
Male (numbers, %)	22 (68.7%)	63 (48.8%)	20 (64.5%)	5.54	0.06
Female (numbers, %)	10 (31.3%)	66 (51.2%)	11 (35.5%)		
Comorbidity (cases)					
Coronary heart disease	3	7	4	2.31	0.31
COPD	2	2	2	3.22	0.20
Hypertension	10	23	13	5.81	0.06
Immune diseases	6	10	1	5.29	0.07
Use of immune drugs	4	4	1	5.25	0.07
Stroke	2	6	5	5.23	0.07
Diabetes	6	9	4	4.36	0.11
Chronic kidney disease	1	5	3	2.09	0.35
Chronic liver disease	5	6	2	4.90	0.09
Tumor	2	12	1	1.41	0.49
Herpes zoster site (numbers)					
Head and face	22	91	NA	0.04	0.84
Neck	3	3	NA	3.55	0.06
Chest and back	7	20	NA	0.75	0.39
Waist	1	16	NA	2.33	0.13
Limb	1	6	NA	0.14	0.70

Note: NA: Not Applicable; VZV: Varicella-Zoster Virus; COPD: Chronic Obstructive Pulmonary Disease.

IgA and IgM among these three groups (P> 0.05).

Peripheral T lymphocyte subsets in the three groups

ANOVA showed marked differences in the peripheral CD3+, CD4+, CD8+ and CD4+/CD8+ cells (F=9.055, P=0.000; F=10.760, P=0.000; F=3.958, P=0.021; F=6.456, P=0.002; respectively), but significant differences were not observed in the peripheral CD19+ and CD56+ cells (F=1.712, P=0.183; F=1.340, P=0.264; respectively). As compared to control group, the absolute level of CD3+ and CD4+ cells reduced significantly in the herpes zoster group and VZV related encephalitis/meningitis group (P<0.05), and the peripheral CD3+ and CD4+ cells in the VZV related encephalitis/meningitis group were markedly lower than in the herpes zoster group (P<0.05). As compared to the herpes zoster group, the absolute CD8+ cells reduced significantly in the VZV related encephalitis/meningitis group (P<0.05), but there was no significant difference between control group and VZV related encephalitis/meningitis group (P>0.05). When compared with the control group, the CD4+/CD8+ ratio was reduced markedly in the herpes zoster group, but there was no significant difference between control group and VZV related encephalitis/meningitis group (P>0.05), all as shown in **Table 2**.

Multivariate logistic regression analysis

The variables with significant difference in the ANOVA (CD3+, CD4+, CD8+ and CD4+/CD8+) were included into the multivariate logistic regression analysis as independent variables. Results showed that the peripheral CD3+, CD4+, CD8+ cells and CD4+/CD8+ ratio were not the independent risk factors of CNS infection of VZV (P>0.05) (**Table 3**).

Prognosis of patients with VZV encephalitis/meningitis on discharge

According to the prognosis criteria, 23 of the 32 patients with VZV encephalitis/meningitis had favorable prognosis, with 17 males and 6 fe-

Table 2. Immune function of patients in three groups

	VZV encephalitis/meningitis group (n=32)	Herpes zoster group (n=129)	Control group (n=31)	F	P
CD3+ (×10^9/L)	0.78±0.42*,#	1.04±0.43*	1.23±0.41	9.055	0.000
CD19+ (×10^9/L)	0.17±0.12	0.21±0.13	0.24±0.17	1.712	0.183
CD4+ (×10^9/L)	0.44±0.26*,#	0.58±0.27*	0.76±0.30	10.760	0.000
CD8+ (×10^9/L)	0.30±0.17#	0.41±0.21	0.40±0.21	3.958	0.021
CD4+/CD8+	1.77±1.07	1.63±0.82*	2.36±1.61	6.456	0.002
CD56+ (×10^9/L)	0.20±0.10	0.25±0.16	0.26±0.18	1.340	0.264
C3 (g/L)	1.21±0.27	1.30±0.97	1.11±0.23	0.710	0.491
C4 (g/L)	0.40±0.14	0.41±0.28	0.40±0.15	0.020	0.985
IgA (g/L)	2.44±1.03	2.35±1.00	2.10±0.88	1.007	0.367
IgG (g/L)	11.39±3.20	11.75±2.74	12.04±3.02	0.346	0.708
IgM (g/L)	1.01±0.47	1.11±0.57	0.89±0.54	1.910	0.151

Note: VZV: Varicella-Zoster Virus; C3: Complements 3; C4: Complements 4; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M. *P<0.05 *vs* control group; #P<0.05 *vs* herpes zoster group.

Table 3. Multivariate logistic analysis of risk factors of concomitant encephalitis/meningitis in patients with VZV infection

Variable	*β value*	*SE value*	*Wald*	*OR value*	*95% CI*	*P* value
CD3+	0.000	0.004	0.005	1.000	0.992-1.008	0.946
CD4+	0.002	0.005	0.195	1.002	0.993-1.011	0.659
CD8+	0.002	0.005	0.154	1.002	0.993-1.011	0.694
CD4+/CD8+	-0.185	0.377	0.240	0.831	0.397-1.741	0.707

males of age 51.1±17.2 years, while the other 9 patients had unfavorable prognosis, with 5 males and 4 females of age 61.7±17.1 years. There was no significant difference in age and gender between favorable and unfavorable prognosis groups (P>0.05) (**Table 4**).

Immunity related variables in VZV encephalitis/meningitis patients with different prognosis

In patients with unfavorable prognosis, the absolute peripheral CD3+ and CD4+ cells were significantly lower than in those with favorable prognosis (P<0.05). However, no significant differences were observed in the CD8+, CD4+/CD8+, CD19+, CD56+, C3, C4, IgA, IgG and IgM (P>0.05) (**Table 4**).

Correlation analysis between T lymphocyte subsets in peripheral blood and prognosis of patients with VZV encephalitis/meningitis upon discharge

In the VZV encephalitis/meningitis group, the peripheral CD3+ and CD4+ cells were positively related to the prognosis on discharge (r=0.3852, P=0.0295; r=0.3719, P=0.0361; respectively), but CD8+ cells and CD4+/CD8+ ratio had no relationship with the prognosis (r=0.2928, P=0.1039; r=0.0414, P=0.8197; respectively).

Discussion

VZV is a ubiquitous, exclusively human alpha herpes virus. It is transmitted by droplets or contact. The primary infection mainly causes varicella, then VZV can ascend along sensory axons or fuse with neurons through infected T cells, reaching the dorsal spinal root ganglia or cranial ganglia [16-18]. After recovery from primary VZV infection, VZV can reside in the human body. In case of aging or immune function impairment, the latent VZV in the ganglion can be re-activated, replicating in large numbers and transfer to the skin along sensory nerve fibers and resulting in typical unilaterally aggregated blisters, erythema, and pain, which is also known as herpes zoster [19]. Herpes zoster often causes complications of peripheral and central nervous systems, such as postherpetic neuralgia (PHN), cranial neuritis,

Table 4. Immunity related variables in VZV encephalitis/meningitis patients with different prognosis

	Favorable prognosis VZV encephalitis/meningitis group (n=23)	Unfavorable prognosis VZV encephalitis/meningitis group (n=9)	t/χ^2	P
Age (mean ± SD) (years)	51.1±17.2	61.7±17.1	1.57	0.13
Gender				
Male (numbers, %)	17 (73.9%)	5 (55.6%)	1.01	0.31
Female (numbers, %)	6 (26.1%)	4 (44.4%)		
CD3+ ($\times10^9$/L)	0.96±0.50	0.54±0.31	2.29	0.03
CD19+ ($\times10^9$/L)	0.21±0.15	0.14±0.08	1.21	0.24
CD8+ ($\times10^9$/L)	0.34±0.19	0.22±0.16	1.68	0.10
CD4+ ($\times10^9$/L)	0.57±0.33	0.30±0.16	2.19	0.04
CD56+ ($\times10^9$/L)	0.19±0.10	0.24±0.10	1.28	0.21
CD4+/CD8+	1.88±1.09	1.73±1.03	0.23	0.82
C3 (g/L)	1.19±0.28	1.24±0.25	0.45	0.66
C4 (g/L)	0.38±0.16	0.44±0.11	0.98	0.34
IgA (g/L)	2.45±1.05	2.42±1.06	0.07	0.95
IgG (g/L)	11.35±3.24	11.48±3.36	0.09	0.93
IgM (g/L)	1.10±0.52	0.84±0.33	1.33	0.19

Note: VZV: Varicella-Zoster Virus; C3: Complements 3; C4: Complements 4; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M.

encephalitis, meningitis and myelitis, which significantly affect the quality of life of these patients. The CNS complication (such as encephalitis and meningitis) is one of the most serious complications of VZV infection and may even cause death if it is serious enough [3-5, 20]. The clinical manifestations of VZV related encephalitis/meningitis have the characteristics of heterogeneity and complexity, which often cause misdiagnosis, and missed diagnosis often occur, especially in blistering herpes zoster patients with intracranial infection [21, 22]. In the present study, 161 patients with herpes zoster were included in this study and all the patients had skin herpes zoster. The clinical examinations confirmed that 32 patients had CNS complications of VZV infection (elevated white blood cells and protein concentration, and positive for VZV DNA in CSF).

The pathogenesis of herpes zoster is closely related to the immunity of human body. B lymphocytes and T lymphocytes mediate humoral immunity and cellular immunity, respectively. Studies have shown that, in the pathogenesis of herpes zoster, the body's defense is dominated by cellular immune responses, and the function of T lymphocyte subsets in the body is crucial for the maintenance of normal immune function [12, 23, 24]. In the present study, T lymphocyte subsets were examined to reflect the cellular immune function, and the compliments and immunoglobulins in the peripheral blood were detected to refect the humoral immune function. Xing et al. [25] investigated the peripheral T lymphocyte subsets in 76 patients with acute herpes zoster and 38 healthy subjects by flow cytometry. Their results showed that the T cell mediated immune function was significantly compromised in patients with acute herpes zoster. Vukmanovic-Stejic et al. [26] investigated the peripheral blood of 133 healthy volunteers who had a history of varicella and their results showed that the VZV-specific CD4+ T cells in the blood were gradually reduced with the increase of age. This study also confirmed that patients with herpes zoster have cellular immune dysfunction and immunoregulatory disorder. Compared with control group, the absolute peripheral CD3+ cells, CD4+ cells and CD4+/CD8+ ratio were significantly reduced in the patients with herpes zoster ($P<0.05$), while the serum levels of C3, C4, IgG, IgA and IgM (factors reflecting humoral immunity) were comparable between groups ($P>0.05$). These results were similar to previous findings: patients with herpes zoster had abnormal cellular immunity, especially in the phenomenon of specific cellular immunosuppression [27].

PHN is the most common complication of herpes zoster. Studies have revealed that there is a clear relationships of the changes of T lymphocyte subsets with herpes zoster and PHN. In patients with herpes zoster, the number of lymphocytes in the peripheral blood changes, and some inflammatory factors and lymphocyte subsets can predict the severity of PHN [28, 29]. However, the changes of peripheral blood lymphocyte subsets are still poorly understood in patients with VZV encephalitis/meningitis which is one of the serious complications of herpes zoster. T lymphocytes are the most important cell group in the cellular immune system. Under normal conditions, T lymphocyte subsets interact and balance to ensure normal immune function. When the number and function of different lymphocyte subsets become abnormal, the immune function will become disorded and cause a series of pathological responses, increasing the risk of viral infection. CD3+ T lymphocytes are a marker of mature T lymphocytes in the peripheral blood, and CD4+ T lymphocytes can assist to activate B cells and cytotoxic T lymphocytes and induce their production of antibodies to activate macrophages. Studies have revealed that the significant decrease of CD3+ and CD4+ cells in the peripheral blood can cause severe autoimmune dysfunction [30]. Our study indicated that the CD3+ and CD4+ cells in the peripheral blood were significantly reduced in the patients with VZV related encephalitis/meningitis as compared to the patients with herpes zoster alone and the controls. This suggests that the immunoregulation becomes disordered in patients with VZV related encephalitis/meningitis, and the pathogenesis of VZV related encephalitis/meningitis is closely related to the dysfunction of T lymphocyte subsets in these patients. Laing et al. proposed that the changes in immune cells were more complicated in patients with disease levels of different severity [31]. Further logistic regression analysis revealed that CD3+ and CD4+ cells were not independent risk factors for CNS infection of VZV. These results may be related to the small sample size and the failure to include other risk factors. Thus, more clinical studies with a larger sample size are needed to confirm our findings in the future.

The clinical manifestations of VZV related encephalitis/meningitis vary among patients and the prognosis is quite different in different patients. Moreover, the prognosis is related to a variety of factors. Corral et al. [6] investigated the prognosis of 98 patients with CNS infection of VZV and found that the time between herpes zoster and the onset of neurological symptoms was negatively correlated with the prognosis. Yan et al. [7] found that the favorable prognosis of VZV related encephalitis/meningitis was related to the early antiviral therapy. Herlin et al. [8] investigated the clinical information of 92 patients with VZV related encephalitis between 2015 and 2019 in Denmark. They found that the main risk factors for unfavorable prognosis of VZV related encephalitis included age, cerebral vasculitis and Glasgow Coma Scale (GCS) <15. However, there is no consensus about the relationship between immunosuppression and unfavorable prognosis of VZV related encephalitis/meningitis [6, 12-14]. Therefore, in the present study, the peripheral T lymphocyte subsets were examined to reflect cellular immunity of patients with VZV encephalitis/meningitis, and the relationship between immune function and prognosis was further analyzed. Among these patients, 23 patients were diagnosed with favorable prognosis on discharge, accounting for 71.9% of the total VZV patients. The peripheral CD3+ and CD4+ cells were positively correlated with the prognosis of patients. This indicates that monitoring of peripheral CD3+ and CD4+ cells in patients with herpes zoster deserves further investigations.

There were several limitations in this study: The first, this was a retrospective single-center study with small number of participants and short duration of the study, although the criteria for VZV encephalitis/meningitis were strict, as the presence of VZV DNA in the CSF and the clinical manifestations were both required for the diagnosis. The second, there are no objective variables for the assessment of prognosis in patients with VZV related encephalitis/meningitis and the variables used for the assessment of prognosis were relatively subjective in the present study, which may bias our findings. The third, in the analysis of prognostic factors upon discharge, only the factors related to immune function were included, while many other factors possibly affecting the prognosis of these patients were not included.

In conclusion, this study indicates that herpes zoster patients, especially those with concomi-

tant encephalitis/meningitis, present cellular immune dysfunction and immunoregulatory disorder, which are mainly manifested as marked decrease of peripheral CD3+ and CD4+ cells. Moreover, the peripheral CD3+ and CD4+ cells may be employed for the prognostic prediction of patients with VZV related encephalitis/meningitis. Of note, more prospective multi-center studies with large sample size are needed to further confirm our findings in the future.

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Disclosure of conflict of interest

None.

Address correspondence to: Hua Zhang, Department of Anesthesiology and Pain Management, The Third People's Hospital of Hangzhou, Hangzhou 31009, Zhejiang, China. Tel: +86-571-87827280; E-mail: 185490156@qq.com; Yongxing Yan, Department of Neurology, The Third People's Hospital of Hangzhou, Hangzhou 31009, Zhejiang, China. Tel: +86-571-87823154; E-mail: yyxing20@126.com

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