Original Paper

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Relationship Between Impulsivity and Plasma Uric Acid Levels in Patients with Substance Use Disorders

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ABSTRACT:

Relationship between impulsivity and plasma uric acid levels in patients with substance use disorders

Objective: Impulsivity is an important neurobiological process that contributes to individual differences in substance use disorder vulnerability. Uric acid has been mentioned to be telated to some psychiatric disorders characterized by impulsivity. No other study has yet examined the relationship between UA plasma concentration and impulsivity in patients with substance use disorders.

Methods: Eighty patients diagnosed with substance use disorders and eighty healthy controls were included. A protein-rich diet was given to all subjects for one week. Blood samples were obtained and plasma uric acid levels were recorded as in mg/dl after being centrifuged for 15 min at 3000 X g and kept at -80°C. Impulsivity was evaluated using the Turkish version of Barrat Impulsivity Scale (BIS).

Results: The mean uric acid concentrations (t/χ^2=3.3; p<0.05) were significantly higher in the patients with substance use disorders compared to the healthy control group. Additionally, total BIS scores (t/χ^2=2.4; p<0.05), Attentional Impulsiveness scores (t/χ^2=2.1; p<0.05), and Motor Impulsiveness scores (t/χ^2=2.6; p<0.05) were statistically significantly higher in the patients with substance use disorder. There was a negative mild, statistically significant correlation between UA plasma levels in the patients with substance use disorder and total BIS scores (r=-0.278; p<0.05), and Motor Impulsiveness subscales scores (r=-0.302; p<0.01). Multiple linear regression analysis revealed that plasma UA levels were found to be statistically significantly associated with the Motor Impulsiveness scores in the patients with substance use disorder (p=0.007).

Conclusions: This preliminary study is the first study that explores how uric acid levels were associated with impulsivity in patients with substance use disorder. Further studies with larger sample size are needed to tease out confounding factors and replicate our findings.

Keywords: impulsivity, uric acid, substance use disorder

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INTRODUCTION

Impulsivity is a ubiquitous human behavior that can be both beneficial and detrimental to our everyday lives. For example, the ability to act on impulse may allow someone to seize a valuable opportunity, or to make a disastrous decision that person then lives to regret. Impulsivity, broadly defined as an action without foresight, is a multidimensional psychological construct that includes two key components: impulsive choice or the preference for immediate reward over a larger delayed reward; and impulsive action, or the inability to inhibit a prepotent behavioral response[1].

As mentioned in the previous studies, impulsivity is an important component of some psychiatric disorders including attention deficit/hyperactivity disorder (ADHD), mania, pathological gambling, and substance use disorders (SUD)[2]. Furthermore, impulsivity is an important neurobiological process that contributes to individual differences in substance use disorder vulnerability[3]. There is a large and consistent research literature showing that individuals with SUD are more likely to prefer an immediate small reward over a larger delayed reward and additional evidence that delayed discounting is prospectively associated with addiction risk[4,5]. Furthermore, impulsivity has been related to varying degrees of deficits in several cognitive functions such as risk taking, quick decision making, and lack of planning[6]. Therefore, impulsivity could play a crucial role as a mediator of the association between behavior and outcomes of the substance use[7].

Since, growing literature showing that impulsivity is a potential risk factor for substance use, there is an ever-increasing importance in determining additional biomarkers associated with this attribute. Uric acid (UA) is the end product of purine metabolism which was formed by the liver and mainly excreted by the kidneys. In recent years, UA has been mentioned in relation to many psychiatric disorders characterized by impulsivity. It was found that UA levels of pathological gamblers are increased when they are primed for monetary rewards, but not when they played checkers without betting[8]. Likewise, in children reported as having hyperactive symptoms by their teachers, a positive correlation between these symptoms and UA plasma levels were found, and UA has been linked to hyperactivity[9]. It was also suggested that UA plasma levels decreased more when patients with attention deficit hyperactivity disorder (ADHD) with impulsivity symptoms were given methylphenidate for 24 weeks compared with when they were given placebo[10]. Besides, in a study comparing UA plasma levels in unipolar depression patients without comorbidity and unipolar depression with ADHD comorbidity, it is revealed that UA plasma levels were higher in the comorbid unipolar depression with ADHD group than the unipolar depression group without ADHD, and healthy controls[11].

Uric acid is the end product of purine catabolism and increased uric acid plasma levels may indicate increased purinergic turnover and reduced adenosinergic transmission. Adenosinergic transmission dysfunction may determine the emergence of manic symptoms due to fact that one of the key functions of adenosinergic receptors in the human brain is to inhibit the release of other neurotransmitters and limit cellular excitability[12]. Adenosine particularly inhibits the release of glutamate, dopamine, and noradrenaline[13].

To our knowledge, no other study has yet examined the relationship between UA plasma concentration and impulsivity in patients with SUD. In the present study, we aimed to examine the relationship of UA plasma level with impulsivity in patients who met the DSM-5 criteria for SUD.

METHODS

Study Sample

The study was performed in January 2015 in the Alcohol and Substance Dependence Treatment Center of a specialized psychiatry hospital in Istanbul, Turkey. This study was approved by the Ethical Committee of Üsküdar University. Written informed consents were obtained from the participants following the study protocol was thoroughly explained. The cost of measuring UA plasma levels was funded by the Investigation Budget Fund of the Acıbadem Healthcare Group Hospital. Eighty patients diagnosed with SUD based on DSM-5 criteria, interviewed by two independent psychiatrists, and eighty healthy controls were included. One of the inclusion criteria for participation to the study was that subjects were not on any psychotropic medications for their current condition. Subjects with comorbid psychiatric disorder diagnosis or other medical diseases including gout, hypertension, renal

stones, chronic renal disease, chronic inflammatory disease, and hypertriglyceridemia were excluded along with those were with other severe or unstable medical conditions. Due to the fact that alcohol intake increases both UA concentration by reducing excretion[14] and increasing UA production[15], patients with alcohol use disorder were also excluded.

Procedure

We attempted to match prognostic factors in both study and control group especially for protein intake. In a study by Choi et al.16, using multivariate analysis, total protein intake were not associated with higher UA levels in a nationally representative sample of adults (14,809 participants; 6,932 men and 7,877 women) in the US. Therefore, a protein-rich diet ordered by a dietician was given to all subjects for one week who were determined to be medically healthy following a physical and neurological examination and laboratory testing. Subjects' self-reports were taken into account to check whether they were compliant with the diet. At the end of one week diet, blood samples were obtained and plasma UA levels were recorded in mg/dl after being rotated for 15 min in a centrifuge with 3000 rotations and kept at -80°C. Impulsivity level was evaluated by using the Turkish version of Barrat Impulsivity Scale (BIS)[17,18].

Statistical Analysis

Statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables in the study were compared by chi-square analysis. Descriptive statistics were calculated as frequency and percent. For all analyses, $p<0.05$ was regarded to be statistically significant. The UA plasma levels and BIS scores were normally distributed, and relationships between these variables were analyzed using Pearson's correlation test. A multiple linear regression model was used to identify independent predictors for UA plasma levels. The model fit was assessed using appropriate residual and goodness-of-fit statistics. A 5% type I error level was used to infer statistical significance.

RESULTS

There were no statistically significant differences in terms of age and gender between two groups (see Table 1). Statistically significant differences in the mean UA concentrations ($t/\chi^2=3.3$; $p=0.005$) was found between the SUD patients (M= 5.4 mg/dL, SD=1.1) and the healthy control group (M=4.6 mg/dL, SD= 0.9).

Additionally, total BIS scores ($t/\chi^2=2.4$; $p=0.015$), Motor Impulsiveness scores ($t/\chi^2=2.6$; $p=0.001$), and Attentional Impulsiveness scores ($t/\chi^2=2.1$;

Table 1: Comparison of BIS scores and plasma uric acid levels between SUD and healthy controls

	SUD n= 80	HC n= 80	t/χ^2	p
Age (Mean±SD)	26.7±4.9	31.2±8.3	1.1	0.273
Gender (F/M)	6/74	10/70	0.615	0.762
BIS subscale scores (Mean±SD)				
Motor Impulsiveness	23.4±5.8	14.1±2.2	2.6	0.001
Attentional Impulsiveness	17.2±3.6	11.8±2.1	2.1	0.027
Non-planning Impulsiveness	29.1±4.9	27.3±5.3	0.9	0.263
Total BIS score (Mean±SD)	69.7±11.8	51.2±9.1	2.4	0.015
UA plasma levels (Mean±SD)	5.4±1.1	4.6±0.9	3.3	0.005
Diagnosis n (%)				
Cannabis Use Disorder	54(67.4)			
Opioid Use Disorder	11 (13.8)			
Cocaine Use Disorder	7 (8.8)	-	-	-
Alcohol Use Disorder	4 (5)			
Inhalant Use Disorder	4 (5)			

Table 2: Correlations between BIS scores and UA plasma levels

n=80	Total BIS score		BIS/Motor Impulsiveness score		BIS/Attentional Impulsiveness score		BIS/Non-planning Impulsiveness score	
	r	p	r	p	r	p	r	p
UA plasma levels	-0.278*	0.012	-0.302**	0.007	-0.200	0.075	-0.174	0.123

*Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level

Table 3: A multiple linear regression analysis when BIS scores were independent variables

Model	Independent variables	B	t	p	95% Confidence Interval for B Lower Bound	Upper Bound
1	BIS Total Score	-0.006	-0.267	0.830	-0.051	0.039
	Motor Impulsiveness Score	-0.048	-1.022	0.275	-0.141	0.045
	Age	0.008	0.464	0.644	-0.028	0.045
2	Motor Impulsiveness Score	-0.059	-2.745	0.008	-0.101	-0.016
	Age	0.008	0.438	0.663	-0.028	0.044
3	Motor Impulsiveness Score	-0.059	-2.796	0.007	-0.102	-0.017

Dependent variable: UA plasma levels

p=0.027) were statistically significantly higher in the SUD patients compared to healthy control group. Among all the patients, 4 (5%) of them had Alcohol Use Disorder, 54 (67.4%) of them met the criteria for Cannabis Use Disorder, 11 (13.8%) of them had Opioid Use Disorder, 7 (8.8%) of them met the criteria for Cocaine Use Disorder and 4 (5%) of them had Inhalant Use Disorder. The distribution of the patients' diagnosis is given in Table 1.

There was a negative, mild, statistically significant correlation between UA plasma levels in the SUD patients and total BIS scores (r=-0.278; p=0.012), and Motor Impulsiveness subscale scores (r=-0.302; p=0.007) as shown in Table 2.

When UA Plasma level was taken as the dependent variable and BIS Total Score, BIS/ Motor Impulsiveness Score and age were taken as independent variables in separate regression analysis; it was found that only the BIS/ Motor Impulsiveness Score (β=-0.059, p=0.007) was significantly predictive of plasma UA level, explaining 7.9% of the variance in the plasma UA level (F=7.818, df=1, p=0.007, adjusted R^2=0.079) (see Table 3). Based on multiple linear regression analysis, the UA plasma level was found to be statistically significantly associated with the Motor Impulsiveness scores in the SUD patients (p=0.007).

DISCUSSION

In order to explore the mechanisms underlying impulsive behavior, the nature of impulsivity itself needs to be defined in operational terms that can be used as the basis for empirical examination. Additionally, individual differences in neurocognitive aspects of impulsivity (i.e., lack of cognitive and motor inhibition, delay discounting and impulsive decision-making) in patients with SUD are linked to unfavorable treatment outcomes including high dropout rates and difficulties in achieving and maintaining abstinence[19]. Evidence from genetic and neuroimaging studies suggest a neurophysiological basis for impulsivity, and there is wide interest in identifying biomarkers associated with this trait. UA is one of the promising candidates as a biomarker associated with impulsivity[2,8] due to fact that allopurinol has been demonstrated effective in controlling manic episode[20]. Additionally, Lorenzi et al. reported that temperamental characteristics such as increased drive, disinhibition, hyperthymia, or irritable temperament were associated with increased UA plasma levels in individuals with no psychiatric diagnosis[21].

This is the first study exploring the relationship between impulsivity and plasma UA levels in SUD

patients. Our findings indicated that impulsivity scores and UA plasma concentration were higher in SUD patients compared to healthy control subjects as it was expected. On the other hand, within group analysis, impulsivity and plasma UA levels in SUD patients were negatively correlated, which was not consistent with our expectations. This result was interpreted in the context of possible metabolic effects of illicit substances used by the patients. In this study, we found statistically significant but mild-to-moderate correlations between impulsivity scores and plasma uric acid levels in SUD patients. We can be confident that these correlations are not due to chance alone. However, lower correlation coefficients (r=-0278; r=-0302 can provide an insight on existence of a weak correlation between them.

UA plasma levels and impulsivity of the patients with SUD were found to be higher than healthy controls. Whereas, there was a significantly negative correlation between plasma uric acid levels and impulsiveness scores of patients with SUD. A multiple linear regression was used to identify possible independent predictors for UA plasma levels. In this model, Motor Impulsivity scores were found to be a significant predictive power for UA plasma concentration. This finding supports the notion that plasma UA levels would be predicted with a certain form of impulsivity in patients with SUD, which are combination of "acting on the spur of the moment" and perseverance, "a consistent life style".

The BIS/ Motor Impulsiveness Score was predictive of plasma UA level, but explaining only 7.9% of the variance in the plasma UA level. Although 7.9% of the variance might be interpreted as large portion of the variance in the plasma UA level remains unclear, this type of information can still be valuable.

This present study has some limitations. First, the severity of the substance use disorder (abuse versus dependence) has not been examined. Another limitation of the present study was that while trying to control dietary variables that may be associated with serum UA level and chronic medical conditions, some variables might in fact be associated with both UA level and impulsivity. These variables were not controlled. Another limitation is that we have not examined the relationship between the specific type of substance use disorder or duration of the substance disorder with serum uric acid levels. We also have not examined the effects of cigarette smoking and body mass index on serum UA levels, which would present as a limitation. And finally, we did not differentiate trait impulsivity and momentary 'state' impulsivity, where both determinant might increase impulsive decisions differently and might increase the tendency to use illicit substances. Our study is the first study that explores how UA levels were associated with impulsivity in patients with substance use disorder. Further studies with larger sample size are needed to eliminate such limitations and replicate our findings. These findings would lay the groundwork for studying the cognitive and neurobiological substrates of impulsivity, and the role of impulsive behavior as both facilitator and a result of substance use.

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