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Study on the Correlation Between Serum Macrophage Migration Inhibitory Factor and Cognitive Impairment after Stroke and Its Relationship with Serum Inflammatory Factors

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Abstract

Objective: To analyze the correlation between serum macrophage migration inhibitory factor (MIF) and cognitive impairment after stroke, as well as its relationship with serum inflammatory factors. **Methods:** Stroke patients in our hospital from September 2022 to June 2023 were included as the research subjects. They were divided into the control group (without cognitive impairment, n = 43) and the observation group (with cognitive impairment, n = 51) based on whether cognitive impairment occurred. The levels of serum factors and cognitive functions of the two groups were compared, the multiple factors influencing cognitive impairment after stroke were analyzed, and the correlation between the level of serum macrophage MIF and cognitive impairment or inflammatory factors was explored. **Results:** The levels of serum tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and MIF were lower, while the scores of the Montreal Cognitive Scale (MoCa) and the Mini-Mental State Examination (MMSE) were higher in the control group than in the observation group ($p < 0.05$). Combined diabetes, hypertension, hyperlipidemia, TNF-α, IL-6, and MIF were risk factors affecting cognitive impairment after stroke ($p < 0.05$). MIF was negatively correlated with both MoCA and MMSE scores ($p < 0.05$), and positively correlated with the levels of TNF-α and IL-6 ($p < 0.05$). **Conclusion:** The levels of serum TNF-α, IL-6 and MIF have a certain correlation with cognitive impairment in stroke patients, the abnormal increase of which is a risk factor affecting the occurrence of cognitive impairment in stroke patients. Early detection of serum levels of TNF-α, IL-6 and MIF in patients can effectively prevent the occurrence of cognitive impairment and improve the prognosis of patients.

1 Introduction

Stroke is currently the second leading cause of death worldwide, and post-stroke cognitive impairment (PSCI) is one of the main complications after stroke [1]. PSCI refers to a series of syndromes that occur within six months after a stroke and meet the diagnostic criteria for cognitive impairment [2]. The pathogenesis of PSCI remains undefined, possibly involving post-ischemic abnormalities in the neural cognitive domains and damaged neural circuit, or hippocampus function directly impaired by ischemia and hypoxia and consequent one or more cognitive domains impaired, severely impacting the physical and mental health of patients [3]. Hence, early diagnosis and treatment of PSCI are of great significance to intervene in disease progression.

Macrophage migration inhibitory factors (MIFs) are cytokines consisting of 114 amino acid residues, and are secreted by hypothalamic-pituitary-adrenal (HPA) axis, which have an intimate association with cognitive function [4]. It is reported that in patients with Alzheimer's disease and mild cognitive impairment, the production of MIF has increased, this suggests that MIF may be involved in the pathological processes of these diseases and is related to the occurrence of cognitive dysfunction [5]. Previous studies have found that high levels of MIF are associated with moderate to high clinical severity in patients with ischemic stroke and with adverse outcomes at discharge [6]. This study explored the relevance between serum MIF and PSCI, aiming to provide reference for the improvement of the clinical diagnostic level of PSCI.

2 Materials and methods

2.1 General information

A total of 94 stroke patients in our hospital from September 2022 to June 2023 were included as the research subjects. They were divided into the control group (without cognitive impairment, n = 43) and the observation group (with cognitive impairment, n = 51) based on whether cognitive impairment occurred. Collect the general information of the patients, such as gender, age, education, location of stroke, previous history of stroke episodes, hypertension, diabetes, and hyperlipemia.

2.2 Inclusion criteria

All met the diagnostic criteria for stroke revised at the 4th National Conference on Cerebrovascular Disease in 1995 [7], and were confirmed to have first onset by cranial CT or MRI examination. The course of the disease lasted from 1 to 6 months. Vital signs were stable.

2.3 Exclusion criteria

Mental illness; Accompanied by consciousness disorders; Metal foreign objects or implanted electronic devices in the body; Epilepsy; Illiteracy; Obvious aphasia and hearing comprehension impairment, as well as severe hearing or visual impairment; Abnormal function of important organs such as the heart, lungs, liver, and kidneys.

2.4 Detection methods

2.4.1 Serum factor levels

3-5 mL of fasting elbow venous blood was drawn from all patients and were evenly divided into two tubes. One tube of blood was not subjected to anticoagulation. Serum was separated within 2 h (centrifugation: 500-3500 r/min for 5-10 min), and the supernatant was collected. The levels of serum tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and MIF were detected using the double-antibody sandwich enzyme-linked immunosorbent assay method. The indicators such as triglycerides (TG; the enzymatic method), total cholesterol (TC; the cholesterol oxidase method), low-density lipoprotein cholesterol (LDL-C; the endpoint method), high-density lipoprotein cholesterol (HDL-C; the

endpoint method), fasting blood glucose (FBG; the glucose oxidase method), serum creatinine (SCr), and uric acid (UA; the uricase colorimetric method) were measured using an automatic biochemical analyzer and its accompanying reagents.

2.4.2 Cognitive function

The MoCA scale was used to evaluate the cognitive function of all patients, including 11 items in 8 cognitive domains such as attention and concentration, memory, executive ability, language, visual structure skills, abstract thinking, calculation, and orientation. The total score was 30 points, and if the education year was $\leqslant$ 12 years, 1 point will be added [8]. The Mini Mental State Examination (MMSE) was applied to assess the cognitive function of all patients. The MMSE scale had a total score of 30 points, with 27-30, < 27, 21-27, 10-21 and < 10 points indicating normal levels, cognitive impairment, mild cognitive impairment, moderate cognitive impairment, and severe cognitive impairment, respectively [9].

2.4 Statistical methods

Statistical analyses were conducted using SPSS 26.0. Quantitative data that followed a normal distribution were expressed as mean ± standard deviation. Independent sample *t*-test was used for comparison between the two groups. Quantitative data that did not follow a normal distribution were represented using the quartile method [M (P25, P75)], and Mann Whitney U test was used for comparison between the two groups. Qualitative data were described by rate or composition ratio, and contrasted using the χ^2 test. Pearson linear correlation analysis or Spearman rank correlation analysis was exploited for correlation analysis. The difference was considered statistically significant with $p < 0.05$.

3 Results

3.1 Comparison of general information between the two groups of patients

There was no significant difference in the general data between the two groups of patients ($p > 0.05$, Table 1), except for hypertension, diabetes and hyperlipidemia. The number of patients with hypertension, diabetes or hyperlipidemia in the observation group was greater than that in the control group ($p < 0.05$, Table 1).

3.2 Comparison of serum factor levels and cognitive function between two groups of patients

The levels of TNF-α, IL-6, and MIF in the control group were lower than those in the observation group, while the MoCa and MMSE scores were higher than those in the observation group ($p < 0.05$). There was no significant difference in the levels of TC, TG, HDL, LDL, FBG, Scr, and UA between the two groups ($p > 0.05$, Table 2).

3.3 Multi-factor analysis of the factors on cognitive impairment after stroke

Combined diabetes, hypertension, hyperlipidemia, TNF-α, IL-6, and MIF were risk factors affecting cognitive impairment after stroke ($p < 0.05$, Table 3).

3.4 Relevance analyses on MIF and cognitive impairment

The serum MIF level was negatively related to MoCA and MMSE scores ($p < 0.05$, Table 4).

3.5 Relevance analyses on MIF and inflammatory factors

The serum MIF level was positively associated with TNF-α and IL-6 levels ($p < 0.05$, Table 5).

Table 1 Comparison of general information between the two groups of patients.

Project	Control group (n = 43)	Observation group (n = 51)	t/χ^2	p
Gender [case (%)]			0.340	0.560
Male	27 (62.79)	29 (56.86)		
Female	16 (37.21)	22 (43.14)		
Age (year)	69.88±4.66	69.14±3.83	0.853	0.396
Education [case (%)]			-0.114	0.909
Primary school and below	7 (16.28)	8 (15.69)		
Junior high school	10 (23.26)	12 (23.53)		
High school	14 (32.56)	16 (31.37)		
College or above	12 (27.91)	15 (29.41)		
Location of stroke [case (%)]			0.128	0.998
Basal ganglia	7 (16.28)	9 (17.65)		
Thalamus	7 (16.28)	8 (15.69)		
Left hemisphere	10 (23.26)	13 (25.49)		
Right hemisphere	9 (20.93)	10 (19.61)		
Frontal lobe	10 (23.26)	11 (21.57)		
Previous history of stroke episodes [case (%)]			0.099	0.753
First time	25 (58.14)	28 (54.90)		
⩾ 2 times	18 (41.86)	23 (45.10)		
Hypertension [case (%)]			7.589	0.006
No	33 (76.74)	25 (49.02)		
Yes	10 (23.26)	26 (50.98)		
Diabetes [case (%)]			4.741	0.029
No	37 (86.05)	34 (66.67)		
Yes	6 (13.95)	17 (33.33)		
Hyperlipemia [case (%)]			6.023	0.014
No	31 (72.09)	24 (47.06)		
Yes	12 (27.91)	27 (52.94)		

Table 2 Comparison of serum factor levels and cognitive function between two groups of patients.

Project	Control group (n = 43)	Observation group (n = 51)	t/Z	p
TNF-α (ng/mL)	55.75 ± 4.20	63.35 ± 5.50	-7.422	< 0.001
IL-6 (ng/mL)	48.65 ± 5.38	55.85 ± 5.24	-6.557	< 0.001
MIF (μmol/L)	33.56 ± 3.39	37.63 ± 2.81	-6.369	< 0.001
MoCA score (point)	28.00 (28.00, 29.00)	24.00 (23.00, 24.00)	-8.388	< 0.001
MMSE score (point)	29.00 (26.50, 29.50)	25.00 (24.00, 26.00)	-6.240	< 0.001
TC (mmol/L)	4.14 ± 0.65	4.33 ± 0.84	-1.204	0.232
TG (mmol/L)	1.28 ± 0.26	1.29 ± 0.51	-0.058	0.954
HDL (mmol/L)	1.22 (1.02, 1.28)	1.16 (1.07, 1.22)	-0.904	0.366
LDL (mmol/L)	2.53 (2.32, 2.83)	2.38 (2.06, 2.64)	-1.359	0.174
FBG (mmol/L)	5.11 ± 0.41	5.04 ± 0.32	0.952	0.343
Scr (μmol/L)	59.46 ± 7.22	61.42 ± 9.81	-1.085	0.281
UA (μmol/L)	262.39 ± 43.50	267.36 ± 46.95	-0.529	0.598

Table 3 Parameters of the logistic regression model of factors on cognitive impairment after stroke.

Indicator		b	Sb	Wald χ^2	*p*	*OR*	*OR* 95%CI
Gender		1.181	0.949	1.549	0.213	3.257	0.507 - 20.912
Age		0.054	0.110	0.237	0.627	1.055	0.850 - 1.310
Education	Primary school and below (reference)			1.880	0.598		
	Junior high school	0.649	1.448	0.201	0.654	1.914	0.112 - 32.690
	High school	-1.053	1.370	0.591	0.442	0.349	0.024 - 5.114
	College or above	-0.848	1.369	0.383	0.536	0.428	0.029-6.273
Hypertension		2.776	1.083	6.570	0.010	16.063	1.922 - 134.232
Diabetes		2.228	0.984	5.127	0.024	9.284	1.349 - 63.886
Hyperlipemia		2.319	1.120	4.293	0.038	10.170	1.133 - 91.254
TNF-α		0.315	0.117	7.274	0.007	1.371	1.090 - 1.724
IL-6		0.165	0.081	4.186	0.041	1.179	1.007 - 1.381
MIF		0.311	0.143	4.728	0.030	1.364	1.031 - 1.805
Constant		-45.832	13.684	11.218	< 0.001		

Table 4 Relevance analyses on MIF and cognitive impairment.

Indicator	r_s	*p*
MoCA	-0.481	< 0.001
MMSE	-0.296	0.004

Table 5 Relevance analyses on MIF and inflammatory factors.

Indicator	*r*	*p*
TNF-α	0.502	< 0.001
IL-6	0.387	< 0.001

4 Discussion

Timely diagnosis of PSCI is extremely important for controlling disease progression and improving prognosis. Therefore, finding a diagnostic method with high accuracy has gradually become a key research focus in clinical diagnosis. Accordingly, this study explored the correlation between MIF indicators and post-stroke cognitive impairment, as well as their relationship with serum inflammatory factors.

The results of this study showed that the levels of TNF-α , IL-6, and MIF were elevated in the serum of observation group, and the serum MIF level was negatively correlated with the cognitive function of PSCI patients, yet positively correlated with the serum TNF-α and IL-6 levels, indicating that the serum MIF level was closely related to the cognitive function and inflammatory response of PSCI patients.

PSCI patients produce a stress response in their bodies, which can promote the secretion of adrenocorticotropic hormones and activate the HPA axis, thereby producing a large amount of MIF that activates various pro-inflammatory cytokines under stress [10]. Reportedly, high inflammation can damage cognitive function, and MIF can exacerbate the inflammatory state of the body, bind and aggregate β-amyloid proteins, activate complement, and further damage nerve cells, leading to neuronal

degeneration and apoptosis, which may be closely related to cognitive impairment in PSCI patients [11].

This study conducted a single factor analysis on the clinical data of PSCI patients. The results showed that hypertension, diabetes, diabetes, hypertension, hyperlipidemia, TNF-α, IL-6, and MIF were the risk factors for cognitive impairment after stroke. Due to the decline in body function and the presence of various comorbidities, a higher proportion of the elderly population suffer from PSCI. For patients with diabetes, diabetes can increase blood coagulation and viscosity, which has a great impact on hemodynamics [12]. Under the long-term effect of hypertension (especially with elevated diastolic blood pressure), the walls of small arteries in the brain undergo severe degeneration, and the diameter of the vessel gradually narrows. Owing to the abnormal changes in hemodynamic factors, small arteries are occluded, thereby damaging the cognitive function of the patients [13,14]. The mechanisms by which TNF-α and IL-6 concentrations increase are relatively similar, both mainly attributed to damage to human brain blood vessels [15]. As a kind of inflammatory marker related to acute and chronic inflammation, MIF releases a variety of proteolytic enzymes under the action of various cytokines and growth factors when the level of MIF rises, thus affecting the stability of plaque, promoting the occurrence of atherosclerotic diseases, and further aggravating patients' cognitive impairment [16].

In conclusion, serum TNF-α, IL-6 and MIF levels have a certain correlation with the occurrence of cognitive impairment in stroke patients, and their aberrant upregulation acts as a risk factor for cognitive impairment in stroke patients. Early detection of serum TNF-α, IL-6 and MIF levels can effectively prevent cognitive impairment and improve prognosis. However, this study has limitation in small sample size, and the conclusion still needs to be verified by expanding the number of research cases.

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Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Substantial contributions to conception and design: Z.Y. and W.L. Data acquisition, data analysis and interpretation: X.W., Q.M. and H.X. Drafting the article or critically revising it for important intellectual content: All authors. Final approval of the version to be published: All authors.

Ethics Approval and Consent to Participate

This study was approved by Medical Ethics Committee, and patients were informed and agreed.

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Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Supplementary Materials

Not applicable.

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