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Significance of interleukin and matrix metalloproteinase in patients with cognitive dysfunction after single valve replacement

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Abstract. – OBJECTIVE: To investigate the changes in serum neurological function parameters, interleukin (IL) and matrix metalloproteinase (MMP) in patients with cognitive dysfunction after single valve replacement.

PATIENTS AND METHODS: 51 cases of senile patients with cognitive dysfunction after general anesthesia were selected as the observation group, and 51 senile patients without cognitive dysfunction after general anesthesia were selected as the control group. Serum neurological function parameters and IL and MMP levels were examined and compared between the two groups. The detected levels were also compared among patients with mild, moderate and severe cognitive dysfunction in the observation group. The relationship between these serum biomarkers and postoperative cognitive dysfunction was analyzed.

RESULTS: The serum neurological function parameters and IL and MMP levels were significantly higher in the observation group than those in the control group. Levels in the severe cognitive impairment group were higher than those in the mild and moderate groups, while those in the moderate group were higher than those in the mild group. Logistic analysis showed that the above indices were closely related to postoperative cognitive dysfunction in elderly patients with general anesthesia. The differences between the groups were statistically significant ($p < 0.05$).

CONCLUSIONS: Elderly patients with postoperative cognitive dysfunction after valve replacement surgery were presented with abnormalities in serum neurological function parameters and IL and MMP levels. There were significant differences in these indices between patients with varying degrees of cognitive dysfunction.

Key Words:
Postoperative cognitive dysfunction, Single valve replacement, IL, MMP.

Introduction

Postoperative cognitive dysfunction (POCD) refers to the persistent dysfunction in memory, abstract thinking and orientation in patients after anesthesia, accompanied by a decline in social abilities; namely, changes in postoperative personality, social competence and cognitive ability[1,2]. Such changes can seriously affect the patients' social life after valve replacement, drastically lowering their quality of life[3-5]. In recent years, there has been clinical research concerning the prevention and control of POCD. However, since there is a lack of research on the hematological parameters related to POCD, it is important to conduct further studies on this topic. In patients with postoperative cognitive dysfunction, the levels of expression of interleukin (IL) and matrix metalloproteinase (MMP) and their clinical significance are not yet clear. In this paper, we investigated the relationship between serum neurological function parameters and IL and MMP levels and cognitive dysfunction in elderly patients after receiving general anesthesia for single valve replacement surgery. These findings may provide a basis upon which to formulate theories and develop strategies for the treatment and prevention of cognitive dysfunction after anesthetic administration.

Patients and Methods

Patients

The research team obtained the approval of the Ethics Committee of the 2nd Affiliated Hospital of Shandong University of Traditional Chinese Medicine and signed written informed consents were obtained from all participants before the study.

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Selection criteria were as follows: (1) patients in need of the valve replacement surgery due to rheumatic valvular disease or other reasons; (2) the valve being replaced was unilateral.

Exclusion criteria were as follows: (1) patients currently prescribed immunosuppressive agents; (2) patients with acute and chronic bacterial and/or viral infections; (3) patients with autoimmune diseases; (4) patients with connective tissue diseases; (5) patients with malignant tumors; (6) patients with liver/renal dysfunction; (7) patients with chronic muscular diseases; (8) patients with peripheral vascular disease, chronic heart failure, thyroid disease, liver/renal insufficiency, major trauma within the past six months or surgeries in the past; (9) patients with diabete mellitus; (10) patients with myocardial infarction, percutaneous coronary angioplasty, coronary artery bypass grafting history within the past six months and recent use of adrenal cortex hormones or other immunomodulator drugs; (11) patients and family members unwilling to cooperate; (12) patients with a history of mental illness[2].

Methods

Cognitive Dysfunction Assessment

Cognitive dysfunction was assessed using the Mini Mental State Examination (MMSE), with responses recorded as follows: "1" indicated a correct answer, "0" indicated error or not knowing, "9" indicated not applicable and "8" indicated a refusal to answer or not understanding. For tabulating the total score, both 8s, 9s were calculated as 0 points, and all 1s were summed for the total points. The maximum score was 30. Dementia is related to the degree of education, so if the elderly were illiterate and scored less than 17 points, with primary school education and scored less than 20 points, or with secondary education (and above) and scored less than 24 points, they were diagnosed with dementia. The scale used for categorization is as follows: 27-30: Normal; 21-26: Mild; 10-20: Moderate; 0-9: Severe.

Detection of Inflammatory Indicators

Enzyme-linked immunosorbent assay (ELISA) was used for the detection of serum inflammatory cytokines levels. The two groups of postoperative patients, after fasting, had 5.0 mL venous peripheral blood drawn for detection. The venous blood samples were sent for examination within 30 min after the collection. First, the samples were centrifuged and then separated and tested for interleukin-18 (IL-18), interleukin-6 (II-6), matrix metalloproteinase-3 (MMP-3) and matrix metalloproteinase-9 (MMP-9). The relevant parameters of a neurological function that were tested are neuron-specific enolase (NSE), S100B protein, myelin basic protein (MBP) and hydrogen sulfide (H_2S). Chemiluminescence and ELISA were used to detect the parameters. The serum neurological function parameters and levels of IL and MMP were compared among patients from the two groups. The parameters of patients in the observation group with mild, moderate and severe cognitive dysfunction were also compared. Furthermore, the relationship between serum levels and postoperative cognitive dysfunction was analyzed.

Surgical Methods

Single valve replacement surgery was performed on each patient according to the following protocol: (1) Preoperative fasting was done for 8 h. Peripheral venous access was opened upon entering the operation room. Under local anesthesia, the radial artery was punctured for the catheter to be placed and then connected to a pressure sensor to monitor arterial pressure. (2) Anesthesia was induced by intravenous injection with 0.05 mg/kg midazolam, 0.3 mg/kg etomidate, 10 μg/kg fentanyl and 0.5 mg/kg cis-atracurium. After tracheal intubation, mechanically controlled ventilation was administered. The dual-chamber central venous catheter was placed in the right subclavian vein to monitor central venous pressure and vasoactive drug concentrations. (3) Retrograde catheterization was done in the right internal jugular vein with the extraction of jugular venous blood for S100B protein detection. (4) Thoracotomy was performed in the center of the thoracic cavity. The ascending aorta and superior and inferior vena cava had catheters placed to establish a cardiopulmonary bypass (CPB). The aortic root was infused with cold cardioplegia. The pericardial cavity was then cooled with ice. The mechanical valve was placed using simple interrupted sutures. Gas in the heart chambers was completely dispelled before re-opening the ascending aorta. After satisfactory hemodynamics, the CPB was concluded with complete hemostasis. The chest was then closed, completing the surgery.

Table I. Comparison of serum neurological function indicators between the two groups.

Group			NSE (μg/L)	S100β (ng/mL)	MBP (μg/L)	H_2S (μmol/L)
Observation	Mild	19	12.11 ± 1.62	0.47 ± 0.09	1.47 ± 0.12	288.33 ± 19.28
	Moderate	17	15.32 ± 1.87[a]	0.43 ± 0.04[a]	2.34 ± 0.33[a]	365.22 ± 21.76[a]
	Severe	15	19.33 ± 3.28[a]	0.16 ± 0.02[a]	3.76 ± 0.28[a]	429.32 ± 32.83[a]
	Total	51	15.55 ± 2.13[a]	0.42 ± 0.05[a]	2.48 ± 0.38[a]	372.43 ± 20.38[a]
Control		51	10.22 ± 1.47	0.12 ± 0.03	1.02 ± 0.24	255.4 ± 18.33

Note: When compared with the control group, the difference in the indicator levels were statistically significant [a]($p < 0.05$).

Statistical Analysis

All measurement data were expressed as mean ± standard deviation ($x \pm s$). SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing and statistical analysis. Independent *t*-test was used to compare the measurement data between groups. Paired *t*-test was used to compare data within each group, and the χ^2-test was used to test the attribute data. Logistic regression was used to assess the relationship between the serum neurological biomarkers and cognitive dysfunction. $p < 0.05$ indicates a statistically significant difference.

Results

General and Clinical Patient Data

51 cases of senile patients with cognitive dysfunction after having single valve replacement between September 2014 and July 2016 were selected for the observation group and 51 cases of senile patients from the same time period without postoperative cognitive dysfunction were taken as the control group. In the control group, there were 27 males and 24 females aged 60-82 years (mean 71.7 ± 5.9 years). The observation group had 28 males and 23 females aged 60 to 86 years, with a mean age of 72.8 (± 5.7 years). There were no statistically significant differences between the two groups ($p > 0.05$).

Comparison of Serum Neurological Function Levels

The levels of serum NSE, S100B, MBP and H2S in the observation group were higher than those in the control group. Within the observation group, levels in the severe group were higher than those in the moderate and mild groups, and levels in the moderate group were higher than those in the mild group. The differences were all statistically significant ($p < 0.05$) (Table I).

Comparison of Serum Levels of IL and MMP

The serum levels of IL-1β, IL-6, MMP-3 and MMP-9 in the observation group were higher than those in the mild and moderate groups. The levels in patients with severe cognitive dysfunction were higher than those in patients with moderate or mild dysfunction, with levels in the moderate group higher than those in the mild group. The differences were all statistically significant ($p < 0.05$) (Table II).

The Relationship Between Serum Neurological Function Parameters, IL and MMP and Cognitive Dysfunction

Serum neurological function parameters, IL and MMP were used as independent variables. Logistic regression analysis was used to analyze the relationship between cognitive dysfunction and these variables. The results suggested that they are closely related (Table III).

Table II. Comparison of serum levels of IL and MMP between the two groups

Group		N	IL-1β (pg/ml)	IL-6 (pg/mL)	MMP-3 (ng/mL)	MMP-9 (ng/mL)
Observation	Mild	19	1.72 ± 0.15	12.35 ± 1.93	15.35 ± 1.89	65.34 ± 5.88
	Moderate	17	2.38 ± 0.27[a]	17.78 ± 2.37[a]	21.32 ± 2.33[a]	71.27 ± 6.77[a]
	Severe	15	4.36 ± 0.23[a]	22.78 ± 2.78[a]	26.77 ± 2.47[a]	81.33 ± 7.44[a]
	Total	51	2.93 ± 0.46[a]	16.78 ± 2.31[a]	23.46 ± 2.34[a]	70.43 ± 5.47[a]
Control		51	1.57 ± 0.12	10.43 ± 1.87	11.46 ± 1.78	59.43 ± 5.43

Note: When compared with the control group, the differences in the serum levels were statistically significant [a]($p < 0.05$).

Table III. The relationship between serum neurological function parameters, IL, MMP and cognitive dysfunction.

Independent variables	WALD value	*p*	OR	95% CI
NSE	12.576	0.002	5.637	2.267-15.467
S100β	8.473	0.001	3.276	1.782-9.956
MBP	12.673	0.002	5.632	1.167-5.783
H2S	8.487	0.001	3.271	1.652-9.476
IL-1β	5.498	0.000	2.376	1.176-5.483
IL-6	8.276	0.001	3.762	1.827-9.874
MMP-3	10.287	0.002	4.837	2.003-12.764
MMP-9	9.372	0.000	4.376	1.982-13.562

Discussion

The pathogenesis of POCD is presently unclear but may involve the central nervous system, endocrine system, and immune system. Possible mechanisms leading to POCD include[6-10]: β-amyloid neurotoxicity, hyperphosphorylation of neuronal microtubule-associated protein tau, central cholinergic system dysfunction, changes in hormone levels, cholesterol metabolic disorders, nitric oxide neurotoxicity and a variety of inflammatory responses induced by activation of the immune system[11-13].

We found in our study that, in postoperative patients with POCD, serum neurological function parameters and levels of IL and MMP were significantly increased compared to the control group ($p < 0.05$). Ramlawi et al[9] have shown that patients with cognitive decline after CPB have plasma inflammatory factors that are significantly higher than those without cognitive dysfunction, which can directly affect the patient's hospital stay after surgery. Based on our findings and previous studies, we believe that patients undergoing CPB for single valve replacement require a high level of care from an anesthesiologist to ensure brain protection. Elderly patients with high basal BP, high blood lipid level, and other underlying diseases, when treated with anticoagulation and thrombolytic therapy, should be given special attention to prevent tissue damage caused by brain tissue ischemia.

Studies have shown that during CPB, surgical trauma, contact between blood and non-biological products, ischemia and reperfusion injury and other factors stimulate the release of inflammatory markers, which can eventually lead to systemic inflammation response syndrome[9,10,15]. In the inflammatory process, peripheral cytokines affect the central nervous system either directly through the blood-brain barrier via active transport or indirectly through the vagus nerve stimulation of cytokine-mediated neuronal interaction with glial cells[16-18]. The increase in inflammatory factors in the brain, such as IL-6, IL-1 and TNF-α, can induce an inflammatory reaction in the brain or directly damage neurons and produce a complement to cause an autoimmune reaction in the brain, further aggravating neuronal damage[13,19]. Clinical manifestations include postoperative disturbance of consciousness in patients, as well as more severe incidences of coma, convulsions, hemiplegia and brain death, all of which can severely affect the patient's recovery[11,12]. Therefore, there is an urgent need for clinical diagnostic criteria to improve the early diagnosis and prevention of POCD[13,14].

Conclusions

We found that 2 days after the surgery, when patients showed increased cognitive dysfunction, IL and MMP expression levels were significantly increased, indicating that IL and MMP proteins are sensitive biomarkers for the early diagnosis of POCD. This finding can help to significantly improve the early diagnosis of POCD, which enables the implementation of measures to effectively alleviate disease progression[19].

Conflict of Interest

The Authors declare that they have no conflict of interests.

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