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The association of uric acid with leukoaraiosis

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Abstract

Objective: To explore the possible correlation between uric acid levels and leukoaraiosis (LA).
Methods: This cross-sectional study enrolled patients who presented with some neurological discomfort (e.g. dizziness, headache, mild cognitive impairment). Potential demographic and clinical risk factors associated with LA, including sex, age, hypertension, diabetes mellitus, smoking, alcohol consumption, dyslipidaemia, plasma fibrinogen, D-dimer, uric acid, and homocysteine, were investigated using univariate and multivariate logistic regression analyses.
Results: A total of 268 patients were enrolled in the study and divided into the LA group ($n = 164$) and the non-LA group ($n = 104$). Compared with the non-LA group, uric acid was significantly higher in the LA group (mean $\pm$ SD: 356.49 ± 121.85 μmol/l versus 289.96 ± 102.98 μmol/l). Multivariate logistic regression analyses showed that uric acid was an independent risk factor for LA (odds ratio 1.285; 95% confidence interval 1.062, 1.556).
Conclusion: Hyperuricaemia was an independent risk factor for leukoaraiosis in Chinese patients.

Keywords
Uric acid, leukoaraiosis

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Introduction

Leukoaraiosis (LA), also known as white matter hyperintensities, is a spot or patch of white matter lesions around the ventricles and subcortex (semioval centre).[1] LA is not only associated with affective disorder and cognitive impairment in the elderly,[2] it is also associated with the incidence, recurrence and prognosis of stroke.[2–4] A clearer understanding of the risk factors associated with the development of LA is required so that treatment can be initiated as early as possible in order to reduce clinical

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symptoms and subsequent serious complications. Uric acid is a metabolic end product of endogenous and exogenous purine metabolism.[5] With an improvement in living standards and a change in diet composition, the levels of uric acid and the prevalence of hyperuricaemia can increase.[6] According a survey undertaken in China, 10% of the total population has hyperuricaemia, which accounts for around 120 million people.[7] The correlation between uric acid and acute ischaemic stroke is still disputed.[8,9] Few studies exist that have investigated the correlation between uric acid and acute ischaemic stroke.[6] The aim of this present study was to investigate the possible correlation between uric acid levels and LA in a Chinese population.

Patients and methods

Study patients

This cross-sectional study consecutively enrolled patients who presented with some neurological discomfort (e.g. dizziness, headache, mild cognitive impairment) at the following three hospitals between May 2013 and May 2014: Department of Neurology, Quanzhou First Hospital, Quanzhou, Fujian Province, China; Department of Neurology, Hospital of Jinjiang City, Jinjiang, Fujian Province, China; and Department of Neurology, Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China. The inclusion criteria were as follows: (i) aged 40–80 years; (ii) no cerebral haemorrhage, intracranial mass, subarachnoid haemorrhage, epidural haematoma and subdural haematoma as confirmed by computed tomography (CT) scans of the head; (iii) able to undergo magnetic resonance imaging (MRI) examination; and (iv) no disorders of consciousness. The exclusion criteria were as follows: (i) acute cerebral infarction; (ii) haemorrhagic stroke, brain tumour, meningitis, and intracranial aneurysm; (iii) cerebral trauma, atrial fibrillation, hepatic, kidney and cardiac failure, severe infection, malignant disease, systemic lupus erythematosus, multiple sclerosis (MS) and genetic disease; (iv) a history of carbon monoxide, food or drug poisoning; (v) patients who cannot take care themselves; (vi) a score on the Montreal Cognitive Assessment scale < 26;[10] (vii) hypoattenuated substantia alba caused by MS, intracranial infection, radiation encephalopathy, carbon monoxide poisoning, Alzheimer's disease, brain trauma, normal hydrocephalus, connective tissue disease, hypotension (blood pressure $< 90/60$ mmHg), postural hypotension, anaemia, demyelinating diseases and adrenoleukodystrophy.

The study was approved by the Ethics Committees of: Quanzhou First Hospital, Quanzhou, Fujian Province, China; Hospital of Jinjiang City, Jinjiang, Fujian Province, China; and Second Affiliated Hospital of Fujian Medical University, Quanzhou, Fujian Province, China (registration numbers: QZSYLL382, JJSYY648, FYDFSEY362). Patients or their family members provided written informed consent.

Magnetic resonance imaging

All patients underwent an MRI examination, including axial T1-weighted images, T2-weighted images, fluid-attenuated inversion recovery images and diffusion-weighted images using a GYROSCAN ACS-NT scanner (magnetic field intensity was 1.5 T, slice thickness 5 mm, interslice gap 0.5 mm; Philips Healthcare, Best, the Netherlands). All images were read by two neuroimaging experts (Y.H.H. and R.W.C.). Leukoaraiosis was diagnosed according to previously published criteria.[1] All patients examined by MRI were subdivided into an LA group and a non-LA group.

Clinical data collection

When the patients attended the hospital, their complete medical history was taken. The routine clinical data from all patients enrolled in the study, including sex, age, smoking status, alcohol consumption, hypertension, diabetes mellitus, coronary artery disease (CAD), fasting blood glucose, globulin, albumin, cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, apolipoprotein-A, apolipoprotein-B, homocysteine, platelet count, haematocrit, fibrinogen, D-dimer and uric acid were collected from the hospital databases using a unified questionnaire. The biochemical and haematological parameters 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).

The presence of atherosclerotic risk factors was standardized as follows: (i) hypertension was recorded when systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg more than three times during the 7 days after a stroke on different days or a history of physician-diagnosed hypertension and/or taking antihypertensive medication; (ii) diabetes mellitus was recorded when there were symptoms (e.g. excessive thirst, frequent or increased urination, especially at night; excessive hunger; fatigue; blurred vision; sores or cuts that won't heal; and weight loss) of diabetes plus a random blood glucose ≥ 11.1 mmol/l, or when there were symptoms of diabetes plus a fasting blood glucose ≥ 7.0 mmol/l, or when there were symptoms of diabetes plus a blood glucose ≥ 11.1 mmol/l at 2 h in an oral glucose tolerance test, or a history of diabetes mellitus; (iii) CAD when there was a history of CAD, or CT angiography or digital subtraction angiography evidence of coronary artery stenosis degree $\geq 50\%$, or typical angina pectoris or myocardial ischaemic changes proven by electrocardiogram; (iv) a history of smoking was considered if >10 cigarettes had been smoked per day for >5 years; (v) a history of alcohol consumption was considered if the patient had been drinking >100 g per day for >5 years.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Data are presented as mean ± SD, mean ± SE or n of patients (%) as appropriate. Comparisons across groups were examined using the χ^2-test for categorical variables and Student's t-test or one-way analysis of variance followed by the Tukey's b test for multiple comparisons of continuous variables. A multivariate logistic regression analysis was performed to find the independent predictor of LA. A P-value < 0.05 was considered statistically significant.

Results

Of the 268 patients who were enrolled in the study, the 164 patients with LA (LA group) had a mean ± SD age of 65.43 ± 9.56 years (range 45–80 years) and 98 were male. The 104 patients without LA (non-LA group) had a mean ± SD age of 52.77 ± 7.05 years (range 40–65 years) and 32 were male. Table 1 presents the demographic and clinical characteristics of the two groups. A total of 124 patients had hypertension, 36 had diabetes mellitus, 24 had CAD, 50 had a history of smoking, and 28 had a history of alcohol consumption.

Univariate analysis demonstrated that there were significant differences between the LA and non-LA groups in terms of uric

Table 1. Baseline clinical and demographic characteristics of the patients with and without leukoaraiosis (LA) who participated in this study to investigate that association between uric acid levels and LA.

Characteristic	LA group $n = 164$	Non-LA group $n = 104$	Statistical significance[a]
Age, years	65.43 ± 9.56	52.77 ± 7.05	$P < 0.001$
Sex, male/female	98/66	32/72	$P < 0.001$
Hypertension, yes/no	108/56	16/88	$P < 0.001$
Diabetes mellitus, yes/no	36/128	0/104	$P < 0.001$
Alcohol consumption, yes/no	24/140	4/100	$P = 0.003$
Smoking, yes/no	38/126	12/92	$P = 0.012$
CAD, yes/no	16/148	8/96	NS
UA, μmol/l	356.49 ± 121.85	289.96 ± 102.98	$P < 0.001$
FIB, g/l	3.28 ± 0.84	2.86 ± 0.67	$P < 0.001$
HCY, μmol/l	15.57 ± 6.22	12.74 ± 4.93	$P < 0.001$
ALB, g/l	49.95 ± 5.06	43.52 ± 3.61	$P = 0.006$
FBG, mmol/l	5.79 ± 2.87	5.14 ± 0.64	$P = 0.026$
LDL-C, mmol/l	1.19 ± 0.41	1.34 ± 0.48	$P = 0.006$
HDL-C, mmol/l	2.95 ± 1.06	2.70 ± 0.96	$P = 0.049$
GLB, g/l	27.04 ± 4.22	26.34 ± 5.56	NS
CHO, mmol/l	4.79 ± 1.20	4.71 ± 0.99	NS
TG, mmol/l	1.45 ± 0.78	1.31 ± 0.88	NS
D-Dimer, μg/l	0.51 ± 0.67	0.43 ± 0.36	NS
PLT, $\times 10^9$/l	225.85 ± 57.54	232.96 ± 64.47	NS
HCT	0.41 ± 0.11	0.40 ± 0.05	NS
Apo-A, g/l	1.24 ± 0.30	1.28 ± 0.26	NS
Apo-B, g/l	0.93 ± 0.33	0.90 ± 0.25	NS

Data presented as mean ± SD or *n* of patients.

[a] χ^2-test for categorical variables and Student's *t*-test or one-way analysis of variance followed by the Tukey's b test for multiple comparisons of continuous variables.

CAD, coronary artery disease; UA, uric acid; FIB, fibrinogen; HCY, homocysteine; ALB, albumin; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; GLB, globulin; CHO, cholesterol; TG, triglycerides; PLT, platelet count; HCT, haematocrit; Apo-A, apolipoprotein-A; Apo-B, apolipoprotein-B; NS, no significant between-group difference ($P \geq 0.05$).

acid ($P < 0.001$), homocysteine ($P < 0.001$), hypertension ($P < 0.001$), sex ($P < 0.001$), diabetes mellitus ($P < 0.001$), smoking ($P = 0.012$), alcohol consumption ($P = 0.003$), age ($P < 0.001$), fibrinogen ($P < 0.001$), albumin ($P = 0.006$), fasting blood glucose ($P = 0.026$), HDL-C ($P = 0.049$) and LDL-C ($P = 0.006$), but other characteristics were not significantly different (Table 1).

Multivariate logistic regression analysis used LA as the dependent variable with the significantly different characteristics from the univariate analysis as the independent variables in order to identify the risk factors for LA. The multivariate logistic regression analysis demonstrated that uric acid, homocysteine, hypertension, age, diabetes mellitus and albumin were independently associated with the presence of LA (Table 2).

Discussion

It is widely acknowledged that LA is one type of presentation of small cerebrovascular disease.[11] The continuous development and wide application of neuroimaging has resulted in ever increasing rates of detection

Table 2. Multivariate logistic regression analyses for independent clinical and demographic risk factors for leukoaraiosis.

Characteristic	B	Standard error	χ^2-test (Wald)	Statistical significance	OR (95% CI)
Hypertension	0.145	0.069	4.430	$P=0.035$	1.156 (1.010, 1.324)
Homocysteine	0.112	0.055	4.170	$P=0.041$	1.118 (1.004, 1.245)
Age	1.511	0.465	10.566	$P=0.001$	4.533 (1.822, 11.275)
Uric acid	0.251	0.096	6.583	$P=0.012$	1.285 (1.062, 1.556)
Albumin	0.222	0.093	5.631	$P=0.017$	1.252 (1.041, 1.513)
Diabetes mellitus	1.217	0.411	8.759	$P=0.003$	3.378 (1.509, 7.565)

OR, odds ratio; CI, confidence interval.

of LA, which has drawn greater attention from neurologists.[2] Uric acid is the metabolic end product of endogenous and exogenous purine metabolism, which are the major components of RNA and DNA.[5] The association between uric acid and acute stroke is still disputed,[8,9] while studies of the relationship between uric acid and LA are limited.[6] A clearer understanding of the risk factors associated with the development of LA is required so that treatment can be initiated as early as possible in order to reduce clinical symptoms and subsequent serious complications. Therefore, it is important to investigate the possible association between uric acid levels and the presence of LA.

This present study found that hypertension, age, hyperhomocysteinaemia, diabetes mellitus and hyperalbuminaemia were independent risk factors for LA, findings that were consistent with the results of previous studies.[12–16] These findings suggest that patients with the risk factors described above should be monitored carefully and offered prophylactic treatment.

In this present study, hyperuricaemia was a risk factor for LA in both the univariate and multivariate logistic regression analyses. Few studies have reported on the relationship between uric acid and LA.[6] Large prospective studies have demonstrated that hyperuricaemia was an independent risk factor of cerebral-cardiovascular diseases.[17,18] Hyperuricaemia can also interfere with the metabolism of lipids and glucose.[15,19] The pathogenesis of hyperuricaemia-promoting LA appears to be consistent with stroke: (i) uric acid promotes LDL-C oxidation and lipid peroxidation, induces vascular endothelial cell dysfunction, and the oxygen free radicals that are created cause an inflammatory reaction of the vascular wall that promotes atherosclerosis; (ii) the inflammatory reaction caused by uric acid crystals activates platelet function, which increases platelet adhesion and starts the coagulation cascade, which ultimately promotes thrombosis; (iii) uric acid causes endothelial dysfunction, promotes the formation of local oxidizing agents and the reaction of inflammatory mediators such as monocyte chemoattractant protein, nuclear factor-κB, interleukin (IL)-1β, IL-6, and tumour necrosis factor-α.[20–23]

In this present study, sex, fibrinogen, HDL-C, LDL-C, fasting blood glucose, smoking and alcohol consumption were risk factors for LA in the univariate analyses, but were not significant in the multivariate logistic regression analyses. This result might have been caused by the small sample size and the cross-sectional nature of the study. The results suggest that larger prospective studies are needed to confirm these preliminary findings.

This present study had several limitations. First, it was a cross-sectional study.

Secondly, the data were obtained from a limited geographical area with a small sample size. Thirdly, other risk factors for LA may exist that were not examined in this present study.

In conclusion, this present study identified hyperuricaemia as a risk factor for LA in Chinese patients.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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