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Original Article

Correlation of serum uric acid, cystatin C and high-sensitivity C-reactive protein with cognitive impairment in lacunar cerebral infarction

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Abstract: Objective: To study the correlation of serum uric acid (UA), cystatin C (Cys-C) and high-sensitivity C-reactive protein (hs-CRP) with cognitive impairment in lacunar cerebral infarction. Methods: Total 198 patients with lacunar cerebral infarction were selected and divided into 4 groups according to their cognitive function, with 65 cases in the normal group, 72 cases in the mild cognitive impairment group, 38 cases in the moderate cognitive impairment group and 23 cases in the severe cognitive impairment group. The hs-CRP, serum UA, Cys-C and Montreal Cognitive Assessment (MoCA) were measured upon admission. Results: There were statistical differences in hs-CRP, UA and Cys-C among the four groups (all $P<0.001$). MoCA was negatively correlated with hs-CRP, UA and Cys-C (all $P<0.001$). Multivariate logistic regression analysis showed that elevated levels of hs-CRP, UA and Cys-C were the influencing factors of cognitive impairment in patients with lacunar cerebral infarction (all $P<0.05$). Conclusion: The levels of hs-CRP, UA and Cys-C in patients with lacunar cerebral infarction increase with the aggravation of cognitive impairment, and high hs-CRP, UA and Cys-C are independent risk factors of cognitive impairment in patients with lacunar cerebral infarction.

Keywords: Serum uric acid, cystatin C, high-sensitivity C-reactive protein, lacunar cerebral infarction, cognitive impairment

Introduction

Lacunar cerebral infarction is a type of cerebral small vessel disease, and its incidence rate in China is increasing annually [1]. Studies have shown that cognitive impairment is common in patients with lacunar cerebral infarction, and it can progress to vascular dementia without intervention, thus seriously affecting patients' quality of life [2, 3]. Cognitive impairment in patients with lacunar cerebral infarction is often a non-dementia vascular cognitive impairment, and can also be considered as the early stage of vascular dementia [4, 5]. At this stage, patients' cognitive function can further deteriorate and develop into dementia, and it can also be reversed and returned to a normal cognitive state [6, 7].

Previous studies have shown that arteriosclerosis is the pathological basis of lacunar cerebral infarction [8]; inflammation and oxidative stress are initiating factors in the occurrence and development of arteriosclerosis [9, 10]. High-sensitivity C-reactive protein (hs-CRP) can reflect the inflammatory state of human body, studies have shown that inflammatory markers are correlated to cognitive impairment [11]. Elevated serum uric acid (UA) can promote oxidative stress, increase the release of inflammatory factors in the body, and accelerate the development of vascular dementia in patients

with vascular cognitive impairment [12]. Cystatin C (Cys-C) is an indicator reflecting glomerular filtration function. In recent years, more and more studies have indicated that the increase of Cys-C is correlated with the occurrence of cerebrovascular diseases, with a certain predictive effect [13]. The early stage of cognitive impairment can be reversed after treatment, but once cognitive impairment progresses to vascular dementia, it will result in lifelong disability. Therefore, it is of great significance to use all relevant indicators to predict the occurrence of cognitive impairment and make an early diagnosis. The correlation between the above three indicators and cognitive impairment is still controversial [14, 15].

Based on this, lacunar cerebral infarction patients with varying degrees of cognitive impairment were included in this study to measure the hs-CRP, UA and Cys-C, so as to provide more clinical evidence for the prevention and treatment of cognitive impairment caused by lacunar cerebral infarction. The reports are as follows.

Materials and methods

Clinical data

A total of 198 patients with lacunar cerebral infarction who were treated in the Neurology Department of Xinhua Hospital of Ily Kazakh Autonomous Prefecture from January 2017 to January 2020 were selected as the research subjects, and they were followed up for 6 months to evaluate their cognitive function. This study was approved by Ethics Committee of Xinhua Hospital of Ily Kazakh Autonomous Prefecture. All patients or their families in this study signed the informed consent forms.

Inclusion criteria

(1) Patients met the diagnostic criteria of lacunar cerebral infarction [16]; (2) the clinical data was complete, and patients were able to cooperate; (3) patients were 18-76 years old; (4) patients were awake upon admission and could complete the scale measurements.

Exclusion criteria

(1) Patients were excluded with: non-vascular cognitive impairment or cognitive impairment caused by Alzheimer's disease; (2) patients who could not cooperate with cognitive function evaluation; (3) patients who were combined with severe cardiopulmonary disease or recent infection; (4) patients who took metabolic drugs affecting hs-CRP, UA and Cys-C within one month of our study; (5) patients with malignant tumors; (6) patients with mental diseases that affect cognition.

Methods and grouping

Methods

Before admission, two tubes of venous blood were extracted, with 5 mL in each tube. Hs-CRP was determined by serum enzyme-linked immunosorbent assay, UA content was measured by automatic biochemical analyzer (Beckman Coulter, USA) and Cys-C was measured by immunoturbidimetry. The kits were all purchased from Shanghai Enzyme Linked Biology Co., Ltd., China.

Grouping

The cognitive function of the patients was measured by Montreal Cognitive Assessment (MoCA), and patients were divided into 4 groups, with 65 cases in the normal group, 72 cases in the mild cognitive impairment group, 38 cases in the moderate cognitive impairment group and 23 cases in the severe cognitive impairment group [17].

Statistical analysis

SPSS 17.0 statistical software was used to analyze the data. Count data was expressed as the number of cases and percentage (n/%). Continuous variables were expressed as mean ± standard deviation ($\bar{x} \pm sd$). Independent sample t-test was used for the data that conformed to a normal distribution and homogeneity of variances. Pearson's chi-square test (χ^2) was used for the analysis of count data. Logistic regression analysis was used to detect the risk factors of cognitive impairment in lacunar cerebral infarction. Univariate analysis was used for variables with differences. The Ward method was used for variable screening, with inclusion level of 0.05 and exclusion level of 0.1. The risk of decline in MoCA cognitive scoring was expressed by the adjusted odds ratio (OR). $P<0.05$ was considered statistically significant.

Table 1. Comparison of general information among the four groups (n, $\bar{x} \pm sd$)

Items	Normal group (n=65)	Mild group (n=72)	Moderate group (n=38)	Severe group (n=23)	χ^2/t	P
Gender (Male/Female)	35/30	40/32	22/16	13/10	0.170	0.982
Age (year)	67.4±7.5	67.9±7.1	68.1±7.6	68.2±7.9	0.110	0.954
Education	11.2±4.4	11.4±4.3	11.5±3.9	11.4±4.5	0.046	0.987
BMI (kg/m^2)	20.39±2.03	20.45±1.99	20.67±2.07	20.78±2.08	0.311	0.817
Combined disease						
Diabetes	34	45	28	19*	8.881	0.031
Hypertension	35	38	24	14	1.437	0.697
CHD	37	41	23	13	0.169	0.982
Smoking	42	51	31	20*	7.803	0.049
Drinking	39	41	32*	20*	13.887	<0.001
Abdominal obesity	23	34*	29*	18*	22.304	<0.001
Carotid atherosclerosis or stenosis	36	39	26	17	4.573	0.208
Hyperhomocy-steinemia	47	62*	30*	23*	10.166	0.017

Note: Compared with the normal group, *P<0.05. BMI: body mass index; CHD: coronary heart disease.

Table 2. Comparison of hs-CRP, UA and Cys-C among the four groups

Items	hs-CRP (mg/L)	UA (μmol/L)	Cys-C (mg/L)
Normal group (n=65)	3.45±0.73	302.32±52.87	0.92±0.27
Mild group (n=72)	5.78±1.14***	416.23±48.34***	1.19±0.38***
Moderate group (n=38)	7.23±1.21***,###	433.64±53.34***,#	1.39±0.41***,#
Severe group (n=23)	8.76±1.28***,###,&&&	465.73±54.23***,###,&	1.62±0.41***,##,&
χ^2/t	189.124	94.552	27.372
P	<0.001	<0.001	<0.001

Note: Compared with the normal group, ***P<0.001; compared with the mild group, #P<0.05, ##P<0.01, ###P<0.001; compared with the moderate group, &P<0.05, &&&P<0.001. hs-CRP: high-sensitivity C-Reactive Protein; UA: uric acid; Cys-C: Cystatin C.

Table 3. Correlation of hs-CRP, UA and Cys-C with MoCA

MoCA	r	P
hs-CRP (mg/L)	-0.825	<0.001
UA (μmol/L)	-0.718	<0.001
Cys-C (mg/L)	-0.475	<0.001

Note: MoCA: Montreal cognitive assessment; hs-CRP: high-sensitivity C-Reactive Protein; UA: uric acid; Cys-C: cystatin C.

Results

Comparison of general information

There were no differences in gender, age, education, body mass index (BMI), hypertension, carotid atherosclerosis or stenosis, and coronary heart disease among the four groups (all P>0.05). There were statistical differences in diabetes, smoking, drinking, abdominal obesity and hyperhomocysteinemia (all P<0.05). See **Table 1**.

Comparison of hs-CRP, UA and Cys-C among the four groups

There were statistical differences in hs-CRP, UA and Cys-C among the four groups (all P<0.001). With the aggravation of the disease, hs-CRP, UA and Cys-C showed an upward trend (all P<0.05). See **Table 2**.

Correlation of hs-CRP, UA and Cys-C with MoCA

Hs-CRP, UA and Cys-C were negatively correlated with MoCA scores (all P<0.001). See **Table 3** and **Figures 1**-**3**.

Influencing factors of cognitive impairment in patients with lacunar cerebral infarction

Multivariate logistic regression analysis showed that elevated levels of hs-CRP, UA and Cys-C were the influencing factors of cognitive impairment in patients with lacunar cerebral infarction (all P<0.05). See **Tables 4** and **5**.

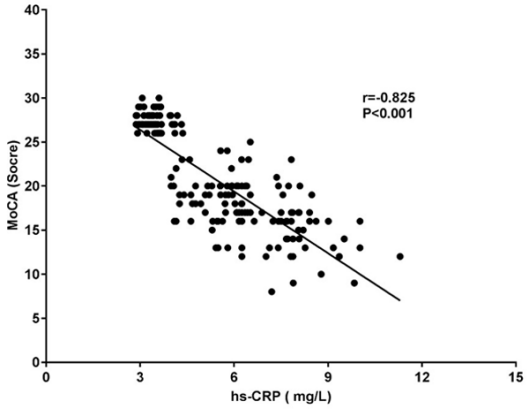

Figure 1. Correlation study between hs-CRP and MoCA. MoCA: Montreal cognitive assessment; hs-CRP: high-sensitivity C-Reactive Protein.

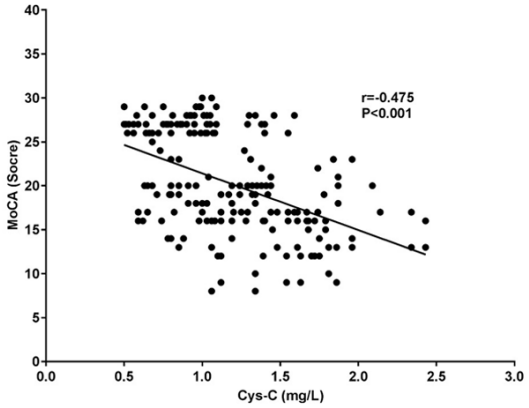

Figure 3. Correlation study between Cys-C and MoCA. MoCA: Montreal cognitive assessment; Cys-C: cystatin C.

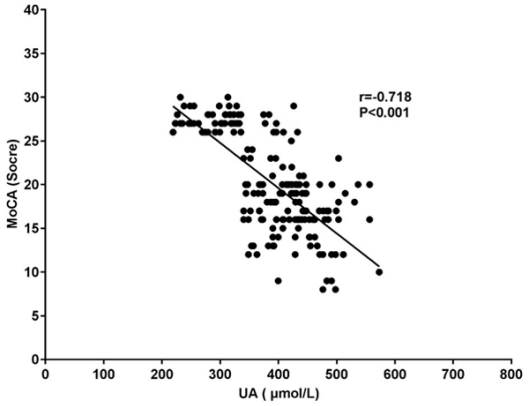

Figure 2. Correlation study between UA and MoCA. MoCA: Montreal cognitive assessment; UA: uric acid.

Discussion

Lacunar cerebral infarction is a common type of cerebral small vessel disease, of which the main pathogenesis is arteriosclerosis [18]. Studies have found that patients with lacunar cerebral infarction are prone to cognitive impairment [19, 20]. Inflammatory factors not only play an important role in the occurrence and development of lacunar cerebral infarction, but also accelerate the occurrence of cognitive impairment after cerebral infarction in an inflammatory state [11, 21]. Some studies have found that the expression of hs-CRP increases in patients with vascular dementia, which may be related to the involvement of hs-CRP in the formation of atherosclerosis [22]. Another study showed that the expression of hs-CRP in patients with non-dementia vascular cognitive impairment increased and was negatively correlated with the MoCA score [23]. However, some studies have found that there is no correlation between the level of hs-CRP and the occurrence of vascular dementia [14]. In this study, it was shown that with the aggravation of cognitive impairment, hs-CRP level presented an increasing trend, which was negatively correlated with MoCA score, and was an independent risk factor for cognitive impairment in patients with lacunar cerebral infarction.

UA has a wide range of physiological functions in the body [24]. The antioxidant properties of UA can reduce the occurrence of oxidative stress and may have a certain neuroprotective effect [25, 26]. However, with the oxidative stress response, UA level significantly increased. The anti-oxidation of UA transformed to pro-oxidation due to the high concentration, which can further promote the oxidation of lipoproteins in atherosclerotic plaques and the proliferation of smooth muscle cells, ultimately lead to vascular endothelial damage [27]. Studies have shown that UA in dementia patients with Alzheimer's disease and Parkinson's disease is shown to have antioxidant effects, it can protect nerve cells and effectively prevent the occurrence of cognitive impairment. However, high levels of UA in patients with vascular dementia have been found to cause brain white matter atrophy and cognitive decline [28-30]. Studies have indicated that uric acid-lowering therapy may have better clinical benefits for high-risk patients who may develop cognitive impairment [31]. Another study also showed that high levels of UA can promote vascular endothelial damage, produce oxidative stress and promote the release of

Table 4. Independent variable assignment table of influencing factors of cognitive impairment in patients with lacunar cerebral infarction

Influencing factors	Independent variable	Assignment
Diabetes	X1	Yes =1, no =0
Smoking	X2	Yes =1, no =0
Drinking	X4	Yes =1, no =0
Abdominal obesity	X5	Yes =1, no =0
Hyperhomocysteinemia	X6	Yes =1, no =0
hs-CRP (mg/L)	X7	>10 mg/L=1, ≤10 mg/L=0
UA (μmol/L)	X8	Male ≥420 μmol/L or female ≥360 μmol/L=1, male <420 μmol/L or female <360 μmol/L=0
Cys-C (mg/L)	X9	>1.09 mg/L=1, ≤1.09 mg/L=0

Note: hs-CRP: high-sensitivity C-Reactive Protein; UA: uric acid; Cys-C: Cystatin C.

Table 5. Influencing factors of cognitive impairment in patients with lacunar cerebral infarction

Influencing factors	β	SE	Wald value	OR value (95% CI)	P
hs-CRP (mg/L)	0.867	0.192	12.034	2.673 (1.167-3.234)	0.012
UA (μmol/L)	0.893	0.223	13.239	2.873 (1.233-3.582)	0.006
Cys-C (mg/L)	0.728	0.148	10.762	2.089 (1.128-3.122)	0.017

Note: hs-CRP: high-sensitivity C-Reactive Protein; UA: uric acid; Cys-C: Cystatin C; SE: standard error; CI: confidence interval; OR: odds ratio.

inflammatory factors [32]. This study showed that with the aggravation of cognitive impairment, UA in patients presented an increasing trend, which was negatively correlated with MoCA score, and was an independent risk factor for cognitive impairment in patients with lacunar cerebral infarction. The result of this study was consistent with the above-mentioned research mechanism.

Cys-C is a reliable indicator of renal function, because it is excreted entirely by the kidneys in the body [33]. In recent years, studies have found that Cys-C level is correlated with the occurrence of cognitive impairment [34]. Studies have reported that there is a positive correlation between the increase of Cys-C and cerebral microvascular hemorrhage in patients with stroke [35]. Cys-C can interfere with the phagocytosis and chemotaxis of granulocytes, promote the release of inflammatory factors, and participate in the occurrence of arteriosclerosis [36]. In elderly patients, increased Cys-C can lead to an increased incidence of cognitive impairment. In patients with renal insufficiency, the higher the Cys-C level, the worse the level of cognition [37]. Another study also found that high levels of Cys-C can induce atherosclerosis, cause damage to vascular walls, promote the release of inflammatory factors and aggravate nerve cell damage [38]. This study showed that with the aggravation of cognitive impairment, Cys-C in patients presented an upward trend, which was negatively correlated with MoCA score. Cys-C was an independent risk factor for cognitive impairment in patients with lacunar cerebral infarction and related to the above research mechanism. In this study, although there were differences in diabetes, smoking, drinking, abdominal obesity, hyperhomocysteinemia and other factors in different groups, they were not independent risk factors leading to cognitive impairment. The result was inconsistent with previous studies and might be related to the small sample size in this study.

The sample size in this study is small, which requires being further expanded in future research. Moreover, the observation time was short, and the follow-up time needs to be further increased to explore the correlation of hs-CRP, UA and Cys-C with cognitive impairment.

To sum up, hs-CRP, UA and Cys-C in patients with lacunar cerebral infarction increase with the aggravation of cognitive impairment, and they are all negatively correlated with MoCA scores. High hs-CRP, UA and Cys-C are independent risk factors of cognitive impairment in patients with lacunar cerebral infarction.

Disclosure of conflict of interest

None.

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