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Research article

Serum uric acid and impaired cognitive function in community-dwelling elderly in Beijing

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HIGHLIGHTS

- The association between serum uric acid and cognitive impairment was investigated.
- Uric acid levels were lower in subjects with cognitive impairment.
- High levels of serum uric acid were associated with a decreased risk of cognitive impairment.

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ABSTRACT

The relationship between serum uric acid (sUA) and cognitive function is contradictory. This study assessed the association between sUA and cognitive impairment in 10,039 community–dwelling subjects aged ≥55 years living in Beijing, China. Participants underwent determination of sUA and an evaluation of cognitive function using the scholarship-adjusted Mini-Mental State Examination (MMSE): MMSE ≤17 for illiterates; MMSE ≤ 20 for primary school graduates (≥6 years of education); and MMSE ≤ 24 for junior school graduates or above (≥9 years of education). Among the 10016 persons with valid MMSE scores, the prevalence of cognitive impairment was 9.14%. A multivariate logistic regression model including demographic, clinical and genetic parameters was performed to assess the relationship between sUA and cognitive impairment. Persons with cognitive impairment had lower sUA levels than those with normal cognitive function: (302.30 ± 82.80 vs. 312.20 ± 84.01 μmol/L, p = 0.001). After adjusting for age, sex, lifestyle, relevant diseases and the apolipoprotein E (APOE) ε4 allele, stepwise logistic regression showed that participants with higher levels of sUA had a lower risk of cognitive impairment (hazard ratio (HR): 0.78; 95% confidence interval (CI): 0.62–0.96; p = 0.022). In this baseline cross-sectional population-based sample, high levels of sUA were associated with a decreased risk of cognitive impairment.

1. Introduction

It has been estimated that the number of people living with dementia worldwide would increase to 115.4 million in 2050 [1].The prevalence and incidence of dementia increase significantly with aging [2]. With the rapid aging of the population in China, the rising prevalence of cognitive impairment is an important public health concern. Currently, there is no effective treatment to cure or prevent cognitive impairment. Thus, it is important to identify risk factors for cognitive impairment and dementia.

Several socioeconomic, metabolic and genetic factors have been reported to be associated with cognitive impairment [3,4]. Previous studies have suggested that both vascular disorders and oxidative stress play an important role in the pathogenesis of cognitive impairment [5,6]. The presence of the apolipoprotein E (APOE) ε4

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allele may increase the risk of Alzheimer's disease (AD) and vascular dementia (VAD) [7,8]. In recent years, a number of studies have concluded that the levels of serum uric acid (sUA) are associated with cognitive function, but this finding remains contradictory. Uric acid (UA) is associated with hypertension, cardiovascular disease and stroke [9,10]. UA might also increase the risk of cognitive impairment and dementia via vascular pathology [11,12]. Previous studies have found that higher levels of UA are associated with poorer cognition [13,14]. However, as a major natural antioxidant, UA might reduce oxidative stress and thus play a protective role against cognitive impairment [15]. Recently, several studies have suggested that higher levels of UA are associated with a lower risk of cognitive impairment [16] and decreased risk of incident dementia [17].

The association between sUA and cognitive function may be confounded by other factors, such as lifestyle and relevant diseases, particularly cardiovascular or cerebrovascular diseases [14]. However, few studies have adequately corrected for all of the confounders, including genetic factors.

The aim of this study is to examine the association between sUA and cognitive function independent of lifestyle, relevant diseases and the apolipoprotein E (APOE) $\varepsilon 4$ allele in a large sample of the elderly living in a community.

2. Materials and methods

2.1. Study population

This study is a secondary analysis of data obtained from the Beijing Longitudinal Study on Aging II (BLSA II) project. The participants in our study were from the BLSA II prospective cohort, which was initiated in 2009. Using a stratified multiphase sampling design, it included representative samples from three urban districts and one rural county, including 18 administrative districts or counties in Beijing [18]. Long-term residents with an age $\geq$55 years in each household were recruited for the study. A total of 10039 individuals were enrolled in the baseline survey, among which 10016 participants with valid MMSE scores underwent analysis in our study. This study was approved by research ethics boards at Xuanwu Hospital of Capital Medical University. Informed signed consent was obtained from all participants prior to their participation in the study.

2.2. Data collection

Face-to-face interviews were conducted by trained physicians and nurses. The questionnaire included demographic data, medical history, medications and functional assessments. Furthermore, physical examinations were recorded, such as blood pressure, weight, height and waist-to-hip ratio (WHR), and blood samples were taken to test the serum levels of glucose, total cholesterol (TCH), triglycerides (TG) and low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL-C), blood urea nitrogen(BUN), serum creatinine (CRE), and sUA for all subjects at baseline. Fasting sUA and other biochemistry indicators were determined using the Sysmex Chemix-180 automatic biochemical analysis device (Sysmex Infosystems, Kobe, Japan). APOE genotype was examined at baseline for all participants. Genomic DNA was extracted from peripheral blood leukocytes via a modified phenol/chloroform extraction procedure. The APOE genotype was examined using one-stage polymerase chain reaction (PCR) as described by Wenham [19]. To evaluate cognitive function, a validated Chinese version Mini-Mental State Examination (MMSE) [20] was performed on the day prior to blood testing. Geriatric Depression Scale-15 items (GDS-15) [21] were used to assess depression.

2.3. Definitions

Hyperuricemia was defined as a sUA level >416 μmol/L in men and >356 μmol/L in females [22,23]. Diabetes was defined as fasting glucose $\geq$ 7 mmol/L, having already-diagnosed diabetes or use of an anti-diabetic therapy. Hypertension was defined as systolic blood pressure (SBP) $\geq$140 mmHg, diastolic blood pressure (DBP) $\geq$ 90 mmHg, use of antihypertensive agents or having already-diagnosed hypertension. Obesity was defined as a body mass index $\geq$28 kg/m^2. Smoking status was defined as a current smoking status. Hypercholesterolemia was defined as TG $\geq$ 2.26 mmol/L, TCH $\geq$ 6.22 mmol/L, LDL $\geq$ 4.14 mmol/L, and HDL <1.04 mmol/L. A GDS score of 5 or more was used to categorize subjects as having depressive symptoms. Stroke was defined as a self-reported history of already-diagnosed stroke at baseline. Heart disease was defined as a history of myocardial infarction, coronary heart disease, congestive heart failure, or angina (self-report or cardiac medications use).

MMSE is a widely used measure of global cognitive function. The score ranged from 0 to 30, with higher scores representing better cognitive function. We stratified cutoffs by educational level because a lower educational level was observed in the present study population. As validated in the previous study, cognitive impairment was defined as: MMSE $\leq$17 for illiterates; MMSE $\leq$ 20 for primary school graduates ($\geq$6 years of education); and MMSE $\leq$ 24 for junior school graduates or above ($\geq$9 years of education) [24].

2.4. Statistical analyses

All data analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, U.S.A). According to the baseline score of the MMSE, the population was divided into two groups (cognitive impairment and normal cognitive function). For all continuous variables, the results were reported as the mean and standard deviation (m $\pm$ s.d.). Student's *t*-tests were used to compare the means between groups. Chi-square tests were employed to test between-group differences in categorical variables. The odds ratios (OR) and 95% confidence interval of having a 'cognitive impairment' compared to 'normal cognitive function' associated with high sUA levels were examined using a linear logistic regression model. Mixed effects models adjusting for (1) sUA, demographic and lifestyle variables; (2) sUA, demographic and lifestyle, relevant diseases and apolipoprotein E (APOE) $\varepsilon 4$ carrier variables were used to evaluate the association between sUA and cognitive impairment. Two-sided p-value was determined. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics of participants and prevalence of cognitive impairment

The participants' demographic, lifestyle, genetic and clinical characteristics were presented for the entire sample size according to their cognitive status in Table 1. Among the 10016 persons with valid MMSE scores, the mean age was 70.57 $\pm$ 7.72 (55–100 years) and 3876 (38.70%) subjects were male, 78.50% of subjects lived in an urban area and 7.89% of subjects lived alone. Moreover, 9.39% of individuals were APOE $\varepsilon 4$ carriers. The mean cognitive function of MMSE was 26.81 $\pm$ 3.98 (0–30). The prevalence of cognitive impairment was 9.14%. The mean UA level was 311.24 $\pm$ 83.95 (20–703 μmol/L). There were 1813 participants with hyperuricemia and only 20 subjects with low sUA ($\leq$120 μmol/L).