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The correlation between inflammatory biomarkers and vascular cognitive impairment in patients with cerebral small vessel disease

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Abstract

Objective: To investigate the correlation between plasma inflammatory biomarkers MMP-9, Lp-PLA2, IL-6, TNF-α and vascular cognitive impairment in patients with cerebral small vessel disease (CSVD), and to provide theoretical evidence for the early diagnosis and treatment of cognitive impairment in patients with cerebral small vessel disease. *Methods:* A total of 400 patients admitted to the Department of Neurology, Xuzhou Central Hospital, for treatment of CSVD from January 2019 to June 2023 were randomly selected. The cognitive function of the patients was assessed using the Montreal Cognitive Assessment (MoCA) scale. Based on the scores, the patients with CSVD were divided into a normal cognition group (n=196) and a cognitive impairment group (n=204). According to the severity of cognitive impairment, the cognitive impairment group was further divided into mild cognitive impairment group (n=100), moderate cognitive impairment group (n=59),and severe cognitive impairment group (n=45). A healthy control group of 100 individuals who underwent physical examinations during the same period was included. The correlation between plasma inflammatory biomarkers MMP-9, Lp-PLA2, IL-6, TNF-α and vascular cognitive impairment was studied. *Results:* Compared with the healthy control group, the levels of smoking, homocysteine (HCY), carotid artery plaque formation, MMP-9, Lp-PLA2, IL-6, TNF-α in the normal cognition group and cognitive impairment group of patients with CSVD were significantly increased, with statistical significance ($P<0.05$). Moreover, the levels of smoking, HCY, carotid artery plaque formation, MMP-9, Lp-PLA2, IL-6, TNF-α in the cognitive impairment group were higher than those in the normal cognition group, with statistical significance ($P<0.05$). Multivariate logistic regression analysis showed that after controlling for confounding factors such as smoking, HCY, and carotid artery plaque formation, MMP-9, Lp-PLA2, IL-6, and TNF-α in patients with CSVD were still positively correlated with vascular cognitive impairment ($P<0.05$) and were independent risk factors. Compared with the mild cognitive impairment group, the levels of plasma MMP-9, Lp-PLA2, IL-6, and TNF-α in patients with moderate and severe cognitive impairment were significantly increased, with statistical significance ($P<0.05$); compared with the moderate cognitive impairment group, the levels of plasma MMP-9, Lp-PLA2, IL-6, and TNF-α in patients with severe cognitive impairment were significantly increased, with statistical significance ($P<0.05$). There was a negative linear relationship between plasma inflammatory biomarkers MMP-9, Lp-PLA2, IL-6, and TNF-α levels and cognitive function scores ($P<0.05$).
Conclusion: Plasma MMP-9, Lp-PLA2, IL-6, and TNF-α are independent risk factors for vascular cognitive impairment in patients with CSVD. Plasma MMP-9, Lp-PLA2, IL-6, and TNF-α levels in patients with CSVD are positively correlated with the severity of vascular cognitive impairment.

Keywords: Cerebral small vessel disease, vascular cognitive impairment, matrix metalloproteinase 9, phospholipase A2, interleukin-6, tumor necrosis factor-α

INTRODUCTION

In recent years, with the aging population worldwide and the advancement of imaging technologies such as magnetic resonance

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imaging (MRI), the incidence and detection rate of cerebral small vascular disease (CSVD) have been increasing annually. CSVD mainly refers to a group of clinical syndromes characterized by pathological and radiological changes resulting from structural or functional alterations in intracranial small vessels (diameter20-200μm) due to various reasons. CSVD is a major cause of vascular cognitive impairment (VCI), known as Small Vascular Disease Cognitive Impairment (SVD-VCI).[1,2] Literature reports that about 45% of VCI in individuals over 60 years old is associated with SVD, and this proportion increases with age.[3] SVD-VCI has an insidious onset and is often overlooked in the early stages. As the disease progresses, it can lead to a series of related symptoms, including cognitive impairment, mood disorders, and Parkinsonian symptoms, ultimately progressing to vascular dementia, severely affecting the patient's quality of life and neurofunctional recovery.[4] Therefore, early detection, diagnosis, and intervention of SVD-VCI are of great significance. In recent years, the role of neuroinflammation in SVD and SVD-VCI has been increasingly recognized by scholars. Novel inflammatory molecular biomarkers such as Matrix Metalloproteinases 9 (MMP-9), Phospholipase A2 (Lp-PLA2), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) have become research hotspots in recent years.[5-7] However, there are few studies exploring the relationship between plasma inflammatory molecular markers and VCI in patients with CSVD. Therefore, this study analyzes the relationship between the levels of MMP-9, Lp-PLA2, IL-6, and TNF-α in the plasma of CSVD patients and vascular cognitive impairment, aiming to provide a theoretical basis for the early diagnosis and intervention of SVD-VCI.

METHODS

Data collection

Patients admitted to the Department of Neurology at Xuzhou Central Hospital from January 2019 to June 2023, diagnosed with ischemic CSVD were included as the case group.

Inclusion criteria: All patients met the diagnostic criteria for ischemic CSVD as outlined in the 2021 "Chinese Consensus on the Diagnosis and Treatment of Cerebral Small Vessel Disease". Patients did not exhibit cognitive impairment prior to the onset of the disease. Cognitive impairment in the cognitive dysfunction group was caused by SVD, with imaging showing multiple lacunar infarctions and/or extensive white matter degeneration, without evidence of large vessel disease (lesion diameter>15 mm) and without cortical or watershed infarcts. The Hamilton Depression Scale score was<17, excluding depression. Patients were able to complete neuropsychological tests and voluntarily participated by signing an informed consent form.

Exclusion criteria: Patients with Alzheimer's disease, depression, Parkinson's disease, intracranial tumors, infections, trauma, multiple sclerosis, severe liver or kidney dysfunction, or rheumatic autoimmune diseases. Patients who were unwilling or unable to complete neuropsychological tests or hematological examinations were also excluded.

Additionally, 100 healthy individuals who underwent routine physical examinations at our hospital during the same period were collected as the normal control group. Inclusion criteria for the control group were normal cranial MRI or CT scans, with age, gender, and educational level matching those of the experimental group, and normal cognitive function. This study was approved by the Ethics Committee of Xuzhou Central Hospital.

Outcome assessment

The Montreal Cognitive Assessment (MoCA) was used to assess the degree of cognitive impairment in patients. After admission, trained neurologists administered the MoCA to evaluate cognitive function. A MoCA score of<26 indicated cognitive impairment. Scores between 17-25 indicated mild cognitive impairment, 10-16 indicated moderate cognitive impairment, and≤9 indicated severe cognitive impairment. The tests were independently completed by two neurologists. On the morning of the second day after admission, fasting venous blood was drawn to measure blood lipids, homocysteine (HCY), and other blood parameters. Enzyme-linked immunosorbent assay (ELISA) was used to detect plasma levels of MMP-9, Lp-PLA2, IL-6, and TNF-α. The detection methods followed the operating instructions of the corresponding reagent kits (MMP-9 and Lp-PLA2 kits were purchased from Jiangsu Enzyme Immunoassay Industrial Co., Ltd.; IL-6 and TNF-α kits were purchased from eBioscience, USA).

Statistical analysis

Statistical analysis was performed using SPSS 26.0. Measurement data that followed a normal distribution were expressed as mean ± standard deviation and were compared among multiple groups using one-way analysis of variance (ANOVA). The LSD method was used for pairwise comparisons. Measurement data that did not follow a normal distribution were expressed as median (interquartile range), with the Kruskal-Wallis H test used for multiple group comparisons, the Nemenyi test for pairwise comparisons, and the Mann-Whitney U test for two-group comparisons. Categorical data were expressed as percentages and compared using the χ^2 test. After adjusting for confounding factors, multivariate logistic regression was used to analyze the independent risk factors for SVD-VCI. Additionally, multivariate logistic regression was used to analyze the relationship between the levels of inflammatory markers in SVD patients and the severity of SVD-VCI. A P-value of <0.05 was considered statistically significant.

RESULTS

General information

Comparison of general information among patients with CSVD with normal cognition, those with cognitive impairment, and the normal control group. A total of 400 patients with CSVD were included, comprising 203 males and 197 females, aged 61-89 years (67.07±4.93). Using the MoCA, 204 cases were assessed as the cognitive impairment group, including 104 males and 100 females, aged 61-89 years (65.77±5.37). The normal cognition group included 196 patients, comprising 99 males and 97 females, aged 61-86 years (65.54±5.43). Additionally, 100 healthy individuals from our hospital's health examination during the same period were collected as the normal control group, including 54 males and 46 females, aged 53-78 years (64.84±5.27). Their cranial MRI or CT showed no abnormalities, and their age, gender, and education level were matched with the experimental groups, with normal cognitive function. The results showed no statistically significant differences in gender, age, years of education, smoking, alcohol consumption, hypertension, diabetes, coronary heart disease, uric acid levels, and low-density lipoprotein levels among the three groups (P>0.05), indicating that the general information among the three groups was comparable. Compared to the healthy control group, both the cognitively normal group and the cognitive impairment group had higher rates of smoking and carotid plaque numbers, with statistically significant differences (P<0.05). The cognitive impairment group had higher smoking rates and carotid plaque numbers than the cognitively normal group, with statistically significant differences (P<0.05). Serum levels of MMP-9, Lp-PLA2, IL-6, and TNF-α were significantly elevated in both the cognitively normal and cognitive impairment groups, with statistically significant differences (P<0.05); these levels were higher in the cognitive impairment group compared to the cognitively normal group, with statistically significant differences (P<0.05). (Table 1)

Outcomes

Multivariate logistic regression analysis of inflammatory factors and VCI in patients with CSVD

Cognitive impairment in patients with CSVD was used as the dependent variable, while smoking, HCY, carotid plaque formation, MMP-9, Lp-PLA2, IL-6, and TNF-α were included as independent variables in the multivariate logistic regression model. The results show that after controlling for smoking, HCY, and carotid plaque formation, MMP-9, Lp-PLA2, IL-6, and TNF-α remain positively correlated with VCI (P<0.05) and are independent risk factors, as shown in Table 2.

The relationship between plasma inflammatory factors and the severity of vascular cognitive impairment in patients with CSVD

Compared with the mild SCD-VCI group, the levels of MMP-9, Lp-PLA2, IL-6, and TNF-α in the moderate and severe SCD-VCI groups increased, and the differences were statistically significant (P<0.05); compared with the moderate SCD-VCI group, the levels of MMP-9, Lp-PLA2, IL-6, and TNF-α in the severe SCD-VCI group increased, and the differences were statistically significant (P<0.05). See Table 3 for details.

Multiple linear regression analysis of plasma inflammatory factors and the severity of VCI in patients with CSVD

Taking the MOCA score as the dependent variable and the levels of plasma inflammatory factors MMP-9, Lp-PLA2, IL-6, and TNF-α as

Table 1: Comparison of general information among patients with CSVD with normal cognition, cognitive impairment, and normal control group

Index	Normal Control Group (n=100)	Cognitively Normal Group (n=196)	Cognitive Impairment Group (n=204)	F/χ2	*P*
Demographics					
Male/Female	54/46	99/97	104/100	0.347	0.841
Age / years	64.84±5.27	65.54±5.43	65.77±5.37	1.017	0.362
Education /years	9.19±2.49	8.94±2.98	9.46±3. 08	1.587	0.206
Drinking / cases	25	49	60	1.198	0.549
Smoking/case	19	54	68	6.876	0.032
Vascular risk factors					
Hypertension / cases	57	104	109	0.458	0. 795
Diabetes / cases	14	26	32	0.492	0.782
Heart Disease / cases	9	18	24	0.924	0.630
Hyperuricemia/cases	10	19	23	0.289	0.865
HCY (umoL/L)	15.20±4.40	17.73±4.16*	18.73±4.65*#	21.649	<0.001
LDL-C (mmoL/L)	3.30±0.95	3.42±0.82	3.29± 1.01	1.068	0.345
carotid plaque	61	134*	167*#	25.627	<0.001
Biological indicators					
MMP-9/ (μg/L)	572.61(466.68,680.18)	706.82 (574.65,804.60)*	961.91 (729.35,1182.65)	136.04	<0.001
Lp-PLA2/ (μg/L)	26.79(24.92,29.41)	34.00 (31.29,36.40)*	42.98 (35.39,48.87)*#	267.396	<0.001
IL-6 / (pg/ML)	4.47(4.07,4.81)	6.82 (5.74,7.87)*	8.92 (7.27,10.43)*#	269.779	<0.001
TNF-α / (pg/ML)	1.05(1.24,1.44)	1.41 (1.14,1.63)*	1.63 (1.45,1.89)*#	111.79	<0.001

*Compared with the normal control group, P<0.05; #Compared with the cognitively normal group, P<0.05. HCY: Homocystinuria; LDL-C: Low-Density Lipoprotein Cholesterol; MMP-9: Matrix Metalloproteinase-9; Lp-PLA2: Lipoprotein-Associated Phospholipase A2; IL-6:Interleukin-6; TNF-α:Tumor Necrosis Factor-alpha

Table 2: Logistic regression analysis of related factors of cognitive impairment in patients with cerebral small vessel disease

Index	β	SE	Waldχ^2	Exp (B)	95%CI	*P*
HCY	0.056	0.029	3.636	0.057	0.998~1.121	0.057
MMP-9	0.002	0.001	10.587	1.002	1.001~1.003	0.001
Lp-PLA2	0.168	0.027	38.633	1.183	1.122~1.247	<0.001
IL-6	0.470	0.084	31.409	1.600	1.357~1.885	<0.001
TNF-α	1.047	0.434	5.811	2.849	1.216~6. 676	0.016
Smoking	0.140	0.329	0.181	1.150	0.604~2.192	0.670
carotid plaque	0.136	0.315	0.187	1.146	0.618~2.122	0.666

HCY: Homocystinuria; MMP-9: Matrix Metalloproteinase-9; Lp-PLA2: Lipoprotein-Associated Phospholipase A_2
IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-alpha

independent variables, a multiple linear regression analysis was conducted. The results showed that there was a negative linear relationship between the levels of plasma inflammatory factors MMP-9, Lp-PLA2, IL-6, and TNF-α and the MOCA score (P<0.05), indicating that as the levels of MMP-9, Lp-PLA2, IL-6, and TNF-α in the plasma of patients with CSVD increased, the severity of cognitive impairment gradually aggravated. See Table 4 for details.

DISCUSSION

As the population ages, the incidence of VCI is increasing annually. It is estimated that approximately 45-80% of VCI cases are caused by SVD.[8] SVD primarily includes white matter lesions and lacunar infarctions, with patients often exhibiting subtle clinical symptoms and lacking specific indicators. Typically, there are no obvious focal neurological deficits, such as hemiplegia, and cognitive dysfunction is often the first manifestation, which is frequently overlooked in the early stages. Eventually, it inevitably progresses to vascular dementia. Therefore, identifying early plasma biomarkers for diagnosis and effective intervention targets has been a research focus in recent years.[7] In recent years, reports have found that neuroinflammatory reactions play an important role in the occurrence and development of SVD and the formation of VCI.[9-11]

Endothelial dysfunction and disruption of the blood-brain barrier (BBB) are early pathological changes in SVD. Studies have confirmed that under the influence of neuroinflammation, damage to endothelial cells can increase BBB permeability, leading to arterial wall hardening, which ultimately results in white matter lesions and neuronal death, thereby impairing cognitive function. The novel inflammatory molecular marker MMP-9 is a multifunctional endopeptidase involved in neuroinflammatory processes through interactions with its substrates. As a metalloproteinase, activated MMP-9 degrades type IV collagen in the basement membrane, compromising BBB integrity, increasing the permeability of vascular endothelial cells, and releasing signals that activate cytokines and inflammatory chemokines. This exerts neurotoxic effects, damaging neural pathways such as

Table 3: Comparison of MMP-9, Lp-PL-A2, IL-6 and TNF-α levels in different degrees of cognitive impairment groups of CSVD

Groups	No. of patients	MMP-9/(μg/L)	Lp-PLA2/ (μg/L)	IL-6 (pg/ML)	TNF-α(pg/ML)
Mild	100	775.03±246.31	36.67±4.87	7.57±1.59	1.45±0.17
Moderate	59	1032.38±288.83*	45.81±3.29*	9.3±1.70*	1.74± 0.17*
Severe	45	1205.09±202.56*#	70.47±5.30*#	12.23±1.58*#	2.05± 0.12*#
F		50.716	895.901	128.234	229.225
P		<0.001	<0.001	<0.001	<0.001

*Compared with the Mild group, P<0.05; #Compared with the Moderate group, P<0.05.
MMP-9: Matrix Metalloproteinase-9; Lp-PLA2: Lipoprotein-Associated Phospholipase A_2; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-alpha

Table 4: Multiple linear regression analysis of plasma inflammatory factors and the severity of vascular cognitive impairment in patients with CSVD

Index	B	β	SE	t	*P*	95% CI
MMP-9	-0.005	-0.234	0.001	-6.214	<0.001	-0.006~-0.003
Lp-PLA_2	-0.199	-0.457	0.023	-8.636	<0.001	-0.244~-0.153
IL-6	-0.262	-0. 102	0.114	-2.299	0.023	-0.487~-0.037
TNF-α	-5.754	-0.262	1.055	-5.454	<0.001	-7.834~-3.673

subcortical circuits and association fibers, thereby affecting cognitive function.[12] Animal studies have shown that high expression of MMP-9 is significantly associated with hyperintensities and rarefaction in white matter.[13] An animal study by Adelis demonstrated that the expression of MMP-9 in the hippocampal region of rats was upregulated in a rat model of cognitive impairment induced by intracerebroventricular injection of streptozotocin. They also found a negative correlation between MMP-9 levels and cognitive function, suggesting that high expression of MMP-9 may lead to various cognitive dysfunctions.[14] The results of this study are consistent with the literature, indicating that elevated MMP-9 levels in patients with ischemic SVD are associated with the occurrence and severity of VCI. Multiple studies have confirmed the impact of MMP-9 on cognitive impairment, making MMP-9 a promising therapeutic target. Further research on MMP inhibitors could potentially improve cognitive dysfunction.

Lp-PLA2 is an enzyme derived from inflammatory cells that is specific to blood vessels. It plays an important role in lipid metabolism, prefrontal cortex function, and cognitive function, primarily by activating inflammatory responses and endothelial cell destruction pathways, which damage nerve cells and neural pathways, leading to cognitive impairment.[15] Studies have indicated that high levels of Lp-PLA2 are significantly associated with cognitive decline and are a risk factor for the progression of VCI to vascular dementia.[16-18] Our study observed the levels of Lp-PLA2 in patients with ischemic small vessel disease. The results showed that plasma Lp-PLA2 levels in the cognitive impairment group were higher than those in the normal cognitive group, and plasma Lp-PLA2 levels in the severe cognitive impairment group were higher than those in the mild-to-moderate cognitive impairment group, suggesting that elevated Lp-PLA2 may increase the risk of cognitive impairment in ischemic small vessel disease. Lp-PLA2 levels could serve as a predictive marker for the occurrence and severity of cognitive impairment in SVD patients.

IL-6, a pro-inflammatory factor secreted by phagocytes and lymphocytes, can be used as an important marker for assessing the severity of cerebral infarction and predicting prognosis.[19] TNF-α, primarily produced by macrophages and monocytes, promotes inflammation and has neurotoxic effects. It is a regulatory factor that mediates apoptotic pathways, triggering cell death after ischemia and playing a central role in the inflammatory cascade. It can induce the production of cytokines such as IL-8 and IL-6, exacerbating brain injury and increasing the volume of the infarcted area.[20] Several studies have indicated that the expression levels of IL-6 and TNF-α in plasma correlate with the severity of cognitive impairment.[21,22] Another study has shown that hippocampal volume is negatively correlated with plasma IL-6 concentration, suggesting that neuroinflammation may act on the hippocampus through IL-6, leading to reduced gray matter volume in the hippocampus and subsequent cognitive dysfunction. Our research supports previous literature, showing that elevated levels of IL-6 and TNF-α in patients with ischemic small vessel disease are associated with the occurrence and severity of cognitive impairment. This suggests that plasma IL-6 and TNF-α may be involved in the development of SVD and VCI.

Plasma inflammatory factors can be measured using well-established, inexpensive, and easy-to-operate kits. By detecting the levels of inflammatory factors in the blood, it is possible to provide early indications of SVD. Combined with the MoCA scale, this approach can serve as an effective means of predicting SVD-VCI, which is important for the early identification, early intervention, and prognosis assessment of SVD and SVD-VCI. This method is suitable for widespread adoption in medical institutions at all levels.

DISCLOSURES

Data availability: The data supporting the results of the study are available by contacting the corresponding author.

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Conflicts of interest: None

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