A STUDY ON THE CORRELATION OF COGNITIVE DYSFUNCTION AFTER STROKE WITH THE LEVELS OF VILIP-1 AND HS-CRP IN SERUM

YANG LI[1#], XIU-QIN WU[2#], QI FAN[3], FU-SHUN WANG[3], JIAN-ZHONG LI[3], QING YANG[*]
[1]Psychological center, school of management, Nanjing forest police college,P.R.China, 210023 - [2]Nanjing University of Chinese Medicine Hanlin College, P.R.China, 225300 - [3]School of Psychology, Nanjing University of Chinese Medicine, P.R.China, 210023
[#]*They contributed equally to this work*

ABSTRACT

Objective*: To investigate the variations in levels of visinin-like protein-1 (VILIP-1) and high sensitive C-reaction protein (hs-CRP) in cognitive dysfunction after stroke and the clinical significance.*

Methods*: A total of 110 patients with ischemic stroke (Stroke group) were divided into two groups according to the MoCA scale at 3 months after attack, i.e. the cognitive dysfunction (n=53) and normal cognition group (n=57); at the same time, 50 subjects who attended the physical examination were enrolled in the control group. General data of patients were collected from patients, including gender, age, education years, disease history and biochemical indexes, and enzyme-linked immunosorbent assay was carried out to detect the levels of VILIP-1 in and immuno-scatter turbidmetry to detect the levels of hs-CRP in serum of all groups.*

Results*: In 110 stroke patients, there were 53 with cognitive dysfunction (48.18%). In the stroke group, the level of VILIP-1 was higher than that in the control group [(449.20±100.77) ng·L-1vs. (332.78±92.13) ng·L-1; t=6.95, p<0.001]. In the cognitive dysfunction group, the level of VILIP-1 was higher than that in the normal cognition group [(530.72±72.05) ng·L-1vs. (373.41±50.00) ng·L-1; t=12.965, p<0.001]. Significant increases were identified in HIHSS score and hs-CRP in the cognitive dysfunction group in comparison with the levels of normal cognition group, and the difference had statistical significance (p<0.01), suggesting that the level of hs-CRP goes up against the severity in cognitive dysfunction with aggravation in nerve functions.*

Conclusion*: After stroke, VILIP-1 is increased in patients with cognitive dysfunction, suggesting that it can serve as a predictor for cognitive dysfunction after stroke; hypertension and the level of VILIP-1 in serum are independent risk factors of cognitive dysfunction after stroke, indicative of the importance of antihypertensive therapy. In light of the close correlation between hs-CRP and cognitive dysfunction after stroke, it can be used to evaluate the severity of cognitive dysfunction of patients.*

Keywords*: Stroke, cognitive dysfunction, VILIP-1; hs-CRP.*

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Introduction

After attack of stroke, patients usually manifest motor or verbal dysfunction, and cognitive dysfunction in some cases, which, however, are ignored in clinical practice frequently[(1, 2)]. A follow-up study[(3)] indicated that 64% of stroke patients are complicated with cognitive dysfunction: Cognitive dysfunction is involved in the recovery of stroke patients and directly affects the functional recovery of patients, which has been considered as one of the factors contributing to the stroke-related morbidity. Thus, prompt and accurate cognitive evaluation is quite important for the recovery of stroke patients. Currently, clinical evaluation of cognitive functions depends on the symptoms, manifestations, imaging examination and psychological scores; nevertheless, biological indexes are more convenient in data

retrieval and operation in comparison with the above mentioned methods, showing a magnificent significance for clinical screening.

Visinin-like protein-1 (VILIP-1), belonging to the family of neuronal calcium sensor visinin/recoverin, is considered as a potential indicator of brain injury and degenerative lesions[4, 5]. However, there remains no literature reporting whether VILIP-1 can serve as a predictive factor for cognitive dysfunction after stroke. High sensitive C-reactive protein (hs-CRP), a stress-activated protein in acute inflammation and the most important and sensitive inflammatory indicators, can reflect the acute inflammatory responses after ischemic infarction of brain tissues in the acute phase of cerebral infarction. Studies have shown that inflammatory indicators can reflect not only peripheral disease, but also the cerebrovascular pathogenesis related to the dementia[6].

Few studies have investigated the relation between cognitive ability of patients with acute stroke and hs-CRP. In this study, we aimed to analyze the levels of VILIP-1 and hs-CRP in stroke patients, to investigate the correlation between the onset and degree of cognitive dysfunction after stroke and the levels of VILIP-1 and hs-CRP, so as to provide clinical evidence for early prediction and intervention.

Material and methods

Subjects

A total of 110 patients with stroke who were treated in this hospital between April 2017 and December 2017 were enrolled as stroke group, and diagnoses were made in accordance with the diagnostic criteria of Diagnosis and Treatment Quality Control of Ischemic Stroke (2012 Edition). Among 110 patients, there were 69 males and 41 females aged between 40 and 80 years old, and the disease course lasted for 3 months. According to the MoCA scale (Beijing Edition), three months after stroke, patients in the stroke group were divided into the cognitive dysfunction group (n=53; MoCA score < 26 points) and normal cognition group (n=57; MoCA score ≥ 26 points).

According to the MMSE scores, 53 patients with cognitive dysfunction were further divided into mild (n=21), moderate (n=18) and severe (n=14) subgroups. In the same period, 50 subjects who attended physical examinations were enrolled as control group, in which there were 30 males and 20 females aged between 40 and 80 years old. All subjects had no previous onset of stroke or any other psychological diseases. Based on the evaluations of corresponding scales, patients with depression, severe aphasia, blindness, deafness, organic diseases in central nerve system (encephalitis and intracranial tumors), severe mental diseases (schizophrenia and mania) accompanied with cognitive impairment, anomaly in thyroid hormones, and those with scores of improved Rankin scale ≥ 4 points. Informed consents of all subjects and/or their families were obtained.

Research methods

Collection of general data

We collected the general data, including gender, age, education years, history of disease and biochemical analysis of blood of all subjects, and the NIHSS score was recorded at admission.

Laboratory examinations

VILIP-1 measurement: Enzyme-linked immunosorbent assay was carried out to detect the levels of VILIP-1 in serum of all groups with kits provided by Shanghai Westang Biotechnology Co., Ltd. in accordance with the instructions of manufacturer.

hs-CRP measurement: In the morning, fasting elbow venous blood was collected for hs-CRP determination in serum with the corresponding reagent provided by Orion (Finland) using the immuno-scatter turbidmetry in range from 0.01 mg/L to 10.0 mg/L. 0 to 3 mg/L was set as normal reference.

Statistical methods

SPSS 19.0 software was used for data analysis. Measurement data were presented as mean ± standard deviation ($\bar{x}\pm s$), and least significant difference-t (LSD-t) was adopted for pairwise comparison. Enumeration data were compared through chi-square test; correlation between the level of VILIP-1 in serum and MoCA score was probed using Pearson correlation analysis. Multi-factor Logistic regression analysis was employed to analyze the factors influencing the cognitive dysfunction. $P<0.05$ suggested that the difference had statistical significance.

Results

Comparison of the general data between the stroke group and control group

No statistical significance was identified in differences of the general data, including gender, age and education years among three groups (p>0.05; Table 1).

Group	n	Gender (male/female)	Age (years)	Education years (years)
Cognitive dysfunction group (Stroke)	53	35/18	65.39±11.73	7.71±4.02
Normal cognition group (Stroke)	57	34/23	64.86±11.62	7.46±3.93
Control group	50	30/20	63.11±10.79	7.54±4.35

Table 1: Comparison of the general data between the stroke group and control group ($\bar{x}\pm s$)
SD: standard deviation.

Comparison of the levels of VILIP-1 in serum among groups

In the stroke group, the level of VILIP-1 was higher than that in the control group ((449.20±100.77) ng·L-1vs. (332.78±92.13) ng·L-1; t=6.95, p<0.001). In the cognitive dysfunction group, the level of VILIP-1 was higher than that in the normal cognition group ((530.72±72.05) ng·L-1vs. (373.41±50.00) ng·L-1; t=12.965, p<0.001).

Comparisons of NIHSS and hs-CRP levels between the cognitive dysfunction group and the normal cognition group

In the cognitive dysfunction group, NIHSS score ranged from 14 to 23 points with an average of (18.4±2.9) points; in the normal cognitive group, NIHSS score ranged from 12 to 22 points with an average of (16.3±2.4) points, and the difference between two groups had statistical significance (p<0.01). In the cognitive dysfunction group, the level of hs-CRP was (19±5) mg/L, significantly higher than (13±5) mg/L of the normal cognition group (p<0.01; Table 2).

Group	n	NIHSS score	hs-CRP (mg/L)
Cognitive dysfunction group	53	18.4 ±2.9	19±5*
Normal cognition group	57	16.3 ±2.4	13±5

Table 2: Comparisons of NIHSS and hs-CRP levels between the cognitive dysfunction group and the normal cognition group ($\bar{x}\pm s$).
*Note: *p<0.01 vs. normal cognition group.*

Comparisons of NIHSS scores and level of hs-CRP in serum among patients with varying cognitive dysfunction

The level of hs-CRP goes up against the severity in cognitive dysfunction with aggravation in nerve functions (Table 3).

Group	n	NIHSS score	hs-CRP (mg/L)
Mild	21	15.3±2.3	16±8
Moderate	18	18.3±2.8*	20±17*
Severe	14	19.5±2.4*#	22±14*#

Table 3: Comparisons of NIHSS scores and level of hs-CRP in serum among patients with varying cognitive dysfunction ($\bar{x}\pm s$)
*Note: *p<0.01 vs. mild cognitive dysfunction group; #p<0.05 vs. moderate cognitive dysfunction group.*

Discussion

The risk of cognitive dysfunction after stroke is almost 6 to 9 times that of those without stroke, and a higher risk usually emerges within 6 months after stroke[7, 8]. A 6-month follow-up study on the cognitive dysfunction after stroke[9, 10] shows that the highest incidence rate (32.0%) of cognitive dysfunction is found at 3 months after stroke. In this study, we selected 110 patients with ischemic stroke as subjects, and performed MoCA analysis at 3 months after stroke. Results showed that there were 53 patients with cognitive dysfunction (48.18%). Despite the correlation between the incidence of cognitive dysfunction and stroke, not every patient with cognitive dysfunction is certainly considered as vascular types. It may be induced by vascular factors, but also by the degenerative factors, or both.

Vermeer et al.[11] reported that stroke can aggravate the condition of Alzheimer's disease. Andin et al.[12] revealed that 40% of vascular dementia patients conform to the manifestations of Alzheimer's disease pathologically, while the autopsy report of vascular dementia patients shows that pathological changes are seen in 58% of Alzheimer's disease patients, and 42% of patients present combined pathological changes of cerebrovascular disease and Alzheimer's disease. Moreover, amyloid-beta changes and neurofibrillary tangles, hallmarks of Alzheimer's disease, are also found in 43% of the vascular dementia patients.

VILIP-1, mainly expressed in brain neurons, can bind to the Ca2+ to regulate the calcium bal-

ance, and regulate the molecular changes in downstream network through Ca2+-dependent signal, thereby exerting the biological effect[13-15]. It has been shown[16] that in pathological process of Alzheimer's disease, VILIP-1 can drive the aggravation of tau protein to induce the neuronal toxicity, implicating its key role in the Alzheimer's disease. Wang et al.[17] confirmed that in comparison with the healthy control, level of VILIP-1 in serum in the acute phase of patients with stroke is relatively higher. Kester et al.[17] found the correlation between the level of VILIP-1 in cerebrospinal fluid and the progression of Alzheimer's disease, and believed that VILIP-1 can predict the disease progression and cognitive dysfunction of patients. In this study, the level of VILIP-1 in the stroke group was higher than that in the control group, and the cognitive dysfunction group was also higher than the normal cognition group, suggesting that VILIP-1 is closely correlated with the cognitive dysfunction after stroke.

As a stress-induced protein in acute inflammatory responses, CRP is scarcely found in serum or plasma under the normal status. When it comes to trauma or inflammation-induced tissue injuries, CRP is released into the blood, which is regulated by interleukin-6 (IL-6). Tissue injuries, ischemia or hypoxia results in an acute increase of CRP level in serum, reaching to nearly hundreds time that of the normal concentration. With the restoration of tissue structure and function, or recovery of inflammation, CRP level is also recovered[18, 19]. Thus, CRP can be used as a non-specific early indicator for diagnosis and differential diagnosis of many diseases, and the indicator for evaluating the efficacy and prognosis. Served as the predictive indicator for risk of cardiovascular or cerebrovascular diseases, CRP at concentrations between 3 and 10 mg/L is detectable, which, however cannot be fulfilled through regular methods (8 to 10 mg/L). Thus, hs-CRP is considered for its wider detection range between 0.01 and 10.00 mg/L, which makes the CRP measurement more sensitive. It is reported that inflammatory indicators can reflect not only the peripheral diseases, but also pathogenesis of the dementia-related cerebrovascular diseases[20].

Some studies have discovered that patients with a higher level of CRP manifest severe cognitive impairment. In this study, we found that hs-CRP is closely correlated with cognitive dysfunction of patients after stroke, i.e. the level of hs-CRP in patients with cognitive dysfunction after stroke was higher than that in those with cognitive dysfunction that was not caused by stroke, and there was a positive correlation between MMSE and NIHSS scores, suggesting that the severity of cognitive dysfunction is increased against the level of hs-CRP in serum with aggravation of nerve functions. Thus, we inferred that measurement of hs-CRP level in serum may reflect the impairment of cognitive ability and nerve functions of patients with cognitive dysfunction after stroke. hs-CRP exerts functions in cognitive dysfunction after stroke through the following possible mechanism: In presence of hs-CRP, NO production is reduced with dysregulation in endothelial cells caused by enhanced monocyte aggregation, proliferation and migration of vascular smooth muscle cells and activation of complement system, resulting in variations in cerebrovasculopathy and destruction of the integrity of subcortical loop in frontal lobe, thereby giving rise to the cognitive dysfunction[21].

After stroke, increased hs-CRP might also affect the restoration of cognitive function by inhibit the angiogenesis, which may be realized through the pathways above[22]; pro-inflammatory responses of hs-CRP may also contribute to the toxicity on neurons, thereby aggravating the impairment of cognitive dysfunction[23].

In conclusion, after stroke, VILIP-1 is increased in patients with cognitive dysfunction, suggesting that it can serve as a predictor for cognitive dysfunction after stroke; hypertension and the level of VILIP-1 in serum are independent risk factors of cognitive dysfunction after stroke, indicative of the importance of antihypertensive therapy. In light of the close correlation between hs-CRP and cognitive dysfunction after stroke, it can be used to evaluate the severity of cognitive dysfunction of patients.

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Corresponding author
QING YANG
Hospital of Jilin University, two blood transfusion department
No. 71 Xinmin Street, Changchun, Jilin, China,1 30000
Email: 13844056540@163.com
(China)