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ORIGINAL ARTICLE

Association of uric acid with stenosis of intracranial and extracranial arteries in elderly patients with cerebral infarction

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Abstract

Background To determine whether uric acid (UA) and intracranial and extracranial atherosclerosis stenosis of elderly patients suffering from ischaemic stroke are inter-related.

Methods Elderly patients with ischaemic stroke underwent computed tomography angiography (CTA) were enrolled between October 2015 and December 2017. We collected clinical assessment, image data, and laboratory tests, and divided patients into four groups: (1) intracranial stenosis atherosclerosis (ICAS) group, (2) combined intracranial and extracranial atherosclerosis stenosis (COAS) group, (3) extracranial carotid stenosis atherosclerosis (ECAS) group, and (4) non-cerebral stenosis atherosclerosis (NCAS) group. We used univariate and multiple logistic regression analyses to explore potential predictors.

Results We included 408 patients in this study, then divided them into elder group ($n = 196$) and young- and middle-aged group ($n = 212$). In old stroke patients, 72 cases (36.73%) were classified as the ICAS group, 45 cases (22.96%) as the COAS group, 21 cases (10.71%) as the ECAS group, and 58 cases (29.59%) as the NCAS group. The level of UA was comparatively higher ($p = 0.033$) in ICAS than in NCAS. Compared with the group which had only one stenosis artery, UA was substantially increased in patients with more than one stenosis intracranial artery ($p < 0.001$). With a multivariable analysis, UA was an independent predictor for intracranial stenosis of elderly patients (OR = 1.003, $p = 0.042$), but the relationship between extracranial artery stenosis and uric acid was negative.

Conclusions Hyperuricaemia is a risk factor of intracranial artery stenosis rather than of ECAS in elderly patients with cerebral infarction.

Keywords Atherosclerotic · Cerebral infarction · Arterial stenosis · Uric acid

Introduction

Cerebral infarction at an old age is a societal challenge with a rising incidence. Intracranial and extracranial arteriopathies are the pathological foundations of ischemic stroke [1, 2]. The influence of uric acid (UA) on cardio-cerebrovascular disease is controversial [3, 4]. Few studies had explored the relation between UA and cerebral atherosclerosis stenosis. We aimed to assess the different levels of UA between ICAS, ECAS, and NCAS among elderly patients with cerebral infarction.

Materials and methods

Study subject

Our study included people who suffered from cerebral infarction (≤ 7 days of onset) admitted to our facility retrospectively between October 2015 and December 2017. We classified them into four groups based on their vascular imaging as follows: (1) intracranial stenosis atherosclerosis (ICAS) group, (2) combined intracranial and extracranial atherosclerosis stenosis (COAS) group, (3) extracranial carotid stenosis atherosclerosis (ECAS) group, and (4) non-cerebral stenosis atherosclerosis (NCAS) group. The elder group included patients older than 60 years and the young- and middle-aged group included

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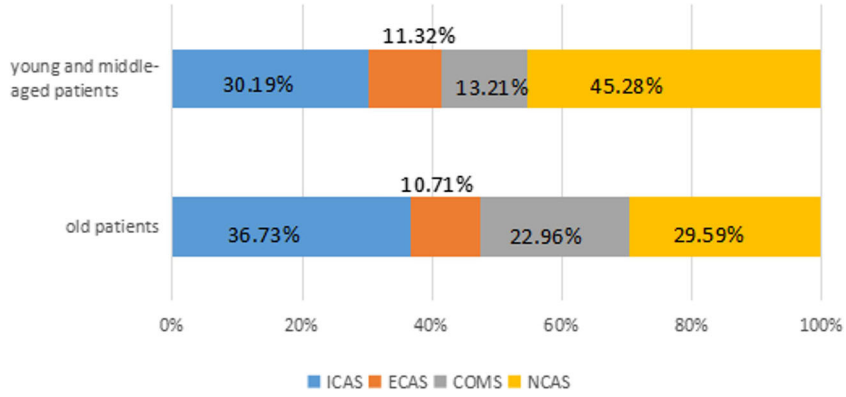

Fig. 1 Distribution of cerebral atherosclerosis stenosis in different age

patients not older than 60 years. We collected data on clinical assessments, imaging studies, and laboratory tests.

Subject inclusion criteria: (1) patients with stroke matched with the 2010 Guidelines for the Chinese Diagnosis and Treatment of Acute Ischemic Stroke [5]; (2) age > 18; (3) examined by CTA.

Subject exclusion criteria: (1) age ≤ l8; (2) vascular imaging and laboratory tests were incomplete; (3) had drugs affecting uric acid metabolism use in 3 months (for example, diuretics, anti-gout drug); (4) stroke of other determined aetiologies.

This study was approved by the Ethics Committees of Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China. Informed consents were signed by patients or their family members.

Blood tests

Blood samples for fasting concentrations were drawn in the morning within 24 h. Serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), UA, low-density lipoprotein cholesterol (LDL-C) fibrinogen (Fib), haemoglobin A1C (HbAlC), and homocysteine (HCY) were analysed using a Beckman AU680 Chemistry System and a Beckman LH 780 haematology analyser according to the manufacturer's instructions (Beckman Coulter, Brea, CA, USA).

Computed tomography angiography

Computed tomography angiography (CTA) was performed in all patients using a 64-slice double source CT from Siemens AG. The vascular images were evaluated by two independent reviewers (M.M.L and Y.H.H).

Definition on stenosis of intracranial and extracranial arteries

The intracranial arteries included the intracranial portion of the carotid artery (I-ICA) (C4-C7), middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral

Table 1 Baseline characteristics among groups

Clinical characteristics	ICAS $n = 72$	ECAS $n = 21$	COAS $n = 45$	NOCS $n = 58$
Age (years)	72.15 ± 5.73	74.19 ± 4.81	72.18 ± 5.22	73.34 ± 5.59
TC (mmol/L)	4.98 ± 1.11	5.36 ± 1.00*	5.28 ± 1.15*	4.63 ± 1.26
TG (mmol/L)	1.49 ± 0.70	1.44 ± 0.71	1.45 ± 0.86	1.43 ± 1.00
HDL-C (mmol/L)	1.14 ± 0.30	1.28 ± 0.30	1.16 ± 0.33	1.21 ± 0.30
LDL-C (mmol/L)	3.20 ± 0.86	3.31 ± 0.73*	3.37 ± 0.87*	2.71 ± 0.90
UA (μmol/L)	340.59 ± 91.83*	341.09 ± 83.17	350.56 ± 93.77*	304.34 ± 99.34
Glycosylated haemoglobin (%)	6.13 ± 2.69	5.94 ± 2.46	5.36 ± 3.14	6.17 ± 2.41
HCY (μmol/L)	11.92 ± 6.63	10.16 ± 3.49	11.54 ± 9.12	11.55 ± 6.90
Fib (g/L)	3.67 ± 1.39	3.29 ± 1.21	3.44 ± 1.25	3.40 ± 1.88
Gender (male)	36(50.0%)	13(61.9%)	31(68.9%)	40(69.0%)
Hypertension (*n* (%))	54(75.0%)	11(52.4%)	34(75.6%)	36(62.1%)
Diabetes (*n* (%))	25(34.7)	9(42.9%)	14(31.1%)	14(24.1%)
Smoker (*n* (%))	21(29.2%)	8(38.1%)	18(40。0%)	23(39.7)

*$p < 0.05$ vs NCAS

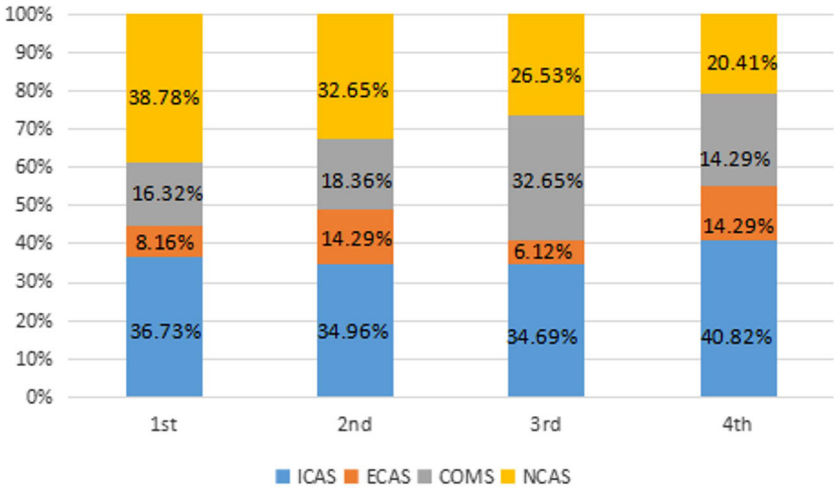

Fig. 2 Distribution of group according to UA

artery (PCA), intracranial portion of vertebral artery (I-VA) (V4), and basilar artery (BA). The extracranial arteries included the carotid artery (CCA), external carotid artery (ECA), the extracranial portion of internal carotid artery (E-ICA) (C1), the extracranial portion of vertebral artery (V1-V3), and the subclavian artery (SCA).

Statistical analysis

We used SPSS20.0 for statistical analysis. Data were performed as mean ± SD, or SE, or *n* of subjects (%).We used the chi-square test for categorical variables and *t* test or one-way analysis of variance for continuous variables. We performed multivariable logistic regression analysis to identify the independent predictor. Results were given by ORs and their 95% CIs. *p* value < 0.05 was considered statistically significant.

Results

One hundred ninety-six elderly patients were enrolled in this research, and 212 young- and middle-aged patients at the same time, altogether 408 patients. The elder group had a mean ± SD age of 72.73 ± 5.37 years (range 65–89 years) and 120 were male.

Distribution of cerebral atherosclerosis stenosis

In old patients, 72 (36.73%) were classified as ICAS, 45 (22.96%) as COAS, 21 (10.71%) as ECAS, and 58 (29.59%) as NCAS. In young- and middle-aged patients, 64(30.19%) were classified as ICAS, 28 (13.21%) as COAS, 24 (11.32%) as ECAS, and 96(45.58%) as NCAS. Compared with young- and middle-aged patients, cerebral artery stenoses often happen in old people, especially intracranial artery stenoses (Fig. 1).

The proportion of old patients with different numbers of stenoses of intracranial arteries was as follows: 53 (27.04%) of one artery, 35 (17.18%) of two arteries, and 29 (14.80%) of three or more arteries.

The proportion of old patients with different numbers of stenoses of extracranial arteries was as follows: 41 (20.92%) of one artery, 15 (7.65%) of two arteries, and 9 (4.59%) of three or more arteries.

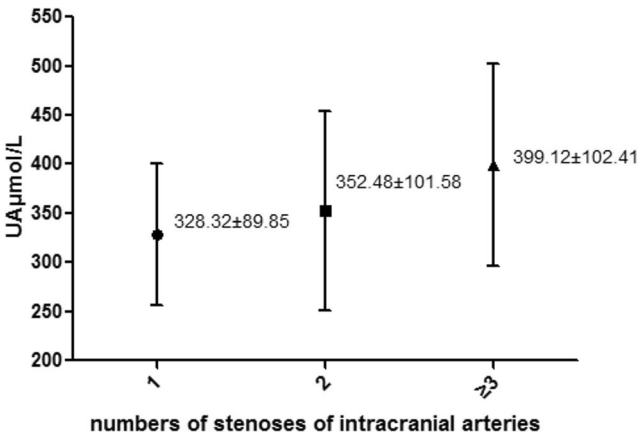

Fig. 3 Serum levels of UA according to severity of ICAS

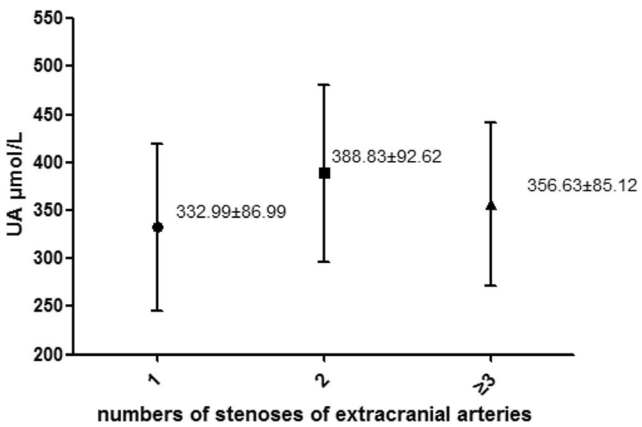

Fig. 4 Serum levels of UA according to severity of ECAS

Table 2 Multivariate logistic regression analyses for predictors of ICAS

	B	Wald	*p*	OR	OR (95% CI)
Age	− 0.04	2.003	0.157	0.961	0.909–1.016
TC	− 0.475	1.156	0.282	0.622	0.261–1.479
LDL-C	0.79	2.122	0.145	2.202	0.761–6.371
UA	0.003	4.116	0.042	1.003	1.000–1.007
Diabetes	− 0.024	0.005	0.946	0.977	0.492–1.938
Gender	− 0.301	0.713	0.399	0.74	0.368–1.488
Hypertension	0.653	3.606	0.058	1.922	0.979–3.771

The control group for NCAS group and ECAS group

Single factor analysis

In old patients, compared with NCAS, the ICAS group showed significantly higher frequencies of male ($p = 0.033$, $X^2 = 4.76$). The ICAS, ECAS, and COAS groups showed higher levels of LDL-C ($p = 0.048$, $p = 0.015$, and 0.002, respectively), the TC levels were higher in ICAS and COAS ($p = 0.02$ and $p = 0.08$, respectively), and the UA levels were higher in ICAS and COAS ($p = 0.033$ and $p = 0.018$, respectively). But, there was no statistical difference of other characteristics (Table 1).

Divided UA into quarters (1st ≤ 261.2 μmol/L; 261.2 μmol/L < 2nd ≤ 321.9 μmol/L; 321.9 μmol/L < 3rd ≤ 388.8 μmol/L; 4th > 388.8 μmol/L), where the higher the level of UA, the higher the percentage of cerebral atherosclerosis stenosis would be ($X^2 = 9.231$, $p = 0.024$) (Fig. 2).

Compared with the group which had only one stenosis artery, the advanced stenosis group had higher level of UA ($p < 0.001$) (Fig. 3). The level of UA had no statistical differences in different numbers of ECAS (Fig. 4).

Multivariable logistic analysis

We selected age, TC, LDL-C, UA, diabetes mellitus, gender, and hypertension into multivariable logistic analysis. We found that UA was independently associated with ICAS (OR 0.003, 95% CI 1.000–1.007) (Table 2). But UA was not an independent risk factor of ECAS (Table 3).

Table 3 Multivariate logistic regression analyses for predictors of ECAS

	B	Wald	*p*	OR	OR (95% CI)
Age	0.016	0.313	0.576	1.017	0.960–1.077
TC	− 0.121	0.072	0.788	0.886	0.367–2.140
LDL-C	0.805	2.053	0.152	2.236	0.744–6.723
UA	0.002	1.7	0.192	1.002	0.999–1.006
Diabetes	0.253	0.495	0.482	1.288	0.637–2.605
Gender	0.863	5.096	0.024	2.37	1.120–5.015
Hypertension	− 0.079	0.048	0.827	0.924	0.455–1.876

The control group for ICAS group and NCAS group

Discussion

UA is a final product from purine metabolism [6]. Statistics showed that about 10% of Chinese population suffers from hyperuricaemia by a previous study [7]. The relationship of UA with cardiovascular disease is controversial [3, 4]. It was once thought that UA was an antioxidative substance which could prevent arteriosclerosis [3]. But recently, some prospective researches have showed the level of UA was a significant predictor for cerebral-cardiovascular diseases. Some American scholars argued hyperuricaemia was an independent risk factor for myocardial infarction and cerebral infarction [8]. Sciacqua insisted that UA was a predictor for cardiovascular events among post-menopausal women [4]. Some experts argued that hyperuricemia increased the risk of death and recurrence in stroke patients [9, 10]. According to our study, hyperuricaemia was a predictor of intracranial atherosclerosis stenosis. The level of UA was higher in people who had more lesions of intracranial atherosclerosis stenosis.

Hyperuricaemia plays an important role of pathogenesis of arteriosclerosis: (1) Lipid peroxidation is promoted by UA that creates the oxy-radicals which leads to the inflammation of the vascular wall and promotes atherosclerosis [11]. (2) The excess of UA turns into crystals, triggering severe inflammation in vascular walls [12]. Some research show that there is a large amount of uric acid crystals in atherosclerotic plaques [13]. (3) UA cause the inflammation which leads to platelet activation. That spurs a cascade of coagulation which causes atherothrombosis finally [14]; (4) UA actives local oxidising agents and inflammatory cytokines, for example, interleukin (IL)-1b, tumour necrosis factor-a, and IL-6 [15]; (5) Activation of the renin-angiotensin system related with UA may attack cerebral circulation [16].

In our study, UA was the independent predictor of ICAS, rather than for ECAS. The results proved that risk factors of intracranial and extracranial atherosclerosis stenosis were different which was consistent with Li [17], but different from Kumral [18].This discrepancy might be attributed to ethnic differences [19].

Lanllnei [20] insisted that the component of atherosclerotic plaques was not the same between intracranial and extracranial arteries from autopsies of ischaemic stroke patients. Compared with normal people, some clinical research indicated that there were less antioxidants which had the function to cure atherosclerosis in some degree in intracranial arteries of patients with steno-occlusive intracranial arteries [21]. Moreover some studies found that low wall shear stress and hyperlipemia were main risk haemodynamic factors in the development of atherosclerotic plaque in extracranial arteries

[22, 23]. So, antioxidants played a role of protective factor for intracranial stenosis.

In the current study, TC, LDL-C, age, hypertension, and DM were not the independent predictors of intracranial stenosis or extracranial stenosis, which was not consistent with previous studies [24]. It was due to not only the insufficient sample size but selection bias caused by our retrospective research. So larger studies of diverse populations will be needed.

In conclusion, our research suggests that hyperuricaemia as an independent predictor for intracranial artery stenosis in elderly patients with ischaemic stroke.

Compliance with ethical standards

This study was approved by the Ethics Committees of Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China. Informed consents were signed by patients or their family members.

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