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Original Article

Relationship between blood uric acid level and the onset of acute cerebral infarction

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Abstract: Objective: We discussed the correlation between blood uric acid (BUA) level and the onset of acute cerebral infarction. Method: The measurements of BUA level, blood lipid, blood glucose, and urea and creatinine levels were compared between 640 cases of acute cerebral infarction and 640 healthy cases receiving physical examination. The differences were examined statistically using logistic regression. Result: BUA level of patients with cerebral infarction was higher than that of normal subjects. Correlation analysis indicated that the BUA level was not correlated with age, blood glucose or course of diseases in patients with cerebral infarction; however, it was positively correlated with urea, creatinine, triglyceride and cholesterol, and negatively correlated with length of hospital stay. According to logistic regression analysis, for every increase of BUA level by 1 μmol/L, the risk of acute cerebral infarction decreased by 0.998 time. Conclusion: BUA level of patients with acute cerebral infarction was lower than that in normal subjects; thus BUA level was correlated with the risk of acute cerebral infarction.

Keywords: Cerebral infarction, blood uric acid

Introduction

Blood uric acid (BUA) is the major end product of purine metabolism and the indicator of free radical metabolism. BUA was once held to be a metabolic product with no physiological significance. There is now a growing body of evidences on the correlation between BUA level and incidence and mortality of cardiovascular and cerebrovascular diseases. To confirm this, we analyzed the correlation between BUA level and the onset of acute cerebral infarction.

Elevated serum uric acid independently predicts stroke and excess mortality in the general elderly population. Present evidence indicated that BUA independently associated with increased incidence of fatal stroke [1]. Over the last few years, considerable progress has been made in identifying and treating modifiable risk factors for stroke. BUA has traditionally been thought of as an inert byproduct of the catabolism of ingested and endogenous nucleoproteins and purines [2]. However, if identified as an etiological agent in the pathogenesis of vascular disease, hyperuricemia could be targeted therapeutically in the same way that we now routinely treat other risk factors such as dyslipidemia and blood pressure after stroke. Therefore, in the present study, we aimed to investigate the relation between BUA level and the onset of acute cerebral infarction.

Materials and method

Subjects

Patients with cerebral infarction (case group): From July 2012 to July 2014, 640 patients with cerebral infarction treated at our hospital were included. The course of diseases was less than 15 days; the patients were confirmed by brain CT scan and MRI, and they all satisfied the diagnostic criteria for acute cerebral infarction. There were 439 males and 201 females aged 18-85 years, with range of 67 and male/female ratio of 2.184:1.

Normal subjects (control group): For the control group, 640 normal subjects receiving physical examination during the same period were recruited; they were 439 males and 201 fe-

Table 1. Frequency matching by age

Age group (years)	Number of subjects
≤20	4
21~	7
26~	12
31~	23
36~	52
41~	103
46~	144
51~	119
56~	72
61~	36
66~	28
71~	23
76~	11
81~	6

males aged 18-84 years, with range of 66 and male/female ratio of 2.184:1.

The frequency matching of controls to cases was done by age with an interval of 5 years (**Table 1**).

The difference in gender composition of the two groups was tested by χ^2 test, and P=1.00, indicating no statistically significant difference. No cases in the two groups were combined with gout, leukemia, tumors, diabetic ketoacidosis, hyperlipemia and abnormal renal and liver function.

Methods

Cases with cerebral infarction received brain CT scan or MRI upon admission along with abdominal Doppler ultrasound, ECG, and chest X-ray. Venous blood was drawn to perform routine blood test, liver and kidney function test, lipid complete set and blood glucose detection. The general information of the patients was collected, including age, gender, height, weight and past medical history. The same set of clinical data of normal subjects was collected upon physical examination. The equipments used for detection included biochemical analyzer (ROCHE DDP) and centrifuge (TDZ4A-WS).

Statistical analysis

Statistical analyses were performed using SPSS 21.0 and SAS 9.3 software. χ^2 test, rank correlation test, binary logistic regression and analysis of variance were performed, and P< 0.05 was considered statistically significant.

Results

General information of onset of acute cerebral infarction

Table 2 shows the constituent ratios of acute cerebral infarction sites. Of 640 patients with cerebral infarction, those with multiple lacunar infarctions took up the largest proportion (34.84%), followed by right hemisphere cerebral infarction (29.22%) and left hemisphere cerebral infarction (24.69%).

Table 3 shows the constituent ratios of complications in patients with cerebral infarction. Patients combined with complications accounted for 78.90%. Hypertension had the highest incidence (53.59%), followed by diabetes (32.81%), carotid atherosclerosis (21.41%) and coronary heart disease (19.69%).

Difference in BUA level between the two groups

Except BUA level, all other measurements obeyed normal distribution (P=0.000). Thus the differences in each indicator between the two groups were analyzed by Wilcoxon rank-sum test (**Table 4**). It was found that the two groups differed in BUA level, BUA level being lower in the case group than in the control group (P=0.013).

Correlation analysis

Analysis of correlations between BUA level and other indicators in case group (**Table 5**).

The measurements of BUA, age, urea, creatinine, triglyceride, cholesterol and blood glucose did not obey normal distribution. Therefore, the correlations between BUA level and other indicators were analyzed by Spearman rank-sum test (**Table 5**). It was found that BUA level was not correlated with age, blood glucose and course of disease in case group; however, BUA level was positively correlated with urea, creatinine, triglyceride and cholesterol, and negatively correlated with length of hospital stay.

Analysis of correlations between BUA level and other indicators in control group

In control group, the measurements of BUA, age, urea, creatinine, triglyceride, cholesterol

Table 2. Constituent ratios of cerebral infarction sites

Sites of cerebral infarction	Number of cases	Constituent ratio (%)
Left hemisphere	158	24.69
Left hemisphere, right hemisphere	8	1.25
Left hemisphere, left cerebellum	2	0.31
Right hemisphere	187	29.22
Right hemisphere, right cerebellum	1	0.16
Left cerebellum	13	2.03
Left cerebellum, right cerebellum	9	1.41
Right cerebellum	15	2.34
Multiple lacunar infarction	223	34.84
Other (medulla oblongata, thalamus)	24	3.75

and blood glucose did not obey normal distribution. Therefore, the correlations between BUA level and other indicators were analyzed by Spearman rank-sum test (**Table 6**). It can be seen that BUA level of the control group was not correlated with age, triglyceride, cholesterol and blood glucose, while the correlation was positive with urea and creatinine.

Correlation between BUA level and cerebral infarction

To detect the correlations between cerebral infarction as the independent variable and gender, age, BUA, triglyceride, cholesterol, creatinine, blood glucose and urea as dependent variables, binary logistic regression was performed (**Table 7**). It was found that for every increase of BUA level by 1 μmol/L, the risk of cerebral infarction decreased by 0.998 time (OR: 0.998; 95% CI: 0.996-0.999; P<0.05).

Discussion

The correlations between BUA and cerebrovascular disease have not been established until recently. Some studies suggest that an elevated BUA level is a risk factor of cerebrovascular disease; others indicate exactly the opposite, i.e., high BUA level has a protective effect against ischemic stroke.

Epidemiological features of patients with acute cerebral infarction treated at our hospital

We found that the number of males treated at our hospital for acute cerebral infarction was greater than that of females, and the peak age of onset was 40-55 years. Multiple lacunar infarctions took up the largest proportion, followed by right hemisphere cerebral infarction and left hemisphere cerebral infarction. There were more infarctions of the right internal carotid artery compared to the left internal carotid artery, which agreed with the findings by Lin et al [3]. The patients with complications accounted for 2/3. Hypertension was the complication with the highest incidence, followed by diabetes. This coincided with the ranking of risk factors of cerebral infarction in Chinese Guidelines for the Prevention of Acute Ischemic Stroke [4].

Difference in BUA level between patients with acute cerebral infarction and normal subjects

After excluding the influence of gender and age factors, we found that BUA level in patients with cerebral infarction was lower than that in normal subjects.

There are only limited studies by foreign researchers on the correlation between cerebral infarction and BUA level, and the conclusions drawn are inconsistent. Chamorro A et al. [5] carried out a prospective study on 881 patients with acute cerebral infarction. With confounding factors excluded, it was found that an elevated BUA level predicted good prognosis in cerebral infarction. Multivariate analysis indicated that BUA level had a positive correlation with the prognosis of acute cerebral infarction. For every increase of BUA level by 1 mg/dl, the probability of good prognosis increased by 12%. Therefore, severe cerebral infarction was associated with a reduction in BUA level. During the URICO-ICTUS study [6], 411 patients were included at 90 days after the onset of acute cerebral infarction. They were randomly divided into UA treatment group (211 cases) and placebo group (200 cases) and received injection of 1000 mg UA and placebo, respectively. Observations showed that there were no extra benefits gained from treatment with UA as compared with placebo, and neither was there any aggravation of symptoms. During a small-scale clinical trial consisting of 22 cases with acute cerebral infarction, BUA, ascorbic acid and glutathione levels were measured, based on which the anti-oxidative capacity was estimated. The results indicated that BUA was the major antioxidant and the anti-oxidative capacity of the plasma was significantly negatively correlated with area of cerebral infarct and degree of nerve damage. The above findings confirm the protective effect of elevated BUA level on brain

Table 3. Constituent ratios of complications

Complications	Number of cases	Constituent ratio (%)
Diabetes	37	5.78
Diabetes, hypertension	98	15.31
Diabetes, coronary heart disease	6	0.94
Diabetes, carotid atherosclerosis	19	2.97
Diabetes, hypertension, coronary heart disease	11	1.72
Diabetes, hypertension, carotid atherosclerosis	27	4.22
Diabetes, hypertension, carotid atherosclerosis	3	0.47
Diabetes, hypertension, coronary heart disease, carotid atherosclerosis	9	1.41
Hypertension	136	21.25
Hypertension, coronary heart disease	17	2.66
Hypertension, carotid atherosclerosis	34	5.31
Hypertension, coronary heart disease, carotid atherosclerosis	11	1.72
Coronary heart disease	63	9.84
Coronary heart disease, carotid atherosclerosis	6	0.94
Carotid atherosclerosis	28	4.38
No complications	135	21.10

Table 4. Test for normal distribution and Wilcoxon rank-sum test

Indicator		Test for normal distribution		Wilcoxon rank-sum test	
		Statistic	*P* value	Rank sum	*P* value
BUA	Control group	0.972	0.000	426401.50	0.013
	Case group	0.990	0.000	393438.50	

tissues after ischemic stroke. Bos et al. [7] performed a follow-up investigation on 4385 subjects for 8.4 years in Rotterdam, aiming to understand the correlation between BUA level and heart attack and cerebral apoplexy. They found that the elevated BUA level was an important risk factor of ischemic stroke. In a 1-year follow-up study of 463 patients with cerebral infarction by Chiquete E et al. [8], lower BUA level predicted a better short-term prognosis. Thus BUA level was the marker of severity of cerebral infarction rather than an independent risk factor. In the present study, we found that BUA level of patients with acute cerebral infarction was lower than that in normal subjects, which was suggestive of the protective effect of elevated BUA level on acute cerebral infarction. This agreed with the conclusion by Chamorro A et al.

Among a few studies on the correlation between cerebral infarction and BUA level in China, there are only limited subjects included. The test for normal distribution and statistical analyses are presented in fewer details. It is generally concluded that BUA level of patients with cerebral infarction is higher than that in normal subjects. Wang et al. [9] compared the measurements of BUA level in 55 patients with cerebral infarction and 55 healthy subjects receiving physical examination. Logistic regression analysis revealed that patients with cerebral infarction had higher BUA level as compared with normal subjects. Thus an elevated BUA level indicated greater risk of acute cerebral infarction. Ji et al. [10] performed a comparison of BUA level in 163 patients with cerebral infarction and 67 healthy subjects and found that BUA level was considerably higher in patients with cerebral infarction. Zhang et al. [11] compared BUA levels between 56 patients with acute cerebral infarction and 40 non-infarction patients in the same period, concluding that cerebral infarction was associated with a higher BUA level. Wang [12] compared BUA levels between 86 patients with acute cerebral infarction and 80 normal subjects receiving physical examination. The result indicated a much higher BUA level in cerebral infarction as compared with the control group. The present study had a quite large sample size and the course of dis-

Table 5. Analysis of correlations between BUA level and other indicators

	BUA		Triglyceride		Cholesterol		Blood glucose	
	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value
Age	0.025	0.530	-0.021	0.594	0.090	0.023	0.058	0.144
Urea	0.171	0.000	0.034	0.384	0.104	0.009	0.090	0.023
Creatinine	0.442	0.000	0.145	0.000	0.149	0.000	0.044	0.269
Triglyceride	0.250	0.000			0.411	0.000	0.206	0.000
Cholesterol	0.198	0.000	0.411	0.000			0.066	0.095
Blood glucose	-0.059	0.136	0.206	0.000	0.066	0.095		
Course of disease	0.035	0.105						
Length of hospital stay	-0.073	0.001						

Table 6. Analysis of correlations between BUA level and other indicators in control group

	BUA				Triglyceride		Blood glucose	
	r_s	*P* value	r_s	*P* value	r_s	*P* value	r_s	*P* value
Age	-0.015	0.701	0.000	0.996	0.170	0.000	0.213	0.000
Urea	0.104	0.009	-0.079	0.046	-0.034	0.386	0.028	0.485
Creatinine	0.480	0.000	0.009	0.829	-0.052	0.186	-0.041	0.297
Triglyceride	0.041	0.299			0.217	0.000	0.041	0.295
Cholesterol	-0.021	0.592	0.217	0.000			0.023	0.554
Blood glucose	-0.036	0.362	0.041	0.295	0.023	0.554		

Table 7. Logistic regression analysis of the indicators among all cases

Variable	Partial regression coefficient	Standard error	Wald χ^2	*P* value	OR value	OR value and 95% confidence level	
						Lower limit	Upper limit
Constant	-1.804	0.631	8.168	0.004	0.165		
BUA	-0.002	0.001	6.707	0.010	0.998	0.996	0.999
Triglyceride	2.356	0.185	162.384	0.000	10.552	7.344	15.161
Cholesterol	-1.011	0.094	115.768	0.000	0.364	0.303	0.437
Blood glucose	0.642	0.082	61.217	0.000	1.900	1.618	2.231

ease was less than 30 days. After excluding the influence factors such as gender and age, it was found that the BUA level of patients with cerebral infarction was lower than that of normal subjects. This goes contrary to the findings by many other Chinese researchers.

Correlations between BUA level and other indicators in patients with cerebral infarction

Among patients with acute cerebral infarction, BUA level was not correlated with age, blood glucose level or course of disease; but it had a positive correlation with urea, creatinine, triglyceride and cholesterol and a negative correlation with length of hospital stay. Thus it was concluded that the BUA level in acute cerebral infarction was not influenced by age, blood glucose or course of disease. However, BUA level increased with the increase in liver function test and blood lipid level. A longer hospital stay usually indicated greater severity of disease. For patients with longer hospital stay, the lower the BUA level upon onset, the more severe the disease was. At present, the correlation analyses between indicators in patients with acute cerebral infarction are few.

Correlation between BUA level and cerebral infarction

Through logistic regression analysis, we found that for every increase of BUA level by 1 μmol/L, the risk of cerebral infarction decreased by 0.998 time. This indicated the protective effect of elevated BUA level on cerebral infarction, which agreed with the finding by Chamorro A et al.

Although many studies indicate that elevated BUA level is a risk factor of cerebral infarction, there are some epidemiological and clinical trials discovering that high BUA level is protective

against nerve damage in the brain; BUA level may predict lower risk of cerebral infarction and better prognosis. The main justification of the protective effect of hyperuricemia on brain nerves lies in the associated anti-oxidative capacity. An increase in free radicals is a major cause underlying cerebral infarction, and BUA protects extracellular superoxide dismutase (SOD) and removes the free radicals. We carried out a preliminary analysis on the correlations of BUA, blood lipid and blood glucose levels with the onset of cerebral infarction. But this study was a cross-sectional study. Although the confounding factors such as gender and age were excluded and the sample size was large, we were still unable to fully confirm the causal relationship between BUA level and the risk of acute cerebral infarction. Given the inconsistent conclusions by domestic and foreign researches, more large-scale clinical trials are needed on the influence of BUA level on acute cerebral infarction.

Disclosure of conflict of interest

None.

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