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Original Article

Cellular metabolism changes in bilateral hippocampi in patients with herpes zoster

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Abstract: Objectives: Herpes zoster (HZ) has been found to be associated with arisk of developing dementia. However, changes of cellular metabolism in the hippocampus in HZ have received little attention. This study aimed to investigate the cellular metabolism changes in bilateral hippocampi in acute HZ. Methods: ^{1}H-MRS (magnetic resonance spectroscopy) was used to detect the cellular metabolism of bilateral hippocampi in 62 patients with acute HZ and 12 volunteers (control group) from July 2020 to December 2021. Mini-Mental State Examination (MMSE), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA) and Numerical Rating Scale (NRS) were used to evaluate their cognitive function, depression, anxiety and pain intensity, as well as a the correlation between them. Results: The MMSE score in patients with HZ was not significantly different from that of controls ($P>0.05$), while the scores of HAMD and HAMA were significantly higher ($P<0.05$) than those of controls. Also 12.9% and 21.0% of the patients with acute HZ had depression and anxiety disorders, respectively. The level of Cho/Cr in the left/right hippocampi of HZ patients was significantly lower than that of the control group ($P<0.05$). The level of Cho/Cr in the right hippocampus, duration of disease and NRS score in HZ patients with anxiety/depression were significantly higher than those without anxiety/depression, but the level of NAA/Cr in the right hippocampus was lower ($P<0.05$). The NRS score and duration of disease in HZ patients were positively correlated with the scores of HAMD and HAMA. Conclusion: The cellular metabolism of bilateral hippocampi in patients with acute HZ is altered. Those with longer duration of disease and severe pain are more likely to have depression and anxiety disorder, and the changes in cellular metabolism of hippocampi in those with depression and anxiety were more prominent.

Keywords: Herpes zoster, cognitive function, magnetic resonance spectroscopy, hippocampus, cellular metabolism

Introduction

Herpes zoster (HZ) is an erythematous blistering skin infection caused by varicella zoster virus (VZV) reactivation, which is latent in the ganglion after the first infection of human body. It is more commonly seen in elderly or immunodeficient patients, or those on immunosuppressive agents [1]. In the past decades, the incidence of HZ has been increasing. Since the 40s of the last century, the prevalence of HZ in the elderly and women has increased by more than 4 folds (from 0.76‰ in 1945~1949 to 3.15‰ in 2000~2007) [2]. With the aging population in China, the incidence rate is also increasing, reaching about 1.90~6.42/1,000 [3, 4].

HZ can cause a variety of complications. Some cases can involve the central nervous system and have serious complications of multiple organs, and even lead to death [5]. HZ brings a medical economic burden, but also has a serious negative impact on quality of life. Patients can have fatigue, difficulty in concentrating, anxiety, depression, and reduced daily living and professional functioning [6]. At the same time, recent epidemiologic studies show that herpes zoster is related to the development of dementia. After herpes healing, in addition to complications such as postherpetic neuralgia, cognitive decline may occur in the later stage. Tsai [7] et al. found that the risk of dementia in patients with HZ ophthalmicus was 2.97 folds higher than that in normal people after 5 years, and Chen [8] et al. also found that, excluding other risk factors, the risk of dementia in patients with HZ was 1.11 folds higher than that of normal people. At present, most scholars believe that patients who have suffered

from HZ have a significantly increased risk of dementia in the later stage [7-9]. However, the pathogenesis of cognitive decline caused by HZ remains to be elucidated. At the same time, whether there are cognitive impairment and brain cellular metabolic changes in acute HZ patients remain unclear.

The hippocampus is an important brain area carrying cognitive function, which is closely related to the body's learning ability, memory, and emotional regulation. The changes in cellular metabolism of the hippocampus occur much earlier than those of histomorphology. The common cellular metabolites such as N-acetylaspartate (NAA), choline (Cho) and creatine (Cr) in brain tissue are closely related to cognitive function [10-13]. Therefore, detecting the changes in cellular metabolism of the hippocampus is helpful to detect early and diagnose cognitive impairment. With the development of magnetic resonance scanning and analysis technology, it can non-invasively detect the metabolic function of human brain tissue, which has been rapidly applied in the fields of cognitive neuroscience. Among these, magnetic resonance spectroscopy (MRS) is a non-invasive imaging technology to display the metabolic status of living tissue. Before the changes in histomorphology, MRS can evaluate the degree of tissue change from the perspective of brain metabolism. It has played a great role in the diagnosis of diseases and the evaluation of therapeutic efficacy. In particular, it has great reference value for the evaluation of cognitive function, depression, anxiety, and other emotional disorders [14-17]. Therefore, the cellular metabolism of bilateral hippocampi in acute HZ patients detected by MRS, and the cognitive function, and affective disorders such as depression and anxiety were evaluated in this study. We hope to improve clinicians' understanding of cognitive function in patients with acute HZ.

Materials and methods

General information

Sixty-two patients with acute HZ hospitalized in our hospital from July 2020 to December 2021 were selected, including 31 males and 31 females, 25~88 years-old (mean 62.4±15). Among them, 31 cases had hypertension, 8 cases diabetes, 6 cases coronary heart disease, 5 cases stroke, 5 cases chronic obstructive pulmonary disease (COPD), and 6 cases tumor. Eight cases were complicated by autoimmune diseases, and 4 cases were treated with immunosuppressants. The diagnosis of HZ was made by a dermatologist, based on the characteristic cutaneous eruption (vesicular rash that follows a defined dermatomal pattern and with/without neuropathic pain).

There were 12 cases who came to our hospital for physical examination in the same period of time in the control group, including 9 males and 3 females, 34 to 90 years-old (62.4± 20.0), with 6 cases of hypertension, 2 cases of coronary heart disease, 2 cases of stroke, 1 case of COPD, 1 case of tumor, and 1 case of autoimmune disease.

Methods

Assessment of cognitive function, depression, anxiety and pain: Cognitive function was evaluated by Mini-Mental State Examination (MMSE), including orientation (10 points), language function (8 points), immediate word recall (3 points), delayed recall (3 points), structural imitation (1 point), and computational power (5 points), with a full score of 30 points. The higher the score, the better the cognitive function.

Hamilton Depression Scale (HAMD) (edition of 17 items) was used to evaluate the degree of depression. The project adopts the 5-level scoring of 0~4 points, and the 3-level scoring of 0-2 points as well in some items. The higher the score, the severer the depressive disorder. The total score range is 0-54 points, and a total score of more than 17 points is diagnosed as depressive disorder. At the same time, Hamilton Anxiety Scale (HAMA) was used to evaluate the degree of anxiety disorder, with the total score ranging 0-56 points. The higher the score, the severer the anxiety disorder also. The total score is more than 13 points anxiety disorder is present.

The numerical rating scale (NRS) was used to evaluate the degree of pain. Self-rating was carried out on the scale of 10 points according to the degree, which was divided into 1-10 levels. According to the corresponding figures, the pain can be divided into different degrees, that is, grade 0 means no pain, grade 1-3 means

Table 1. Baseline characteristics of the two groups

Value	Herpes zoster group (62)	Control group (12)
Age (x±s) (years)	62.4±15.0	62.4±20.0
Gender (cases)		
male	31	9
female	31	3
Years of education (years)	7.47±4.43	8.33±4.81
Combined diseases (cases)		
Hypertension	31	6
Diabetes	8	0
Coronary artery disease	6	2
Stroke	5	2
COPD	5	1
Tumor	6	1
Autoimmune diseases	8	1
Use of immune drugs	4	0
MMSE	26.24±4.39	26.42±5.79
HAMD	9.94±7.14	3.83±3.19*
HAMA	11.40±6.62	5.17±4.37*
NRS	3.68±2.45	-
Left hippocampus		
Cho/cr	1.21±0.59	1.67±0.93*
NAA/Cr	1.63±1.04	1.16±0.66
NAA/Cho	1.33±0.85	1.29±0.98
Right hippocampus		
Cho/cr	1.29±0.63	1.88±0.82*
NAA/Cr	1.31±0.89	1.07±0.57
NAA/Cho	1.43±0.87	1.80±0.84

Compared to herpes zoster group *P<0.05.

mild pain, grade 4-6 means moderate pain, and grade 7-10 means severe pain.

All patients completed the assessment within 72 hours after admission by the same trained evaluator.

^{1}H-MRS detection of cell metabolism in bilateral hippocampus: ^{1}H-MRS examination was performed with 1.5T magnetic resonance scanner (GE, USA). ^{1}H-MRS adopts chemical shift imaging for single voxel acquisition, point analysis spectrum sequence scanning, positioning on axial T2W image (voxel size of bilateral temporal lobe hippocampal region at midbrain level is generally 7.5 mm ×7.5 mm ×7.5 mm), and the spectrum acquisition time is about 5-6 minutes.

Baseline calibration and metabolite identification were automatically completed by the spectral analysis software, and presented as the area under the curve (AUC) of each metabolite. The metabolites mainly included NAA, Cr and Cho, with Cr as the reference. The MRI scanner analysis software automatically calculates the ratio of the AUC of each metabolite (NAA/Cr, Cho/Cr, NAA/Cho). All patients were examined for the cell metabolism of the hippocampus by ^{1}H-MRS within 72 hours after admission.

Statistical analysis

SPSS 25.0 software was used for data processing and statistical analysis. The counted data were expressed by frequency and percentage. Chi square test or Fisher exact test were used for comparison between groups. The measured data were expressed as $\bar{x}$±s. The comparison of two sample means was performed by rank sum test, and correlation between the parameters was performed by Pearson correlation analysis. A value of P<0.05 was considered significant.

Ethical consideration

The study was approved by the research ethics committee of our hospital (NO: 2021KA013).

Results

Patient baseline characteristics

There was no marked difference in age, gender, education level, hypertension, diabetes, coronary heart disease, stroke, COPD, tumor, autoimmune disease or immune drug use between two groups (P>0.05) (**Table 1**).

Analysis of cognitive function, depression, anxiety and pain

The MMSE score of HZ group was 26.24±4.39 and that of the control group was 26.42±5.79, and hence there was no significant difference between the two groups (P>0.05) (**Table 1**).

Table 2. Comparison of cell metabolism, MMSE, duration of disease, NRS, HAMD, and HAMA scores in HZ patients with/without depression/anxiety

Value	HZ with depression/ anxiety (15)	HZ without depression/ anxiety (47)
Age (x±s) (years)	57.9±15.8	63.9±14.6
Gender (cases)		
male	9	22
female	6	25
Duration of disease (days)	13.7±6.44	8.53±6.08*
MMSE	26.87±4.32	26.04±4.44
HAMD	17.93±9.00	7.38±3.92*
HAMA	20.13±7.44	8.62±2.91*
NRS	5.0±2.67	3.26±2.25*
Left hippocampus		
Cho/cr	1.17±0.58	1.23±0.60
NAA/Cr	1.67±1.21	1.61±0.99
NAA/Cho	1.22±0.79	1.37±0.87
Right hippocampus		
Cho/cr	1.80±0.66	1.12±0.53*
NAA/Cr	1.27±0.67	1.94±1.19*
NAA/Cho	1.12±0.59	1.37±0.96

Compared to HZ patients with depression/anxiety. *P<0.05.

The mean HAMD score in HZ group was 9.94±7.14, which was significantly higher than that of the control group (3.83±3.19) (P<0.01). The mean HAMA score in HZ group was also higher than that of the control group (11.40± 6.62 vs. 5.17±4.37) (P<0.01). In the HZ group, 8 patients had HAMD scores of >17 and 13 had HAMA scores of >13. The incidences of depression and anxiety were 12.9% and 21.0%, respectively, in the HZ group. The NRS score in HZ patients was 3.68±2.45 (**Table 1**).

Cellular metabolism in bilateral hippocampi

The level of Cho/Cr in the left and right hippocampus of the HZ group was significantly lower than that of the control group (1.21±0.59 vs. 1.67±0.93 on the left; 1.29±0.63 vs. 1.88± 0.82 on the right), (P<0.05), but there was no significant difference in the levels of NAA/Cr and NAA/Cho in hippocampi between the two groups (P>0.05) (**Table 1**).

The level of Cho/Cr in the right hippocampus of HZ patients with anxiety/depression was significantly higher (1.80±0.66 vs. 1.12±0.53), and the level of NAA/Cr was lower (1.27±0.67 vs. 1.94±1.19) than that of HZ patients without anxiety/depression (P<0.05). There was no significant difference in Cho/ Cr, NAA/Cr, and NAA/Cho levels in the left hippocampus (P>0.05) (**Table 2**).

The duration of disease, NRS, HAMD, and HAMA score in HZ patients with anxiety/depression were significantly higher than those without anxiety/ depression, namely 13.7± 6.44 days vs. 8.53±6.08 days; 5.0±2.67 vs. 3.26±2.25; 17.93±9.00 vs. 7.38±3.92; and 20.13±7.14 vs. 8.62± 2.91, respectively (P<0.01). There was no significant difference in gender, age, or MMSE score between the two groups (P>0.05) (**Table 2**).

Correlation analysis

The NRS score of HZ patients was positively correlated with the scores of HAMD and HAMA (r=0.2768, P=0.0294, in HAMD; r=0.3169, P=0.0121, in HAMA), as shown in **Figures 1** and **2**. The duration of HZ patients was also positively correlated with the scores of HAMD and HAMA (r=0.3184, P=0.0117, in HAMD; r=0.3788, P=0.0024, in HAMA), as shown in **Figures 3** and **4**. There was no correlation bet-ween NRS score and duration of disease in HZ patients (r=0.2008, P=0.1176). The levels of Cho/Cr, NAA/Cr, and NAA/Cho had no significant correlation with the scores of MMSE, NRS, HAMD, or HAMA (P>0.05).

Discussion

HZ is caused by reactivation of varicella zoster virus. Its clinical manifestations are clustered papules and transparent blisters distributed in strips not exceeding the midline of the body. Some patients may get neuralgia. At present, the incidence of HZ is increasing and the age of incidence is becoming younger. Epidemiologic data show that HZ develops in about 30% of people over their lifetime [18]. The high number of patients with HZ puts pressure on the utilization of medical resources and increases the economic burden [4]. It also causes various complications of the peripheral

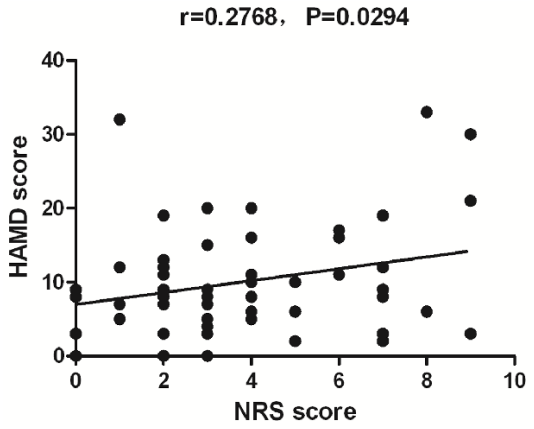

Figure 1. NRS score of HZ patients was positively correlated with the scores of HAMD. r=0.2768, P=0.0294.

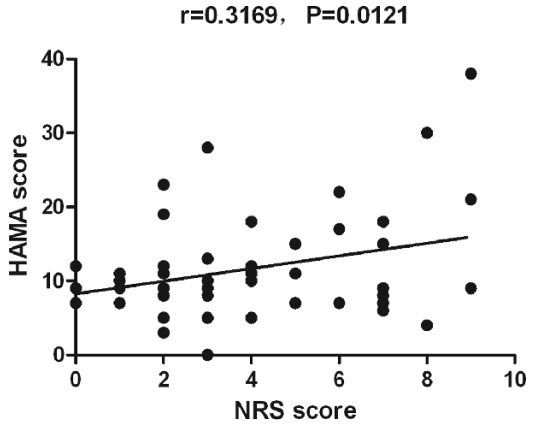

Figure 2. NRS score of HZ patients was positively correlated with the scores of HAMA. r=0.3169, P=0.0121.

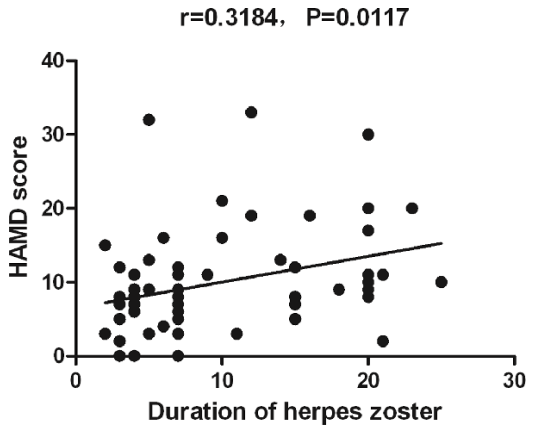

Figure 3. Duration of HZ was positively correlated with the scores of HAMD. r=0.3184, P=0.0117.

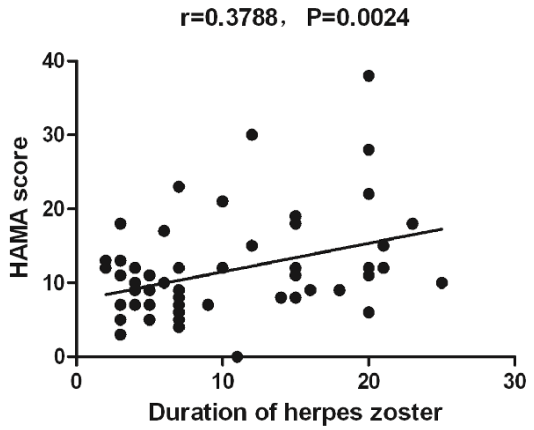

Figure 4. Duration of HZ was positively correlated with the scores of HAMA. r=0.3788, P=0.0024.

and central nervous system [19-21], and seriously affects the quality of life of patients.

Cognition is a process in which the human brain receives external information, processes it, and transforms it into internal psychological activity, and obtains or applies knowledge. It includes memory, language, visual space, execution, calculation, understanding and judgment. When two or more of the above cognitive domains are involved and affect the individual's daily life or social ability, this can be considered as dementia. Dementia may cause a great health care burden worldwide. A neuropsychological scale examination can be used for clinical evaluation of patients' cognitive ability. MMSE is often used in the clinic, as a screening tool for assessing patients' cognitive impairment. Recent studies have found that HZ is closely related to dementia [7-9]. In a 5-year follow-up study, patients with HZ ophthalmicus had a 2.97 fold increased risk of dementia after 5 years compared with the control group [7], Chen et al. [8] found that HZ can occur in any dermatome, with the risk of developing dementia reaching 1.11-fold. Different from previous studies, our study observed an impaired cognitive function in the acute stage of HZ patients. It was found that acute HZ had no obvious clinical symptoms of dementia and no significant difference in MMSE score compared to the control population (P>0.05). Of course, whether these patients are more likely to develop dementia in the later stage requires further long-term follow-up.

This study found that acute HZ had no clinical symptoms of cognitive impairment, but there were significant changes in cellular metabolism in hippocampi. As MRS is an imaging technology for noninvasive analysis of metabolic and biochemical changes in living tissue, it can evaluate brain damage from the perspective of biochemical metabolism before morphologic changes. It has been widely used to check the metabolism of brain tissue, and predict the decline in cognitive ability and the transformation to dementia. NAA, Cho and Cr are the most frequently detected metabolites. NAA is produced by mitochondria and located in neurons. The decrease in NAA is one of the best markers of neuronal and axonal loss in brain tissue [22, 23]; Cho reflects the storage of total choline in the brain and affects cognitive function and mental state. The content of Cr in the brain of the same individual is relatively stable and is often used as a reference to measure the content of other metabolites. This study found that Cho/Cr in the left and right hippocampi in acute HZ was lower than that of the control group, which could reflect the cellular metabolism of cognitive impairment in brain injury before changes in brain histomorphology. Cellular metabolism of hippocampi was changed in acute HZ. Whether it is one of the factors leading to cognitive impairment in the later stage needs a further follow-up study.

Many skin diseases such as HZ and chronic urticaria are closely related to psychological factors [24, 25]. Patients with HZ often suffer from restless sleep and eating and reduced quality of life, and emerge with anxiety and depression symptoms due to the onset of skin pain or pruritus. Studies have shown that the occurrence of HZ and postherpetic neuralgia (PHN) have a negative impact on patients' psychological and subjective emotional experience. About 29% of HZ patients show anxiety or depression. More than half of PHN patients have emotional disorders such as depression and anxiety [26-28]. This study found that the incidence of depression and anxiety in acute HZ was 24.2% (15/62). Many studies have used MRS technology to analyze the characteristics of mental disorders, including depression, bipolar disorder, and post-stroke depression, and found that there were changes in hippocampal cellular metabolism in patients with depression and anxiety [17, 29, 30]. The results of this study were consistent with previous reports. It was found that the changes in cellular metabolism in the hippocampi of HZ patients with depression and anxiety were more obvious, which further suggests the application value of MRS technology in patients with affective disorder.

There were limitations in our study. First, single center research is less representative, and the number of patients included is small. In the future, it will be necessary for us to conduct a multi-center larger sized study to further verify the research results. Second, MRS, MMSE, HAMD, HAMA, and NRS were detected only once. It would be better to dynamically detect their changes in a prospective cohort study to confirm the direct relationship between them. Third, the herpes area, herpes location and treatment were not analyzed in the included patients, which may have affected results.

In conclusion, this study found that although acute HZ had no obvious clinical manifestations of dementia, there were changes of cellular metabolism in hippocampi. HZ patients also had mood disorders such as depression and anxiety in the early stage. The longer the duration of HZ, the severer the degree of neuropathic pain, the greater chance of complication with depression and anxiety. More prominent changes in cellular metabolism in hippocampi in HZ patients with depression and anxiety were seen.

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Disclosure of conflict of interest

None.

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