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Clinical Values of Serum Uric Acid Levels in the Occurrence of Cognitive Impairment in Alcohol-Dependent Patients

ABSTRACT

Objective: Studies have confirmed that uric acid is involved in the regulation of cognitive function. This study aimed to investigate the expression of serum uric acid in alcohol-dependent patients and evaluate its clinical diagnostic value for cognitive impairment.

Methods: Blood sample was collected for assessment of serum uric acid levels. Montreal Cognitive Assessment Scale scores were obtained to assess cognitive function. Anxiety and depression scores on the Symptom Check List 90 scale were used to assess mental health status. The alcohol-dependent patients were divided into non-cognitive impairment and cognitive impairment groups according to Montreal Cognitive Assessment Scale score, and the serum uric acid levels of these groups were analyzed. The receiver operating characteristic curve evaluated the diagnostic value of serum uric acid in cognitive impairment patients. Pearson correlation coefficient evaluated the correlation between uric acid and Montreal Cognitive Assessment Scale score, anxiety score, and depression score. Multivariate logistic regression analyzed the association between each index and cognitive impairment in patients.

Results: Serum uric acid was higher in patients than in controls ($P < .001$). Uric acid was significantly increased in cognitive impairment patients than in non-cognitive impairment patients ($P < .001$). Serum uric acid has certain diagnostic value in patients with cognitive impairment. Anxiety score and depression score were positively correlated with uric acid level, while Montreal Cognitive Assessment Scale score was negatively correlated with uric acid. Additionally, serum uric acid, Montreal Cognitive Assessment Scale score, and anxiety and depression scores were the risk factors for cognitive impairment in patients ($P < .05$).

Conclusion: The abnormal expression of uric acid has a high diagnostic accuracy for distinguishing cognitive impairment from non-cognitive impairment.

Keywords: Alcohol dependence, cognitive impairment, uric acid, diagnosis

Introduction

Alcohol is an important central nervous system depressant, and repeated heavy drinking can cause chronic and permanent damage to the structure and function of brain tissue.[1] According to the statistics of the World Health Organization, there are more than 2 billion drinkers in the world, of which more than 70 million are diagnosed with alcohol-related disorders.[2] Alcohol abuse and dependence have led to serious social and medical problems. In China, data released in 2019 showed that per capita alcohol consumption increased from 4.1 L in 2005 to 7.2 L in 2016, with an increase of 76%. Conversely, the lifetime abstinence rate dropped from 50.9% to 42.1%.[3] According to a report published in *The Lancet* in 2020, alcohol consumption was the primary risk factor for death among people aged 25-49. In 2019, nearly 2.5 million people died from alcohol consumption, of which more than 2 million were men.[4] Any health benefits of drinking alcohol may be outweighed by its toxic effects, which will not

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only damage the individuals' physical health but also result in a series of mental health problems.[5]

At present, it has been demonstrated that alcohol dependence can cause autonomic nerve function injury and vascular endothelial diastolic function, which greatly increases the risk of cardiovascular diseases.[6,7] Additionally, studies have confirmed that the earliest symptom of the influence of alcohol on the central nervous system is the decline of cognitive function. An animal study found that the volume of the hippocampus, cerebellum, and hypothalamus in mice exposed to high alcohol consumption was smaller than that in mice exposed to non-alcohol. Long-term heavy drinking will change the physiological brain function and brain structure of patients with alcohol dependence and then cause damage to the cognitive function of patients with alcohol dependence.[8] When the damage is severe, it can develop into Korsakov's syndrome and chronic encephalopathy syndrome, and the memory and intelligence damage of patients can even reach an irreversible degree.[9]

Uric acid (UA) is the end product of purine nucleotide metabolism, mainly in the form of urate, which has low solubility in human blood.[10] Studies have shown that blood UA levels in patients with vascular dementia are significantly higher than those in normal controls, and UA levels are positively correlated with the severity of dementia.[11] Besides, another study showed that high doses of UA significantly reduced neuroblast viability and enhanced the pro-apoptotic effects of Aβ amyloid in an in vitro model of Alzheimer's disease.[12] Many studies have been conducted on the relationship between UA and cognitive impairment, but there are still relatively few studies on the role of UA in alcohol-dependent patients with cognitive impairment.

In this study, the blood of patients with alcohol dependence was collected to detect the level of serum UA, and the diagnostic value of serum UA on cognitive impairment of patients with alcohol dependence was evaluated, which provided a valuable experimental basis for systematic intervention therapy of patients with alcohol dependence clinically.

Methods

Study Subjects

Sixty-eight patients with alcohol dependence who were hospitalized in Hengshui Seventh People's Hospital were selected as the case group of this study. Inclusive criteria were as follows: (i) the diagnostic criteria of alcohol dependence in accordance with the Tenth Revision of the International Classification of Diseases; (ii) male, aged 30-60 years; (iii) have stopped using alcoholic beverages for more than 14 days and have stopped using sedative drugs instead; and (iv) education level ≥ 9 years. Another 65 normal people were selected as healthy control group. Exclusion criteria were as follows: (i) current or previous other psychoactive substance use disorders (except tobacco); (ii) patients with organic mental disorder; (iii) patients with severe impulsive behavior; (iv) history of central nervous system diseases, such as stroke, tumor, Parkinson's disease, Huntington's disease, epilepsy, and brain trauma; (v) history of serious physical diseases, such as diabetes, hypertension, severe infections, and family history of genetic diseases; (vi) unlicensed concomitant therapy (e.g., antidepressant cholinesterase inhibitors); and (vii) participants with intellectual disabilities. The general information of the alcohol dependence group was collected by the subjects themselves upon admission. This study was approved by the Ethics Committee of Hengshui Seventh People's Hospital (No.20210013). All subjects voluntarily participated in this study, and all enrolled members signed informed consent after full knowledge.

MAIN POINTS

- *Serum uric acid (UA), Montreal Cognitive Assessment Scale score, anxiety score, and depression score were the risk factors for cognitive impairment in alcohol-dependent patients.*
- *The occurrence of cognitive impairment caused by alcohol dependence is closely related to the increase of serum UA levels in alcohol-dependent patients.*
- *Damage to the nervous system caused by the high expression of serum UA may be the main cause of cognitive impairment.*

Acquisition of Blood Samples

For the determination of blood UA, 5 mL of fasting venous blood was taken in the morning at least 7 days after the subjects stopped using alcohol, and UA-regulating drugs should be stopped within 3 days before blood collection. After blood collection, the upper layer of serum was harvested by high-speed centrifugation and stored in −80°C refrigerator for later use. Serum UA was measured by an automatic biochemical analyzer.

Evaluation of Cognitive Function

Cognitive function was assessed by the Chinese version of Montreal Cognitive Assessment (MoCA) scale.[13] The Chinese version of MoCA has reliable internal consistency (Cronbach alpha = 0.82) and the English version (Cronbach alpha = 0.83). Montreal Cognitive Assessment Scale consists of 11 examination items in 8 cognitive fields, including attention and concentration, executive function, memory, language, visual structure skills, abstract thinking, calculation, and orientation. The total score of MoCA is 30, and ≥26 is normal. Otherwise, it is recognized as cognitive impairment.

Evaluation of Mental Health Status

The anxiety and depression of the subjects were evaluated by the anxiety and depression factors in Symptom Check List 90 (SCL-90) scale. The SCL-90 scale included 90 self-assessment items for somatization, compulsion, interpersonal sensitivity, depression, anxiety, hostility, fear, paranoia, and psychosis. If the score of the anxiety factor is more than 30 points, it indicates that the subject has an obvious anxiety tendency, and if the score of depression factor is more than 39 points, it manifests that the subject has an obvious depression tendency.

Data Analysis

Statistical Package for Social Sciences Version 23.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. Data were normally distributed and expressed as mean (SD). Independent sample *t*-test was used to compare continuous variables between two groups, and chi-square test and Fisher's exact test were used to compare categorical variables. Pearson's correlation coefficient analysis was performed to assess the correlation. The receiver operating characteristic (ROC) curve was conducted to evaluate the diagnostic value of serum UA level for cognitive impairment in patients with alcohol dependence. A multivariate logistic regression analysis was used to assess the influence of each index on the progression

from non-cognitive impairment to cognitive impairment in the case group. $P < .05$ was considered to be significantly different.

Results

Comparison of Baseline Data Between Healthy Control and Alcohol Dependence Group

Table 1 shows the general information of the 2 groups. The results suggested that there was no significant difference in age, body mass index, smoking, and alcohol dependence duration between the healthy control group and the patients with alcohol dependence ($P > .05$). Besides, the MoCA score, anxiety score, and depression score of the alcohol-dependent group were significantly higher than those of the healthy control group ($P < .001$).

Serum Uric Acid Levels Are Increased in Alcohol-Dependent Patients and Higher in Those with Cognitive Impairment

Through the detection of serum UA, it was found that the serum UA level of alcohol-dependent patients was significantly higher than that of healthy controls (Figure 1, $P < .001$), indicating that the changes in serum UA may be one of the effects of alcohol dependence on the human body. Additionally, according to the scores of MoCA, alcohol-dependent patients were divided into a cognitive impairment group (n = 37) and a non-cognitive impairment group (n = 31), and the serum UA level of these 2 groups was evaluated. The results revealed that among all alcohol-dependent patients, the serum UA level of cognitive impairment patients was significantly enhanced than that of non-cognitive impairment patients (Figure 2, $P < .001$).

Serum Uric Acid Has Diagnostic Capacity for Cognitive Impairment in Alcohol-Dependent Patients

The ROC analysis of serum UA values in all alcohol-dependent patients showed that serum UA had a good ability to discriminate between people with and without cognitive impairment. The ROC curve in Figure 3 directly revealed that when the cut-off value was 428.26, the AUC of serum UA was 0.899, and the sensitivity and specificity were 80.90% and 82.80%, respectively.

Serum Uric Acid Levels Were Significantly Correlated with Montreal Cognitive Assessment Scale Scores, Anxiety, and Depression Scores

Pearson's correlation coefficient was used to evaluate the correlation between serum UA level and MoCA score, anxiety score, and depression score, respectively. It can be seen from Table 2 that MoCA score ($r = -0.614$, $P < .001$) is negatively correlated with serum UA level, while anxiety score ($r = 0.593$, $P < .001$) and depression score ($r = 0.581$, $P < .001$) are positively correlated with serum UA level.

Table 1. Comparison of Baseline Data Between Control and Case Group

Indicators	Healthy Controls (n = 65)	Alcohol-Dependent Patients (n = 68)	*P*
Age (years)	47.33 (7.77)	48.14 (7.59)	.513
BMI (kg/m^2)	23.49 (2.93)	23.54 (2.86)	.757
Smoking (n, %)	42 (64.62%)	45 (66.18%)	.316
Alcohol dependence duration (years)	6.25 (2.84)	6.41 (2.72)	.491
MoCA score	25.36 (1.58)	21.03 (1.33)	<.001
Anxiety score	26.97 (2.01)	35.21 (2.88)	<.001
Depression score	35.34 (3.27)	44.19 (3.36)	<.001

BMI, body mass index; MoCA, Montreal Cognitive Assessment Scale. Data are presented as mean (SD).

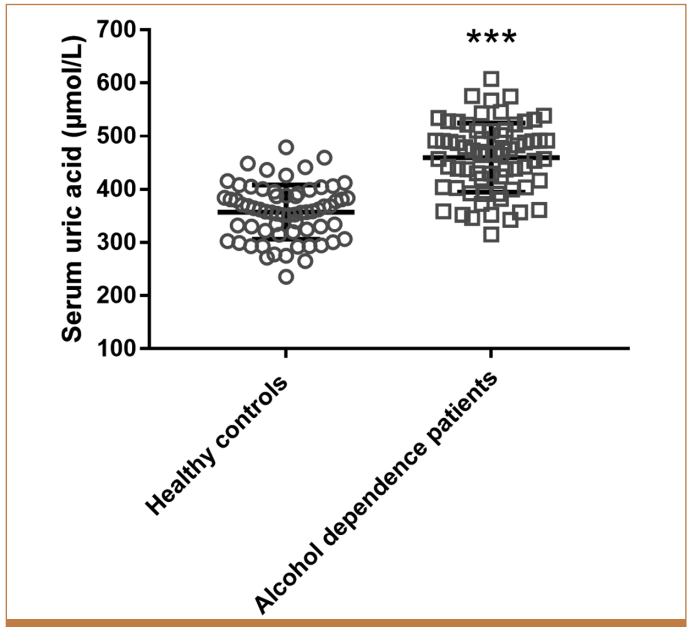

Figure 1. The expression level of serum uric acid. The expression level of serum uric acid in alcohol-dependent patients was significantly increased compared with healthy controls. Independent sample *t*-test was employed to analyze panels. $^{***}P < .001$.

Assessment of Risk Factors for Transition from Non-Cognitive Impairment to Cognitive Impairment

Logistic regression analysis was performed to evaluate the risk factors for conversion of non-cognitive impairment to cognitive impairment for each index in alcohol-dependent patients. As illustrated

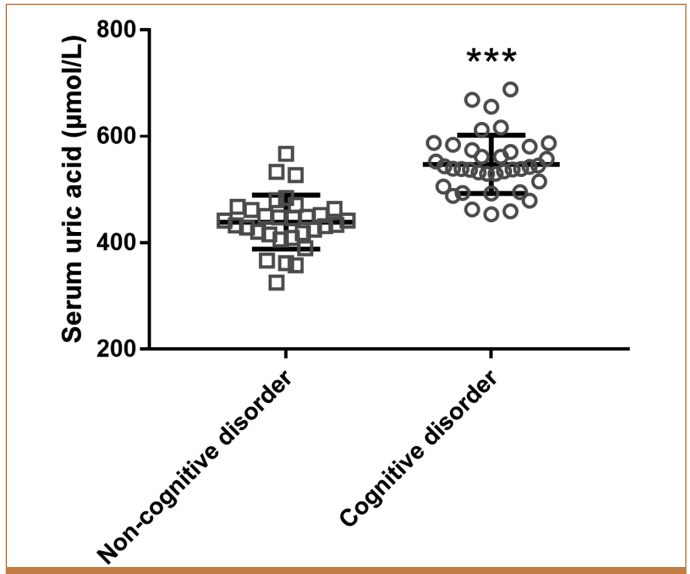

Figure 2. The expression level of serum uric acid. In patients with alcohol dependence, the level of serum uric acid expression in the cognitive impairment group was significantly higher than that in the non-cognitive impairment group. Independent sample *t*-test was employed to analyze panels. $^{***}P < .001$.

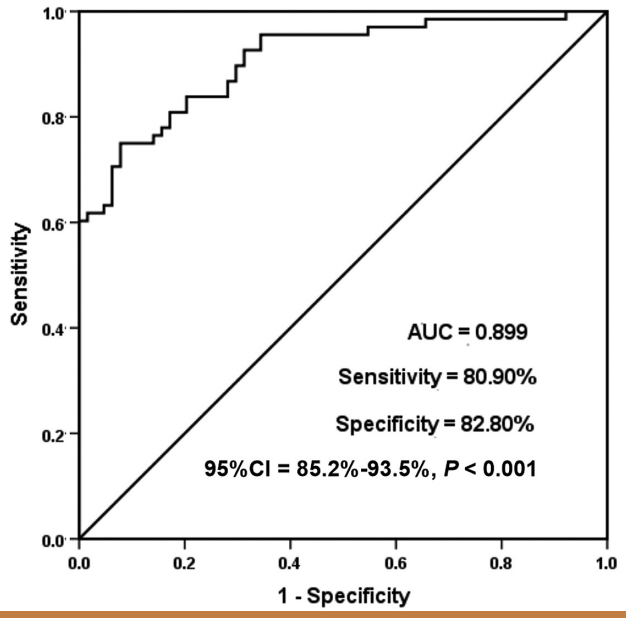

Figure 3 . Receiver operating characteristic (ROC) analysis. The area under the ROC curve of serum uric acid level was 0.899, with a sensitivity of 80.90% and specificity of 82.80%.

Table 2. Correlation Between Serum Uric Acid Level and MoCA Score, Anxiety, and Depression Score

Indexes	Correlation with Serum Uric Acid Level (*r*)	*P*
MoCA score	−0.614	<.001
Anxiety score	0.593	<.001
Depression score	0.581	<.001

MoCA: Montreal Cognitive Assessment Scale.

in Table 3, through analysis, it was observed that serum UA (odds ratio (OR) = 3.705, 95% CI= 1.974-10.256, *P* = .009), anxiety score (OR = 2.303, 95% CI = 1.276-5.327, *P* = .038), and depression score (OR = 2.612, 95% CI = 1.527-6.133, *P* = .021) were independent risk factors for the development of non-cognitive impairment into cognitive impairment.

Discussion

Alcohol is a neuro-inhibitor that can penetrate the blood–brain barrier and has neurotoxic effects.[14] Long-term excessive drinking or alcoholism will lead to alcohol dependence, acute and chronic alcoholism, and extensive and severe damage to the central nervous system, including brain atrophy, toxic myopathy, multiple mental derangement, central nervous system degeneration, metabolic disease, and mental disorders.[15,16] The neuropsychological cognitive impairment caused by alcoholism, called alcohol-induced cognitive impairment, occurs in as many as 50%-80% of patients with alcohol dependence.[17] It is well known that cognitive function is a unique higher neural function of human beings, which involves multiple dimensions, including memory, understanding, attention, language, and executive function.[18] Previous studies have shown that patients with alcohol dependence have different degrees of cognitive impairment due to the influence of the average daily amount of alcohol consumed and the duration of drinking.[19] Cognitive impairment is a transitional stage between normal aging and dementia. Patients have memory impairment and may have mild cognitive impairment in many aspects. The severity of cognitive impairment has not yet reached the standard of dementia. Seriously, however, people with this kind of cognitive impairment can develop dementia without intervention.[20] Therefore, early detection and diagnosis of cognitive impairment are of great practical significance to the alcohol-dependent population.

Uric acid has been shown to have neurotoxic or neuroprotective effects in specific tissues and diseases. Mijailovic et al[21] suggested that UA may be involved in the etiology and clinical manifestations of neurodegenerative and psychiatric diseases in a variety of ways. For example, increased UA may be beneficial for cognitive function due to its antioxidant effect, or it may be a risk factor for cognitive impairment by promoting inflammation. In this study, we found that the level of UA in the serum of alcohol-dependent patients was significantly higher than that of healthy subjects. In addition, it was also found that the concentrations of serum UA in alcohol-dependent patients with cognitive impairment were augmented than that of non-cognitive-impaired alcohol-dependent patients. A previous investigation showed that regular drinkers had higher blood UA concentrations than non-drinkers reported in laboratory tests.[22] Alcohol is metabolized into lactic acid in the body, which inhibits the excretion of UA and accelerates the generation of UA.[23] The interaction between UA and cognitive impairment has been validated in several studies. For example, in a prospective study, there was a significant association between hyperuricemia and white matter atrophy in 814 patients who underwent magnetic resonance imaging and neuropsychological test, which indicated that

Table 3. Relationship Between Different Variables and Transition from Non-Cognitive Impairment to Cognitive Impairment in Patients with Alcohol Dependence

Characteristics	OR	β	Standard Error	95% CI	*P*
Age	1.522	0.363	0.431	0.653-3.806	.203
BMI	1.298	0.322	0.401	0.530-3.499	.253
Smoking	1.754	0.575	0.427	0.781-4.212	.133
Alcohol dependence duration	2.159	0.701	0.414	0.961-4.779	.078
Serum UA	3.705	1.224	0.406	1.974-10.256	.009
Anxiety score	2.303	0.769	0.404	1.276-5.327	.038
Depression score	2.612	0.838	0.404	1.527-6.133	.021

BMI, body mass index; 95% CI, 95% confidence interval; OR, odds ratio; UA, uric acid.
The model includes the age, BMI, smoking, alcohol dependence duration time, serum UA level, anxiety, and depression scores.
The reliability of this model was good (Hosmer and Lemeshow test *P*-value .56).

hyperuricemia was related to cognitive impairment.[24] In addition, in this present study, we also found that a high level of serum UA showed a high clinical application value in distinguishing alcohol-dependent patients with cognitive impairment from those without cognitive impairment. Previous clinical studies have pointed out that the mechanism of alcohol-induced cognitive impairment is the damage of nerve tissue and brain tissue caused by chronic alcoholism after long-term heavy drinking.[25] The symptoms of mild cognitive impairment are mainly inattention, lethargy, and irritability. In severe cases, cognitive impairment such as hallucinations and tremors may occur, which may aggravate the physical and mental health of patients.[26] Other studies pointed out that the disorder of nucleotide metabolism in the human body is the main pathological mechanism of cognitive disorder in patients with alcohol dependence, and blood UA, as biomarkers, can directly reflect the nucleotide metabolism in patients.[27]

Clinically, Wechsler Intelligence Scale, Mini-Mental State Examination, and MoCA scale[28] are often used to evaluate human cognitive function. In this study, MoCA scale, anxiety factor, and depression factor in the SCL-90 scale were selected as screening scales to evaluate patients' cognitive function and mental health status. Studies have shown that alcohol can produce a great number of free radicals and UA substances in the metabolic process of the human body.[29] These free radicals can aggravate the damage of nerve function, thus inducing patients to appear in various mental symptoms, such as depression, fear, and anxiety.[30] In this study, results showed that the MoCA score, anxiety score, and depression score of alcohol-dependent patients were higher than those of healthy controls. More importantly, related studies showed that the MoCA score decreases gradually with the increase of serum UA level, and the anxiety score and depression score increase with the increase of UA level. Particularly, it is also found that the analysis of various indicators in alcohol-dependent populations found that serum UA level, MoCA score, anxiety score, and depression score were risk factors for cognitive impairment in alcohol-dependent patients. That is, an increase in these indicators suggests an increased risk of cognitive impairment in alcohol-dependent populations.

Based on the different roles of UA in different tissues and diseases, several limitations of this study should be noted that cannot be ignored. First, the sample size of this study is small, and samples from a single center may have selection bias, so it is necessary to expand the number of clinical samples for repeated studies. Second, the sample was limited to serum. Studies of cognitive function should focus on the hippocampus or cerebrospinal fluid, if possible. Finally, previous studies have shown that oxidative stress and neuroinflammation are significantly associated with psychiatric disorders such as depression, anxiety, and schizophrenia.[31,32] There is a lack of studies on the association between UA and inflammation and oxidative stress in this study, so it is necessary to actively explore the correlation between cognitive impairment or UA level and inflammation and oxidative stress in future studies. In conclusion, the occurrence of cognitive impairment caused by alcohol dependence is closely related to the increase of serum UA levels in alcohol-dependent patients. The damage of the nervous system caused by the high expression of serum UA may be the main cause of cognitive impairment, and it is also related to the increased risk of anxiety, depression, and other diseases.

Ethics Committee Approval: *Ethical committee approval was received from the Ethics Committee of Seventh People's Hospital of Hengshui (Approval No: 20210013).*

Informed Consent: *Written informed consent was obtained from all participants who participated in this study.*

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